Australian Government
Department of Health
Therapeutic Goods Administration

Risk Management Plan Evaluation Report

Mifepristone/Mifepristol (MS-2 Step)

Submission No: PM-2022-05475-1-5

Sponsor: MS Health Pty Ltd

Updated RMP received: 01 December 2022

Sponsor's Response received: 13 January 2023

Succession 3 Report (round 1 for PM-2022-05475-1-5): 27 February 2023

TGA Health Safety Regulation

RISK MANAGEMENT PLAN EVALUATION REPORT

Submission type: PI update (corresponding to RMP updates)

Sponsor: MS Health Pty Ltd
Generic name: **Mifepristone/Mifepristol**
Trade name: **MS-2 STEP**

Submission No; eSubmission ID: PM-2022-05475-1-5; e004967
RMP file No: 2013/020378
TRIM reference: D22-6199891

AU-RMP: *(EU-RMP not available)*
Initial - Version 0.4; dated 24 November 2022; DLP 31 May 2022
e004967 (0006-) - Risk management plan - Clean
D22-6187939

Succession 2 - AU-RMP version 4.0 (dated 13 January 2023, DLP 31 May 2022)
D23-5035315

Succession 3 - AU-RMP version 4.0 (dated 17 February 2023, DLP 31 May 2022)
D23-5140670

Last evaluated AU-RMP: Version 03; dated 13 November 2014; DLP 28 April 2013
R14/1181088

Date finalised: 27 February 2023 [Succession 3, Round 1 for PM-2022-05475-1-5]

Reason(s) for update: New safety concern added
Removed safety concern
Pharmacovigilance milestone met
Ceased risk minimisation activity

SUMMARY

- On 1 December 2022, MS Health Pty Ltd submitted updated AU-RMP version 0.4 (dated 24 November 2022; DLP 31 May 2022) for MS-2 Step. The EU-RMP is not available. A revised AU-RMP version 4.0 (dated 13 January 2023; DLP 31 May 2022) was provided with the sponsor's response to RMP evaluator's recommendations dated 13 January 2023. On 20 February 2023, the sponsor submitted further changes in AU-RMP version 4.0 (dated 17 February 2023; DLP 31 May 2022) which has been linked to the Category 1, Type J application (PM-2022-05475-1-5). The latest updated AU-RMP (third revision) is being considered as a Succession 3 evaluation as part of submission PM-2022-05475-1-5.
- MS-2 Step is approved for the medical termination of an intrauterine pregnancy, up to 63 days of gestation, in females of childbearing age.
- The most recently evaluated and approved AU-RMP was version 03 (dated 13 November 2014; DLP 28 April 2013) (R14/1181088).
- The reason for this updated RMP is changes to the summary of safety concerns (SoSC) and changes to the risk minimisation plan. The key changes proposed for risk minimisation activities are as follows:
    - To remove the requirement for pharmacists to be registered to be able to dispense the product.
    - To remove the requirement for prescriber recertification.
    - To remove the need for prescribers to complete mandatory training and receive certification to be able to prescribe the product.
    - To remove the requirement for a Sponsor provided 24 hours aftercare service
- As the TGA has previously evaluated RMPs for this product, the focus of this review is on the differences between the AU-RMP versions and revisions to the additional risk minimisation materials.
- The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below:

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Infection, toxic shock syndrome	✓	–	✓	✓[1,2,3]
	Method failure	✓	–	✓	✓[1,2,3]
	Cardiac disorders	✓	–	✓	✓[2,3]
Important potential risks	Inadvertent pregnancy exposure and risk of incomplete abortion with severe bleeding	✓	–	✓	✓[2,3]
	Inadvertent pregnancy exposure (risk of malformations)	✓	–	✓	✓[2,3]
	Potential interaction with CYP3A4 inhibitors or inducers	✓	–	✓	✓[3]
	Potential interaction with products interacting with the glucocorticoid receptor	✓	–	✓	✓[3]
	Induced bronchial asthma	✓	–	✓	✓[3]
	Effects in lactating women	✓	–	✓	✓[3]
	Effects in women with impaired liver function	✓	–	✓	✓[3]
	Effects in women with impaired renal function	✓	–	✓	✓[3]
	Effects in women with malnutrition	✓	–	✓	✓[3]

	Incorrect determination of gestational age	✓	–	✓	✓[3]
	Potential for missed ectopic pregnancy	✓	–	✓	✓[2,3]
	Potential for postnatal developmental delay	✓	–	✓	–
	Potential for off-label use beyond the first trimester	✓	–	✓	✓[3]
	Potential for loss to follow-up	✓	–	✓	–
	Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up	✓	–	✓	✓[3]
Missing information	Inherited porphyria	✓	–	–	–
	Theoretical interaction with NSAIDs	✓	–	–	–
	Potential interaction with products interacting with the progesterone receptor	✓	–	–	–
	Use in adolescents	✓	–	–	–
Pharmacological class effect	Risks related to the use of prostaglandin	✓	–	✓	✓[2,3]

[1] Black box warning
[2] Patient Information and Consent Agreement form
[3] Physician education

- The sponsor has updated the summary of safety concerns in line with recommendations by the RMP evaluator as well as to reflect up-to-date safety information for MS-2 Step. The summary of safety concerns is considered acceptable from an RMP perspective.
- The completed post marketing surveillance study has been removed from the pharmacovigilance plan. Routine pharmacovigilance is proposed for all safety concerns. The sponsor does not propose any additional pharmacovigilance activities. The sponsor is requested to include planned Canadian-specific post-market study in the AU-RMP as the outcomes are applicable to Australia.
- The sponsor proposes to remove from the risk minimisation plan the requirements for prescriber certification and recertification, pharmacist registration and a Sponsor-provided 24 hours aftercare service. Additional risk minimisation activities will consist of a black box warning, Patient Information and Consent Agreement form, and physician education materials. The proposed risk minimisation plan aligns with that in Canada. The RMP evaluator has noted the post-market experience with MS-2 Step, its well-established safety profile, and existing safety frameworks in place. The RMP evaluator has also noted the importance of timely access of this medicine in terms of patient-safety and the need to remove requirements that hinder patient access to reproductive services. The sponsor is requested to keep educational materials in the AU-RMP as these will continue to be made available to prescribers and dispensers.

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1. OUTCOME OF THE EVALUATION

1.1. RECOMMENDATIONS TO THE SPONSOR

The updated AU-RMP (version 4.0, dated 17 February 2023, DLP 31 May 2022) and revised additional risk minimisation materials has been considered.

The recommendations made in the initial evaluation, along with consideration of the sponsor response, are located in Section 6.1.

There are 9 new recommendations after Succession 3 evaluation. Recommendation 19 and 20 are for the TGA delegate/clinical evaluator.

Recommendation 12. The sponsor has submitted the updated RMP version 4.0 (dated 17 February 2023). This RMP has the same version number with a different date from version 4.0 (dated 13 January 2023). To avoid confusion, for future submissions, the sponsor should update the version number and date for each revision.

Recommendation 13. The findings from the Canadian Phase IV study are applicable to Australia and should be included in the AU-RMP as an additional pharmacovigilance activity. The sponsor should include planned submission dates of study reports. When available a revised RMP which considers the completed study outcomes should be submitted to the TGA for review.

Recommendation 14. Further changes to Section V.3 Summary (table) of risk minimisation measures of the AU-RMP, are required:

- Identified risk 'Cardiac disorders' is missing and needs to be added
- Potential risks 'Incorrect determination of gestational age' and 'Potential for loss to follow-up' are missing and need to be added

Recommendation 15. Changes to Table 11 in Section V.1 of the AU-RMP are required:

- Remove 'physician education' as a routine risk minimisation measure as this is considered additional risk minimisation.
- Potential risks 'Potential for off-label use beyond the first trimester' and 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up' are missing and need to be added

Recommendation 16. The Educational program material has been removed from the AU-RMP with the proposed removal of mandatory training program and certification for prescribers. However, it is noted that the sponsor will continue to provide access to prescriber training to support the education of prescribers. Physician education and Patient Information and Consent Agreement form are listed as additional risk minimisation measures in the AU-RMP and these materials should be appended to the AU-RMP. Further, the sponsor should ensure prescribers (and dispensers) are made aware of the availability of MS-2 Step training materials and how to access these.

Recommendation 17. In Section 3.6 of the training manual provided in Succession 2, the sponsor should make the minor editorial change of “administration” to “administered

Recommendation 18. The advice on 24-hour phone service is also provided in the Consumer Medicine Information (CMI). The sponsor should submit the updated CMI to ensure consistent information in the RMP, Product Information (PI), and CMI.

Recommendation 19. This is a recommendation for the TGA delegate/clinical evaluator. The requirement for prescriber certification is included in the approved PI. The sponsor has advised that it will remove this requirement and submit the updated PI following the completion of round 1 evaluation. From the RMP perspective, assessing prescriber competencies is more related to clinical practice than to product risk management. Therefore, the removal of prescriber certification from the RMP is acceptable. It is recommended that the delegate/clinical evaluator considers the proposed PI change from the clinical perspective, and whether advisory committee advice is needed.

Recommendation 20. This is a recommendation for the TGA delegate/clinical evaluator. The provision of 24-hour phone service for patients is included in the approved PI. The sponsor has advised that it will remove this service and submit updated PI following the completion of round 1 evaluation. It is noted that the PI also advises that ‘patients must have the ability to access 24-hour emergency care’. This would ensure timely access to urgent medical attention and intervention. Therefore, the removal of 24-hour phone service is acceptable from the RMP perspective. It is recommended that the delegate/clinical evaluator considers the proposed PI change from the clinical perspective, in particular, whether and how much value the 24-hour phone service adds to patient safety outcomes.

1.2. WORDING FOR CONDITIONS OF REGISTRATION

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> *The MS-2 STEP Australian Risk Management Plan (AU-RMP) (version 4.0, dated 17 February 2023, data lock point 31 May 2022), included with submission PM-2022-05475-1-5, to be revised to the satisfaction of the TGA, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*

2. BACKGROUND

- On 1 December 2022, MS Health Pty Ltd submitted updated AU-RMP version 0.4 (dated 24 November 2022; DLP 31 May 2022) for MS-2 Step. The EU-RMP is not available. The sponsor provided revised Education Program material (included as Appendix 1) with this submission. A revised AU-RMP version 4.0 (dated 13 January 2023; DLP 31 May 2022) was provided with the sponsor's response to RMP evaluator's recommendations dated 13 January 2023. On 20 February 2023, the sponsor submitted further changes in AU-RMP version 4.0 (dated 17 February 2023; DLP 31 May 2022) which has been linked to the Category 1, Type J application (PM-2022-05475-1-5). The latest updated AU-RMP (third revision) is being considered as a Succession 3 evaluation as part of submission PM-2022-05475-1-5.
- MS-2 Step is approved for the medical termination of an intrauterine pregnancy, up to 63 days of gestation, in females of childbearing age.
- The most recently evaluated and approved AU-RMP was version 03 (dated 13 November 2014; DLP 28 April 2013) (R14/1181088).
- The reason for this updated RMP is changes to the summary of safety concerns (SoSC) and changes to the risk minimisation plan. The key changes proposed are as follows:
  - To remove the requirement for pharmacists to be registered to be able to dispense the product.
  - To remove the requirement for prescriber recertification.
  - To remove the requirement for prescribers to complete mandatory training and receive certification to be able to prescribe the product.
  - To remove the requirement for a Sponsor provided 24 hours aftercare service
- This RMP update is linked to the Category 1, Type J application (PM-2022-05475-1-5) that is currently under evaluation due to accompanying changes warranted to the Australian Product Information to support the changes to the risk minimisation plan.
- As the TGA has previously evaluated RMPs for this product, the focus of this review is on the differences between the AU-RMP versions and revisions to the additional risk minimisation materials.

3. CHANGES TO THE SUMMARY OF SAFETY CONCERNS AND PHARMACOVIGILANCE /RISK MINIMISATION ACTIVITIES

The changes to safety concerns and/or activities since the previous RMP evaluation of AU-RMP Version 03 (dated 13 November 2014; DLP 28 April 2013) are presented in the table below (~~Strikethrough~~ text indicates risks that have been removed and **bold** text indicates new/changed risks):

Summary of safety concerns		**Pharmacovigilance**		**Risk Minimisation**	
		Routine	Additional	Routine	Additional
Important identified risks	~~**Bleeding**~~	~~✓~~	~~–[1]~~	~~✓~~	~~✓2,3,4,5,6~~
	Infection, toxic shock syndrome	✓	–1	✓	✓2,3,~~4,5,6~~
	Method failure	✓	–1	✓	✓2,3,~~4,5,6~~
	~~Uterine contractions / cramping~~	~~✓~~	~~–[1]~~	~~✓~~	~~✓2,5,6~~
	~~Uterine infection (endometritis, pelvic inflammatory disease)~~	~~✓~~	~~–[1]~~	~~✓~~	~~✓2,5,6~~
	~~Nausea, vomiting~~	~~✓~~	~~–[1]~~	~~✓~~	~~✓2,5,6~~
	~~Diarrhoea~~	~~✓~~	~~–[1]~~	~~✓~~	~~✓3,5,6~~

	~~**Hypotension**~~	~~✓~~	~~–[1]~~	~~✓~~	~~✓3,5,6~~
	~~**Skin rashes, urticarial**~~	~~✓~~	~~–[1]~~	~~✓~~	~~✓3,5,6~~
	Cardiac disorders	✓	–[1]	✓	✓3,~~5~~,6
Important potential risks	Inadvertent pregnancy exposure and risk of incomplete abortion with severe bleeding	✓	–	✓	✓3,~~5~~,6
	Inadvertent pregnancy exposure (risk of malformations)	✓	–	✓	✓3,~~5~~,6
	Potential interaction with CYP3A4 inhibitors or inducers	✓	–	✓	✓6
	Potential interaction with products interacting with the glucocorticoid receptor	✓	–	✓	✓6
	~~Severe asthma uncontrolled by treatment~~ **Induced bronchial asthma**	✓	–	✓	✓6
	Effects in lactating women	✓	–	✓	✓6
	Effects in women with impaired liver function	✓	–	✓	✓6
	Effects in women with impaired renal function	✓	–	✓	✓6
	Effects in women with malnutrition	✓	–	✓	✓6
	Incorrect determination of gestational age	✓	–	✓	✓6
	Potential for missed ectopic pregnancy	✓	–	✓	✓3,~~5~~,6
	Potential for postnatal developmental delay	✓	–	✓	–
	Potential for off-label use beyond the first trimester	✓	–	✓	✓6
	Potential for loss to follow-up	✓	–	✓	–
	Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up	✓	–	✓	✓6
Missing information	Inherited porphyria	✓	–	–	–
	Theoretical interaction with NSAIDs	✓	–	–	–
	Potential interaction with products interacting with the progesterone receptor	✓	–	–	–
	Use in adolescents	✓	–	–	–
Pharmacological class effect	Risks related to the use of prostaglandin	✓	–	✓	✓3,~~5~~,6

[1] ~~Post-marketing surveillance study~~ (completed)
[2] Black box warning
[3] Patient Information and Consent Agreement form
[4] ~~Optional SMS follow-up text message~~
[5] ~~24-hour nurse after-care call service~~
[6] Physician education

A clean SOSC table is provided below:

Summary of safety concerns		**Pharmacovigilance**		**Risk Minimisation**	
		Routine	Additional	Routine	Additional
Important identified risks	Infection, toxic shock syndrome	✓	–	✓	✓1,2,3
	Method failure	✓	–	✓	✓1,2,3

	Cardiac disorders	✓	–	✓	✓[2,3]
Important potential risks	Inadvertent pregnancy exposure and risk of incomplete abortion with severe bleeding	✓	–	✓	✓[2,3]
	Inadvertent pregnancy exposure (risk of malformations)	✓	–	✓	✓[2,3]
	Potential interaction with CYP3A4 inhibitors or inducers	✓	–	✓	✓[3]
	Potential interaction with products interacting with the glucocorticoid receptor	✓	–	✓	✓[3]
	Induced bronchial asthma	✓	–	✓	✓[3]
	Effects in lactating women	✓	–	✓	✓[3]
	Effects in women with impaired liver function	✓	–	✓	✓[3]
	Effects in women with impaired renal function	✓	–	✓	✓[3]
	Effects in women with malnutrition	✓	–	✓	✓[3]
	Incorrect determination of gestational age	✓	–	✓	✓[3]
	Potential for missed ectopic pregnancy	✓	–	✓	✓[2,3]
	Potential for postnatal developmental delay	✓	–	✓	–
	Potential for off-label use beyond the first trimester	✓	–	✓	✓[3]
	Potential for loss to follow-up	✓	–	✓	–
	Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up	✓	–	✓	✓[3]
Missing information	Inherited porphyria	✓	–	–	–
	Theoretical interaction with NSAIDs	✓	–	–	–
	Potential interaction with products interacting with the progesterone receptor	✓	–	–	–
	Use in adolescents	✓	–	–	–
Pharmacological class effect	Risks related to the use of prostaglandin	✓	–	✓	✓[2,3]

[1] Black box warning
[2] Patient Information and Consent Agreement
[3] Physician education

The sponsor has submitted the updated RMP version 4.0 (dated 17 February 2023). This RMP has the same version number with a different date from version 4.0 (dated 13 January 2023). To avoid confusion, for future submissions, the sponsor should update the version number and date for each revision.

3.1. SUMMARY OF CHANGES TO THE SOSC

In the AU-RMP version 0.4 (dated 24 November 2022; DLP 31 May 2022) for MS-2 Step, the following new safety concerns have been added to the SoSC to align with the Canadian RMP (e004967 (0009-) - Attachment 1 - Canadian RMP) and the PI:

- important identified risk - cardiac disorders
- important potential risk - incorrect determination of gestational age

3.2. RMP EVALUATOR COMMENTS/ RECOMMENDATIONS ON THE SOSC

The Canadian RMP (dated 27 August 2020) was used as the reference RMP in the sponsor's Periodic Benefit-Risk Evaluation Report (PBRER) for mifepristone and misoprostol combipack presentations, covering 01 June 2021 to 31 May 2022 (D22-6031778). The SoSC in the current Canadian RMP:

Identified risk:	Method failure Infection Toxic shock syndrome Cardiac disorders
Potential risk:	Inadvertent risk of pregnancy Induced bronchial asthma Incorrect determination of gestational age Complication arising from the use in undiagnosed ectopic pregnancy
Missing information:	Pregnant and lactating subjects Paediatric patients Geriatric patients Patients with Renal, Hepatic or Cardiac Impairment Off Label use

There are significant differences between the Canadian and Australian RMP.

In the AU-RMP version 0.4 (dated 24 November 2022; DLP 31 May 2022) for MS-2 Step, the below differences with the Canadian RMP (dated 27 August 2020) remain:

- Potential risks: induced bronchial asthma (in contrast with severe asthma uncontrolled by treatment), complication arising from the use in undiagnosed ectopic pregnancy.
- Missing information: patients with renal, hepatic or cardiac impairment.

Potential risk of 'complication arising from the use in undiagnosed ectopic pregnancy' is considered to be captured by 'Potential for missed ectopic pregnancy' included in the AU-RMP. This is satisfactory.

Missing information of 'patients with renal, hepatic or cardiac impairment' is in part captured by potential risks 'Effects in women with impaired liver function' and 'Effects in women with impaired renal function'. Given the classification of cardiac disorders as an important identified risk, and associated warnings in the PI to use with caution in women with risk factors for cardiovascular disease or established cardiovascular disease, this is satisfactory.

Use in pregnant subjects is not listed in the AU-RMP as missing information. This is satisfactory.

The sponsor should be asked to provide reasons on the difference in potential risk of 'induced bronchial asthma' vs 'severe asthma uncontrolled by treatment'.

The sponsor should also be reminded to routinely review the safety concerns in the AU-RMP to ensure it reflects up-to-date safety information. Taking into account the product's reasonable marketing experience (as single ingredient and as combination pack), as well as the fact no additional pharmacovigilance activity is planned to further characterise the risks, the sponsor should evaluate whether any safety concerns can be removed. Further, in the absence of an EU-

RMP, any changes to international RMPs should be assessed to determine whether similar updates are warranted in Australia.

The sponsor is requested to provide a description of the process for maintenance of the AU-RMP (e.g. standard operating procedure document).

3.3. Summary of key changes to Safety Specification - Succession 2 & 3

Changes from AU RMP version 03 to version 4.0	RMP evaluator comment
Removed the following important identified risks: • Bleeding • Contractions / cramping • Uterine infection • Nausea and vomiting • Diarrhoea • Hypotension • Skin rashes / urticaria	This aligns with the Canadian RMP.
Important potential risk "Severe asthma uncontrolled by treatment" changed to "Induced bronchial asthma"	This aligns with the Canadian RMP.

There were no further changes to the safety specification between AU-RMP version 4.0 (dated 13 January 2023; DLP 31 May 2022) and AU-RMP version 4.0 (dated 17 February 2023; DLP 31 May 2022).

The sponsor has noted that AU-RMP also has further potential risks that are not included in the Canadian RMP, or risks that are presented slightly differently.

3.4. RMP Evaluator comments/ recommendations on the SoSC – Succession 2 & 3

The summary of safety concerns is considered acceptable from an RMP perspective.

It is acknowledged that the sponsor has committed to ensuring that any future changes that are made to Canadian RMP will be assessed to determine whether the same updates are also warranted in Australia.

4. PHARMACOVIGILANCE PLAN

4.1. Summary of changes to the pharmacovigilance plan

The post marketing surveillance study of use of mifepristone/mifepristol for early medical abortion within MSIA clinics is now completed. Section III.2 and Section SIII has been updated to capture this.

4.2. RMP Evaluator comments/ recommendations on pharmacovigilance plan

Information regarding the study should be removed from the pharmacovigilance plan in the RMP since final study report/results have been submitted to the TGA for assessment. The study should also be deleted as an additional pharmacovigilance activity in Section V.3 in AU-RMP.

4.3. SUMMARY OF CHANGES TO THE PHARMACOVIGILANCE PLAN – SUCCESSION 2 & 3

The completed study has been removed from the pharmacovigilance plan in the updated AU RMP, as requested.

There were no changes to pharmacovigilance plan submitted in Succession 3.

4.4. RMP EVALUATOR COMMENTS/ RECOMMENDATIONS ON PHARMACOVIGILANCE PLAN – SUCCESSION 2 & 3

There are no additional pharmacovigilance activities in the AU RMP. It is noted that the Canadian RMP includes a planned Canadian-specific post-market study:

Safety Concern	Additional activity	Proposed actions/ outcomes	Planned submission date
		Planned studies	
Method failure, Infection, toxic shock syndrome, cardiac disorders, Inadvertent risk of pregnancy, induced bronchial asthma, incorrect determination of gestational age, Potential for missed ectopic pregnancy	**Canadian Phase IV study**	**A Phase IV Multi-Centre Prospective Study on the Safety of Combination Mifepristone/Misoprostol for Medical Abortion Under 63 Days Gestation Among Canadian Women** **Primary objective: To determine rate of surgical aspiration, for any reason, within 21 days following medical abortion with combination mifepristone/misoprostol**	**TBD**

The findings from the above study are applicable to Australia and should be included in the AU-RMP. The sponsor should include planned submission dates of study reports.

When available a revised RMP which considers the completed study outcomes should be submitted to the TGA for review.

5. RISK MINIMISATION PLAN

5.1. SUMMARY OF CHANGES TO THE RISK MINIMISATION PLAN

The sponsor proposes to remove from the risk minimisation plan:

- the requirement for pharmacist registration to dispense the product
- the requirement for re-certification training for prescribers.

5.2. RMP EVALUATOR COMMENTS/ RECOMMENDATIONS ON THE RISK MINIMISATION PLAN

Detailed evidence/justification to support these proposals have not been provided. The sponsor should provide discussion on:

- additional risk minimisation activities in other countries where MS-2 Step is available compared to Australia
- any safety concerns on the removal of pharmacist registration and prescriber re-certification
- number/percentage of pharmacies registered to dispense MS-2 Step in Australia
- any reports on evaluation of effectiveness of additional risk minimisation activities

Given the reasonable worldwide marketing experience with mifepristone and mifepristol (IBD 28 June 1984 for misoprostol, 29 December 2010 for mifepristone, and MS-2 Step first registered in Australia 04 June 2014), the safety profile is considered well established. Clinical practice and understanding, along with the other additional risk minimisation activities in place, are likely adequate to manage the risks. It is acknowledged that the timeliness of access is essential and corresponds to effectiveness of the product. Final decision on the proposed changes to the risk minimisation plan will be made after review of the sponsor's response.

The sponsor has proposed that 'once registered and certified no re-registration or re-certification is required' for prescribers. It is assumed that this re-certification refers to the periodic renewal of the certificate for the purpose of knowledge maintenance. The sponsor should provide clarification in the RMP on whether and how it plans to inform prescribers of the updated safety information when new evidence becomes available.

The sponsor has stated under 'Restricted Access to MS-2-Step' that the program is to ensure that 'distribution of MS-2-Step is controlled and monitored. With the proposed removal of pharmacist registration, the sponsor should clarify how this is achieved. The sponsor should note, according to the EMA GVP Module XVI, controlled distribution and controlled access programs are different measures that serve different purposes[1].

Further, the sponsor should amend Section V.3 Summary (table) of risk minimisation measures as follows:

- Completed post-marketing surveillance study is still listed as an additional pharmacovigilance activity – this should be removed from the table
- 'Special attention in PSURs' was listed as an additional pharmacovigilance activity – this is considered part of routine pharmacovigilance.
- 'Physician education' is not described as an additional risk minimisation activity for potential risks: Potential interaction with CYP3A4 inhibitors or inducers, Potential interaction with products interacting with the glucocorticoid receptor, Severe asthma

[1]EMA Guideline on good pharmacovigilance practices Module XVI, dated 28 March 2017, EMA/204715/2012 Rev 2, https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-xvi-risk-minimisation-measures-selection-tools_en-3.pdf

uncontrolled by treatment, Incorrect determination of gestational age – this should be revised accordingly

- 'Potential for loss to follow up' is not included – this should be added for completeness

5.3. Summary of changes to the risk minimisation plan – Succession 2 & 3

The sponsor has submitted additional changes to the risk minimisation plan in AU-RMP version 4.0 (dated 17 February 2023; DLP 31 May 2022). In summary, the following changes to the risk minimisation plan are proposed (new in **bold**):

- To remove the requirement for pharmacists to be registered to be able to dispense the product.
- To remove the requirement for prescriber recertification.
- **To remove the requirement for prescribers to complete mandatory training and receive certification to be able to prescribe the product.**
- **To remove the requirement for a Sponsor provided 24 hours aftercare service**

As the requirement for prescriber certification and 24-hour phone service are included in the PI, the sponsor has advised that it will remove these and submit the updated PI following the completion of round 1 evaluation[2].

The sponsor states that this would align the MS-2 Step RMP with the expectations of RMPs of the majority of medicines registered with the TGA, and with expectations around prescriber competency for a medicine that has been in-market for many years with hundreds of thousands Australian women having been prescribed MS-2 Step since it was first registered over 8 years ago.

The information in the AU-RMP regarding restricted distribution has been deleted with the proposed removal of mandatory training program and certification for prescribers.

5.4. RMP Evaluator comments/ recommendations on the risk minimisation plan – Succession 2 & 3

The Sponsor has amended Section V.3 Summary of risk minimisation measures (table) in accordance with the above requested changes. However, further changes are required:

- Identified risk 'Cardiac disorders' is missing and needs to be added
- Potential risks 'Incorrect determination of gestational age' and 'Potential for loss to follow-up' are missing and need to be added

Additionally, the sponsor should make the below changes to Table 11 in Section V.1:

- Remove 'physician education' as a routine risk minimisation measure as this is considered additional risk minimisation
- Potential risks 'Potential for off-label use beyond the first trimester' and 'Potential safety risks in vulnerable groups including women in regional and remote areas of

[2] e004967 (0009-) - Cover Letter - 2023-02 Cat 1, Type J, RMP

Australia, who may be particularly at risk of being lost to follow-up' are missing and need to be added

Misoprostol was first approved in Australia on 7 July 1993, mifepristone on 29 August 2012 and MS-2 Step was registered on 4 June 2014. Given the post-market experience with MS-2 Step in Australia and worldwide, the product's safety profile is well-established. Safety concerns in the SOSC have been removed with this AU-RMP update, which still includes additional potential risks to the Canadian RMP.

Furthermore, it is reasonable to expect that prescribers and dispensers have a level of clinical knowledge of MS-2 Step, or be able to refer to resources available (e.g. the PI) to ensure safe and effective use as like any other medicine. The sponsor will also continue to make the MS-2 Step training materials available to both prescribers and dispensers so that skill levels can be maintained. The patient information and consent form should continue to be implemented.

The sponsor has informed that based on the latest available data in 2020, less than 20% of pharmacists are registered in Australia to dispense MS-2 Step (see Section 6.1, Recommendation 6). As indicated, this presents a patient-safety risk of delayed access to medication, particularly in regional and rural areas as well as for patients whose gestation is approaching the upper limit of MS-2 Step's registered indication.

It is noted that in Australia, there is a government funded service available - healthdirect hotline – which provides 24-hour/7-day health advice from a registered nurse. Moreover, distribution of MS-2 Step will be tracked via general pathways of PBS Authority prescription and PBS dispensing and safety concerns will continue to be monitored by the sponsor under routine pharmacovigilance and reported as necessary as specified in Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements. The sponsor may also be requested to provide a PSUR to the TGA at any time.

The sponsor has pointed out that internationally, in Canada, since 2017 registration of health professionals with Celopharma is no longer required in order to prescribe or dispense Mifeqymiso[3]. The sponsor states no adverse safety signals or additional risk minimisation activities identified in Canada with this change to a broader access regimen. It was noted in the Canadian Monograph for Mifeqymiso[4], it is stated that "*Mifegymiso should be prescribed by health professionals with adequate knowledge of medical abortion and/**or** who have completed a Mifegymiso education program*".

The RMP evaluator has noted the need to remove requirements that hinder patient access to reproductive services. The evaluator has also noted different risk mitigation strategies employed by different comparable overseas regulators.

The US FDA has reviewed and finalised the Risk Evaluation and Mitigation Strategies (REMS) for mifepristone on 3 January 2023. The REMS lists 'requiring healthcare providers who

[3] MIFEGYMISO (mifepristone and misoprostol tablets) - Updates to Product Monograph and Risk Management Plan, accessed 23 February 2023, MIFEGYMISO (mifepristone and misoprostol tablets) - Updates to Product Monograph and Risk Management Plan - Canada.ca

[4] MIFEGYMISO (mifepristone and misoprostol tablets) Canadian Product Monograph, accessed 23 February 2023, 00050659.PDF (hres.ca)

prescribe mifepristone to be certified in the Mifepristone REMS Program' as a goal of the REMS[5].

The RMP evaluator has noted that the advice on 24-hour phone service is also provided in the Australian Consumer Medicine Information (CMI). The sponsor should submit the updated CMI to ensure consistent information in the RMP, PI, and CMI.

The requirement for prescriber certification is included in the Australian Product Information (PI). The sponsor has advised that it will remove this requirement and submit the updated PI following the completion of round 1 evaluation. From the RMP perspective, assessing prescriber competencies is more related to clinical practice than to product risk management. Therefore, the removal of prescriber certification from the RMP is acceptable. It is recommended that the delegate/clinical evaluator considers the proposed PI change from the clinical perspective, and whether advisory committee advice is needed.

The provision of 24-hour phone service for patients is included in the PI. The sponsor has advised that it will remove this service and submit updated PI following the completion of round 1 evaluation. It is noted that the PI also advises that 'patients must have the ability to access 24-hour emergency care'. This would ensure timely access to urgent medical attention and intervention. Therefore, the removal of 24-hour phone service is acceptable from the RMP perspective. It is recommended that the delegate/clinical evaluator considers the proposed PI change from the clinical perspective, in particular, whether and how much value the 24-hour phone service adds to patient safety outcomes.

5.5. RMP EVALUATOR COMMENTS/ RECOMMENDATIONS OF ADDITIONAL RISK MINIMISATION ACTIVITIES

Additional risk minimisation activities consist of a black box warning, Patient Information and Consent Agreement, and physician education.

This is considered sufficient based on the above discussion.

5.6. PRODUCT LABELLING

5.6.1. Product Information

The sponsor should confirm whether the new data from the completed post-market surveillance study study added to Section SIII (Clinical trial exposure) of the AU-RMP version 0.4 (and Section 3.6 of Annex 1.1) will be added to the Australian PI:

> *In an observational cohort study of 15 008 women attending one of 16 Marie Stopes International clinics in Australia for MTOP (gestational age ≤ 63 days) between 1 March 2013 and 30 September 2015, patients were **administered** 200 mg mifepristone orally in-clinic, followed 24- 48 hours later by 800 micrograms of misoprostol buccally, self-administered at home. Method success was defined as complete abortion not requiring surgical intervention. Follow up information was available for 13,078 (87.2%) of the total cohort. Medical abortion was successful in 95.16% (12,445/13,078) of women with follow-up. Higher patient and gestational ages were associated (P < 0.001) with a slight increase in method failure. There were 674 serious adverse events (5.15%), mainly due to method failure. Infection (15; 0.11%)*

[5] US FDA approved REMS for mifepristone, accessed on 24 February 2023, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390

and haemorrhage (17; 0.13%) were rare. One death was recorded (<0.01%); however, an association between EMA and cause of death, necrotising pneumonia, was not established.

Moreover, the sponsor should make a minor editorial change (in ***bold***).

Succession 2 update

The sponsor has confirmed in their response that the Australian PI will be updated with the completed post-market surveillance study data as part of the next submitted Category 1, Type J application (see Section 6.1, Recommendation 4).

5.6.2. Consumer Medicine Information

The sponsor should ensure any PI updates are captured in the CMI where applicable.

5.7. Additional Risk Minimisation Materials

The sponsor submitted revised Educational Program material (with tracked changes) with the AU-RMP update submission (as Annex 1; D22-6187939). There were mostly editorial changes to reflect current approved indication and current practices, as well as inclusion of current post marketing data. Of note, the refresher materials have been removed from the package.

In the training manual (Annex 1.1), the sponsor included interim information regarding a pending TGA application to remove PI precautions regarding rhesus alloimmunisation to align with current Australian and International guidelines. It was recommended that the sponsor only incorporate advice that has been approved.

Succession 2&3 update

At Succession 2, the sponsor had submitted an updated training manual with the requested changes with their response.

At Succession 3, the Educational program material has been removed from the AU-RMP with the proposed removal of mandatory training program and certification for prescribers. However, it is noted that the sponsor will continue to provide access to prescriber training to support the education of prescribers. Physician education and Patient Information and Consent Agreement are listed as additional risk minimisation measures in the AU-RMP and these materials should be appended to the AU-RMP. Further, the sponsor should ensure prescribers (and dispensers) are made aware of the availability of MS-2 Step training materials and how to access these.

The sponsor should make the minor editorial change to Section 3.6 of the training manual to amend “administration” to “administered” (see Section 5.5.1).

6. EVALUATION OF SPONSOR RESPONSE

6.1. Reconciliation of recommendations sent 13 December 2022

The sponsor’s response, dated 13 January 2023, can be found on

TRIM D23-5035315

Docubridge e004967 (0008-) - Response - 2023-01 Response to RFI

The sponsor has provided and updated AU-RMP version 4.0 (dated 13 January 2023, DLP 31 May 2022) with their response.

Recommendation 1: The sponsor is requested to provide reasons on the difference in potential risk of 'induced bronchial asthma' vs 'severe asthma uncontrolled by treatment'.
Sponsor's response: The Sponsor proposes to update the potential risk of 'severe asthma uncontrolled by treatment' to 'induced bronchial asthma'. As currently detailed in the AU-RMP, bronchospasm may occur with some prostaglandins and prostaglandin analogues. The possibility should be borne in mind in patients with a history of asthma. *The potential risk 'induced bronchial asthma' is currently included in the Canadian RMP and is targeted for review and safety surveillance as part of the annual PBRER (reports of induced bronchial asthma are identified using a prespecified list of preferred terms in MedDRA version 16.0).* *A copy of the proposed updated AU-RMP has been provided in Module 1.8.*
RMP evaluator comment: The important potential risk of 'severe asthma uncontrolled by treatment' has been replaced with 'induced bronchial asthma' in line with Canadian RMP in the updated AU-RMP. This is acceptable.

Recommendation 2: The sponsor is requested to provide a description of the process for maintenance of the AU-RMP (e.g. standard operating procedure document). In accordance with the guidance on *Risk management plans for medicines and biologicals* throughout the lifecycle of the product, RMPs must be maintained to incorporate new safety information. Any significant updates are required to be submitted to the TGA for evaluation within a timely manner. In accordance with the *Pharmacovigilance Guidelines*, sponsors should have processes in place (with well-defined responsibilities, requirements and timelines) to ensure they comply with their post-approval commitments. Further, the sponsor is reminded to routinely review the safety concerns in the AU-RMP to ensure it reflects up-to-date safety information. Taking into account the product's reasonable marketing experience (as single ingredient and as combination pack), as well as the fact no additional pharmacovigilance activity is planned to further characterise the risks, the sponsor should evaluate whether any safety concerns can be removed. Further, in the absence of an EU-RMP, any changes to international RMPs should be assessed to determine whether similar updates are warranted in Australia.
Sponsor's response: The maintenance of the AU-RMP is managed via agreements in place with their supplier (Linepharma International Limited). Specifically, the Safety Data Exchange Agreement (SDEA) held between MS Health Pty Ltd and Linepharma International Limited (supplier)includes the responsibilities relating to the AU-RMP. The SDEA specifies that the supplier coordinates an update to the RMP if a significant safety signal is detected, including immediate notification to MS Health of any significant safety issues. Following the receipt of a notification of a significant safety issue from the supplier, MS Health is then responsible for preparation and maintenance of the AU-RMP including any required submission to TGA (according to TGA guidelines including any specified timelines). MS Health is also responsible for implementation of any applicable risk minimisation measures. *Additionally,* s47 [redacted] *(the service provider) have a standard operating procedure in place for the management of safety information. This dictates that the updated AU RMP be submitted to the TGA in accordance with the TGA RMP guidelines.* *Further to the above, the Sponsor has reviewed the safety concerns listed within the AU-RMP and proposes to remove those that have a low risk in regard to the seriousness of the safety concern, a low risk to the individual patient and have minimal impact on public health. The following identified risks have therefore been removed as part of this response:* • *Bleeding* • *Contractions / cramping* • *Uterine infection* • *Nausea and vomiting* • *Diarrhoea* • *Hypotension* • *Skin rashes / urticaria* *A clean and annotated copy of the proposed AU-RMP has been provided in Module 1.8.* *In the absence of the EU-RMP, the Sponsor confirms that the safety concerns that are listed within the AU-RMP and the changes proposed above, align with those detailed in the Canadian RMP (although it is noted that the AU RMP still includes additional potential risks over and above those that are included in the Canadian RMP, or presents these slightly differently). A copy of the Canadian RMP has been provided as Attachment 1 to this response. An assurance is provided that any future changes that are made to Canadian RMP with be assessed to determine whether the same updates are also warranted in Australia (as per the processes defined above).*
RMP evaluator comment: The sponsor's commitment to assess future changes made to the Canadian RMP to determine whether similar updates are warranted in Australia is acknowledged. The sponsor's proposal to remove the above important identified risks is consistent with the Canadian RMP and is acceptable.

Recommendation 3: The sponsor should remove information regarding the completed post-market surveillance study from the pharmacovigilance plan in the RMP as final study report/results have been submitted to the TGA for assessment. The study should also be deleted as an additional pharmacovigilance activity in Section V.3 in AU-RMP.
Sponsor's response: The sponsor has removed the information regarding the completed post-market surveillance study from the pharmacovigilance plan in the RMP. The study has also been deleted as an additional pharmacovigilance activity in Sections III.2 and V.3 of the RMP.
RMP evaluator comment: The AU RMP has been updated as requested.
Recommendation 4: The sponsor should confirm whether the data from the completed post-market surveillance study added to Section SIII (Clinical trial exposure) of the AU-RMP version 0.4 (and Section 3.6 of Annex 1.1) will be added to the Australian PI.
Sponsor's response: The sponsor confirms that they propose to update the Australian PI with the completed postmarket surveillance study data as part of the next submitted Category 1, Type J application
RMP evaluator comment: Noted. This is acceptable.
Recommendation 5: The sponsor should make the following minor editorial change (in **bold**): *In an observational cohort study of 15 008 women attending one of 16 Marie Stopes International clinics in Australia for MTOP (gestational age ≤ 63 days) between 1 March 2013 and 30 September 2015, patients were **administered** 200 mg mifepristone orally in-clinic, followed 24- 48 hours later by 800 micrograms of misoprostol buccally, self-administered at home. Method success was defined as complete abortion not requiring surgical intervention. Follow up information was available for 13,078 (87.2%) of the total cohort. Medical abortion was successful in 95.16% (12,445/13,078) of women with follow-up. Higher patient and gestational ages were associated (P < 0.001) with a slight increase in method failure. There were 674 serious adverse events (5.15%), mainly due to method failure. Infection (15; 0.11%) and haemorrhage (17; 0.13%) were rare. One death was recorded (<0.01%); however, an association between EMA and cause of death, necrotising pneumonia, was not established.*
Sponsor's response: The sponsor has updated the RMP in accordance with the requested minor editorial amendment. A copy of the updated RMP has been provided in Module 1.8.
RMP evaluator comment: The AU RMP has been updated as requested.

Recommendation 6: To support the proposals to remove requirements for prescriber recertification training and pharmacist registration, the sponsor should provide justification/discussion on:

- additional risk minimisation activities in other countries where MS-2 Step is available compared to Australia
- any safety concerns on the removal of pharmacist registration and prescriber re-certification
- number/percentage of pharmacies registered to dispense MS-2 Step in Australia
- any reports on evaluation of effectiveness of additional risk minimisation activities

Sponsor's response: As of December 2022, there are 5,472 pharmacists registered to provide MS-2 Step® to Australian patients. The most recent Dept of Health data (Allied Health factsheets) reports a total of 32,904 pharmacists registered in Australia in 2020 (more recent data not available); indicating only ~17% of pharmacists are currently registered to dispense MS-2 Step to patients.
The challenge of having less than 20% of pharmacists registered to dispense MS-2 Step presents a risk from a patient-safety perspective of delayed access to medication. This is especially so for patients in either regional and remote settings where there may not be an easily accessible registered pharmacist; as well as for patients whose gestation is approaching the upper limit of MS-2 Step's registered indication and for whom timely access to MToP is even more critical. MS Health will continue to make the MS-2 Step training materials available to both prescribers and dispensers so that skill levels can be maintained, but removal of these specific requirements (prescriber recertification, dispenser registration) is expected to improve the ability of patients to receive timely access to their medication.
MS Health notes that within the Canadian setting, since 2017 patients seeking a medical termination of pregnancy are dispensed an identically configured Mifepristone + Misoprostol composite pack by pharmacists who are not required to register prior to dispensing; or physicians who need to recertify. There have been no adverse safety signals or additional risk minimisation activities identified in Canada with this change to a broader access regimen.

RMP evaluator comment: Noted. Considering the proposed removal of mandatory training program and certification of prescribers and dispensers, the sponsor should ensure prescribers and dispensers are aware of the availability of MS-2 Step training materials and how to access these.

Recommendation 7: The sponsor has proposed that 'once registered and certified no re-registration or recertification is required' for prescribers. It is assumed that this re-certification refers to the periodic renewal of the certificate for the purpose of knowledge maintenance. The sponsor should provide clarification in the AU-RMP on whether and how it plans to inform prescribers of the updated safety information when new evidence becomes available.

Sponsor's response: The Sponsor confirms that re-certification refers to the periodic renewal of the certificate for the purpose of knowledge maintenance.
The MS-2 Step composite pack product has been available in Australia for over 8 years (registered 4/6/2014, marketed 1/2/2015). The pack components (Mifepristone + Misoprostol) have been registered for the Medical Termination of Pregnancy in Australia (and globally) prior to this. The product's characteristics, safety and AE profile are relatively well understood. There is no proposed change in the patient population as part of this application and as such, it is unlikely that a significant change to the product's existing safety profile is going to be encountered.
It is noted that prescribing Medical Practitioner's must remain up-to-date on changes to the safety profile for any product that they prescribe. This information is communicated to prescribers via PI updates and notices on the TGA website (as appropriate). In the event of a significant change to the product safety profile and a need to rapidly disseminate information to prescribers, MS Health would utilise the channels mentioned above and also utilise the MS-2 Step prescriber database (which is being proposed to remain in place). MS Health proposes to continue to utilise the standard channels used for other registered medicines when providing updated information to prescribers.

RMP evaluator comment: The sponsor's response is acceptable.

Recommendation 8: The sponsor has stated under 'Restricted Access to MS-2-Step' that the program is to ensure that "distribution of MS-2-Step is controlled and monitored". With the proposed removal of pharmacist registration, the sponsor should clarify how this is achieved. The sponsor should note, according to the EMA GVP Module XVI, controlled distribution and controlled access programs are different measures that serve different purposes.

Sponsor's response: The European Medicines Agency (EMA) guidance; Guideline on good pharmacovigilance practices (GVP), Module XVI, Section XVI.B.2.2 states the following:

"Since a controlled access programme has large implications for all stakeholders, the use of such a programme should be limited and should be guided by a clear therapeutic need for the product based on its demonstrated benefit"

The sponsor's proposed RMP amendments i.e. removing the need for prescriber recertification and removing the need for dispenser registration, is endeavouring to minimise impacts on patients who may otherwise struggle to access their medication in a timely manner. MS Health proposes to continue providing prescriber education and maintain the database of certified prescribers to act as a control on any potential product misuse or abuse.

In addition to this, MS Health highlights the fact that it is the responsibility of the prescriber to ensure that they are compliant with relevant requirements to provide any therapeutic product e.g. they have completed any relevant training and have the required knowledge to prescribe the therapeutic product in question. With respect to the MS-2 Step product, an additional extra level of control is provided during the PBS-script approval process. The majority of MS-2 Step scripts are PBS-scripts; the approval process requires the prescriber to affirm that they are certified to prescribe.

NB: this need to affirm certification exists regardless of whether the product is designated Authority Required or Streamlined Authority.

Given the above, it is unlikely for additional restricted access controls to be required and MS Health highlights the fact that the impetus for removing the requirement for dispenser registration is to improve patient access. Especially those patients located in rural and/or remote settings; and those later in their gestation and for who the timely access to medication is critical (and can be more challenging).

Within this context, the term "Restricted Access to MS-2 Step" (compared to the EMA GVP Module XVI definition, as provided below for ease of reference) may be inappropriate and appears to be a carryover from the preceding RMP document. The sponsor proposes amending this to "Restricted Distribution of MS-2 Step" as the product will continue to be distributed through controlled pharmaceutical supply chains; thus minimising the potential for product misuse or abuse.

EMA GVP Definitions

XVI.B.2.3.1. Controlled distribution system A controlled distribution system refers to the set of measures implemented to ensure that the stages of the distribution chain of a medicinal product are tracked up to the prescription and/or pharmacy dispensing the product. Orders and shipments of product from a single or multiple identified distribution points facilitate traceability of the product. For instance, this sort of measures could be considered for those products controlled in each country under the respective national legislations to prevent misuse and abuse of medicines.

XVI.B.2.2. Controlled access programme A controlled access programme consists of interventions seeking to control access to a medicinal product beyond the level of control ensured by routine risk minimisation measures, i.e. the legal status. Since a controlled access programme has large implications for all stakeholders, the use of such a programme should be limited and should be guided by a clear therapeutic need for the product based on its demonstrated benefit (e.g. it treats a serious disease without alternative therapies; it treats patients who have failed on existing therapies), the nature of the associated risk (e.g. risk is lifethreatening), and the likelihood that this risk can be managed by such a programme. Therefore, controlled access should only be considered as a tool for minimising an important risk with significant public health or individual patient impact for a product with clearly demonstrated benefits but which would not otherwise be available without a programme where patient access is contingent on fulfilling one or more requirements prior to a product being prescribed or dispensed in order to assure its safe use.

Examples of requirements that need to be fulfilled before the product is prescribed and/or dispensed and/or used in a controlled access programme are listed below (they may be included individually or in combination): • specific testing and/or examination of the patient to ensure compliance with strictly defined clinical criteria; • prescriber, dispenser and/or patient documenting their receipt and understanding of information on the serious risk of the product; • explicit procedures for systematic patient follow-up through enrolment in a specific data collection system e.g. patient registry; • medicines made available for dispensing only by pharmacies that are registered and approved to dispense the product. On occasions, a requirement to test or to monitor a patient in a specific way can also be used as a controlled access tool. For example,

monitoring of the patient's health status, laboratory values or other characteristic prior to and/or during treatment, e.g. electrocardiogram, liver function tests, regular blood tests, pregnancy tests (which can be part of a pregnancy prevention programme). Measures should be put in place to ensure that monitoring takes place according to the SmPC where this is critical to risk-benefit balance of the product.

RMP evaluator comment: The section regarding restricted distribution has been removed with the proposed removal of mandatory training program and certification for prescribers.

Recommendation 9: The sponsor should amend Section V.3 Summary (table) of risk minimisation measures as follows:

- Completed post-marketing surveillance study is still listed as an additional pharmacovigilance activity – this should be removed from the table
- 'Special attention in PSURs' was listed as an additional pharmacovigilance activity – this is considered part of routine pharmacovigilance.
- 'Physician education' is not described as an additional risk minimisation activity for potential risks: Potential interaction with CYP3A4 inhibitors or inducers, Potential interaction with products interacting with the glucocorticoid receptor, Severe asthma uncontrolled by treatment, Incorrect determination of gestational age – this should be revised accordingly
- 'Potential for loss to follow up' is not included – this should be added for completeness

Sponsor's response: The Sponsor has amended Section V.3 Summary (table) of risk minimisation measures in accordance with the above requested changes and in other sections as applicable. A copy of the update AU RMP has been provided in Module 1.8.

RMP evaluator comment: Further changes to the table in Section V.3 are required:

- **Identified risk 'Cardiac disorders' is missing and needs to be added**
- **Potential risks 'Incorrect determination of gestational age' and 'Potential for loss to follow-up' are missing and need to be added**

Additionally, the sponsor should make the below changes to Table 11 in Section V.1:

- **Remove 'physician education' as a routine risk minimisation measure.**
- **Potential risks 'Potential for off-label use beyond the first trimester' and 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up' are missing and need to be added**

Recommendation 10: In the revised training manual (Annex 1.1), the sponsor has included interim information regarding a pending TGA application to remove PI precautions regarding rhesus alloimmunisation to align with current Australian and International guidelines. The sponsor should note, the content of additional risk minimisation materials, including training manual should always align with the approved PI and CMI. Updates to training materials should occur concurrently with, or following TGA approved PI changes.

Sponsor's response: The reference to the TGA application to remove PI precautions regarding rhesus alloimmunisation has been removed from the training manual Annex 1.1. An updated training manual (Annex 1.1) has been provided in Module 1.8.

RMP evaluator comment: Reference to interim information regarding the pending TGA application (PM-2022-03010-1-5) has been removed from the training manual as requested.

Recommendation 11: The most recently evaluated AU-RMP was version 03 (dated 13 November 2014; DLP 28 April 2013). MS Health Pty Ltd has submitted updated AU-RMP version 0.4 (dated 24 November 2022; DLP 31 May 2022) for MS-2 Step, noting that the EU-RMP is not available. Chronologically, going from Version 03 to 0.4 is confusing. The sponsor should consider amending the proposed version number.
Sponsor's response: The applicant inadvertently included 0.4 as the next sequential version. To avoid any further confusion (and subsequent errors), the version number has been updated to 4.0.
RMP evaluator comment: Noted. The sponsor has submitted an updated AU-RMP version number 4.0.

APPENDIX 1 – LIST OF ACRONYMS

AE	Adverse Event
ACM	Advisory Committee on Medicines
AU-RMP	Australian Risk Management Plan
CMI	Consumer Medicine Information
DLP	Data Lock Point
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
MHRA	Medicines & Healthcare Products Regulatory Agency
PI	Product Information
PMAB	Prescription Medicines Authorisation Branch
RMP	Risk Management Plan
TGA	Therapeutic Goods Administration

Australian Government
Department of Health
Therapeutic Goods Administration

Risk Management Plan Evaluation Report

Mifepristone/ Misoprostol (MS-2-Step)

Submission No: PM-2022-05475-1-5

Sponsor: MS Health Pty Ltd

Updated RMP received: 01 December 2022

Sponsor's Response received: 13 January 2023

Succession 3 Report (round 1 for PM-2022-05475-1-5): 27 February 2023

Round 2 Report: 20 April 2023

TGA Health Safety Regulation

RISK MANAGEMENT PLAN EVALUATION REPORT

Submission type: PI update (corresponding to RMP updates)

Sponsor: MS Health Pty Ltd
Generic name: **Mifepristone/ Misoprostol**
Trade name: **MS-2-STEP**

Submission No; eSubmission ID: PM-2022-05475-1-5; e004967
RMP file No: 2013/020378
TRIM reference: D22-6199891

AU-RMP: *(EU-RMP not available)*
Initial - Version 0.4; dated 24 November 2022; DLP 31 May 2022
e004967 (0006-) - Risk management plan - Clean
D22-6187939

Succession 2 - AU-RMP version 4.0 (dated 13 January 2023, DLP 31 May 2022)
D23-5035315

Succession 3/Round 1 - AU-RMP version 4.0 (dated 17 February 2023, DLP 31 May 2022)
D23-5140670

Round 2 – AU-RMP version 4.1 (dated 5 April 2023, DLP 31 May 2022)

Last evaluated AU-RMP: Version 03; dated 13 November 2014; DLP 28 April 2013
R14/1181088

Date finalised: 20 April 2023 [Round 2]

Reason(s) for update:
New safety concern added
Removed safety concern
Pharmacovigilance milestone met
Ceased risk minimisation activity
Other:

SUMMARY

- On 1 December 2022, MS Health Pty Ltd submitted updated AU-RMP version 0.4 (dated 24 November 2022; DLP 31 May 2022) for MS-2 Step. The EU-RMP is not available. A revised AU-RMP version 4.0 (dated 13 January 2023; DLP 31 May 2022) was provided with the sponsor's response to RMP evaluator's recommendations dated 13 January 2023. On 20 February 2023, the sponsor submitted further changes in AU-RMP version 4.0 (dated 17 February 2023; DLP 31 May 2022) which has been linked to the Category 1, Type J application (PM-2022-05475-1-5). At Round 2, the sponsor submitted updated AU-RMP version 4.1 (dated 5 April 2023; DLP 31 May 2022) with their S31 response dated 6 April 2023.
- MS-2 Step is approved for the medical termination of an intrauterine pregnancy, up to 63 days of gestation, in females of childbearing age.
- The most recently evaluated and approved AU-RMP was version 03 (dated 13 November 2014; DLP 28 April 2013) (R14/1181088).
- The reason for this updated RMP is changes to the summary of safety concerns (SoSC) and changes to the risk minimisation plan. The key changes proposed for risk minimisation activities are as follows:
    - To remove the requirement for pharmacists to be registered to be able to dispense the product.
    - To remove the requirement for prescriber recertification.
    - To remove the need for prescribers to complete mandatory training and receive certification to be able to prescribe the product.
    - To remove the requirement for a Sponsor provided 24 hours aftercare service
- As the TGA has previously evaluated RMPs for this product, the focus of this review is on the differences between the AU-RMP versions and revisions to the additional risk minimisation materials.
- The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below:

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Infection, toxic shock syndrome	✓	–	✓	✓[1,2]
	Method failure	✓	–	✓	✓[1,2]
	Cardiac disorders	✓	–	✓	✓[2]
Important potential risks	Inadvertent pregnancy exposure and risk of incomplete abortion with severe bleeding	✓	–	✓	✓[2]
	Inadvertent pregnancy exposure (risk of malformations)	✓	–	✓	✓[2]
	Potential interaction with CYP3A4 inhibitors or inducers	✓	–	✓	–
	Potential interaction with products interacting with the glucocorticoid receptor	✓	–	✓	–
	Induced bronchial asthma	✓	–	✓	–
	Effects in lactating women	✓	–	✓	–
	Effects in women with impaired liver function	✓	–	✓	–
	Effects in women with impaired renal function	✓	–	✓	–
	Effects in women with malnutrition	✓	–	✓	–

	Incorrect determination of gestational age	✓	–	✓	–
	Potential for missed ectopic pregnancy	✓	–	✓	✓[2]
	Potential for postnatal developmental delay	✓	–	✓	–
	Potential for off-label use beyond the first trimester	✓	–	✓	–
Missing information	Inherited porphyria	✓	–	–	–
	Theoretical interaction with NSAIDs	✓	–	–	–
	Potential interaction with products interacting with the progesterone receptor	✓	–	–	–
	Use in adolescents	✓	–	–	–
Pharmacological class effect	Risks related to the use of prostaglandin	✓	–	✓	✓[2]

[1] Black box warning
[2] Patient Information and Consent Agreement form

- The sponsor has updated the summary of safety concerns in line with recommendations by the RMP evaluator as well as to reflect up-to-date safety information for MS-2 Step. At Round 2, the sponsor has proposed to remove potential risk 'Potential for loss to follow-up' and this is acceptable from an RMP perspective. However, the sponsor has also removed potential risk 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up', which is not supported as there are additional considerations to this risk with regards to access to further advice or treatment if follow-up does not occur.

- The completed post marketing surveillance study has been removed from the pharmacovigilance plan. Routine pharmacovigilance is proposed for all safety concerns. There is one additional pharmacovigilance activity – an ongoing Canadian post-market surveillance study on the effectiveness and safety of combination mifepristone/misoprostol for medical abortion under 63 days gestation. Further changes to the pharmacovigilance plan in the AU-RMP is recommended.

- The sponsor proposes to remove from the risk minimisation plan the requirements for prescriber certification, pharmacist registration and a Sponsor-provided 24 hours aftercare service. Additional risk minimisation activities will consist of a black box warning, inclusion of CMI and instruction insert in pack, and Patient Information and Consent Agreement form. The sponsor will continue to make educational materials available as support to prescribers and dispensers. The proposed risk minimisation plan aligns with that in Canada. The RMP evaluator has noted the post-market experience with MS-2 Step, its well-established safety profile, and existing safety frameworks in place. The RMP evaluator has also noted the importance of timely access of this medicine in terms of patient-safety and the need to remove requirements that hinder patient access to reproductive services. The proposed changes to the risk minimisation plan are acceptable from an RMP perspective. Further changes to the risk minimisation plan are recommended. The sponsor is also requested to include a copy of the Educational Program materials and Patient Information and Consent Agreement form in the appendix of the AU-RMP.

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1. OUTCOME OF THE EVALUATION

1.1. RECOMMENDATIONS TO THE SPONSOR – ROUND 2

The updated AU-RMP (version 4.1, dated 5 April 2023, DLP 31 May 2022) has been considered.

The recommendations made in the initial evaluation and Round 1 evaluation, along with consideration of the sponsor response, are located in Section 6.1 and 6.2 respectively.

There are 2 outstanding recommendations after Round 2 evaluation:

Outstanding Recommendation 13: The ongoing Canadian post-market surveillance study should also be added to the tables in Section III.3 (Table 10) and V.3 (Summary of risk minimization measures) as appropriate. Refer to the Canadian RMP to identify the safety concerns that will be addressed by this additional pharmacovigilance activity.

It is acknowledged that the sponsor commits to submitting a revised RMP that considers completed study outcomes to the TGA when available. The sponsor should submit key findings from the study as an accompanying document. The full study report is only required upon TGA's request.

Outstanding Recommendation 14: The potential risk 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up' should remain in the SOSC as there are additional considerations to this risk with regards to access to further advice or treatment if follow-up does not occur.

Further, it is noted that this safety concern is not discussed in the PSUR, which uses the Canadian RMP as the reference document. It is requested that the sponsor provide an assessment of this safety concern with the PSUR submission expected August 2023. This assessment may serve to support the removal of this safety concern (can be submitted as an RMP update).

There are 2 new recommendations after Round 2 evaluation:

Recommendation 21. The annotated AU-RMP version 4.1 (dated 5 April 2023) tracks all changes since the approved version 03 (dated 13 November 2014) i.e. marks changes from version 0.4 to the two subsequent versions 4.0 to version 4.1. To avoid confusion and for ease of evaluation, annotated documents should only track the changes made since the last submitted version.

Recommendation 22. The sponsor should make the following changes to the risk minimisation plan:

- Include potential risk 'incorrect determination of gestational age' in Section V.3 Summary of risk minimization measures (table; page 38) in the AU-RMP
- Add potential risk 'Potential for off-label use beyond the first trimester' to Table 11 in Section V.1 of the AU-RMP
- Append the Educational Program materials and Patient Information and Consent Agreement form to the AU-RMP
- In Section V.2 Additional Risk Minimisation Measures
    - Under 'Inclusion of Instruction Insert in Composite Pack Carton', remove text relating to the mandatory training program and certification for prescribers:

      "These arrangements are set up and are accessible via the Sponsor's secure healthcare professional website www.ms2step.com.au, or by calling the company directly. The Sponsor may change the restrictions on supply if in the future an effective control mechanism on prescriber access becomes possible via the PBS."

    - Under 'Prescriber Training', specify availability via the website www.ms2step.com.au

1.2. WORDING FOR CONDITIONS OF REGISTRATION

Wording for conditions of registration will be provided once the outstanding RMP issues are addressed to the satisfaction of the TGA.

1.3. ADVICE TO THE DELEGATE

Recommendations 19 and 20 from Round 1 are for the TGA delegate/clinical evaluator:

Recommendation 19. This is a recommendation for the TGA delegate/clinical evaluator. The requirement for prescriber certification is included in the approved PI. The sponsor has advised that it will remove this requirement and submit the updated PI following the completion of round 1 evaluation. From the RMP perspective, assessing prescriber competencies is more related to clinical practice than to product risk management. Therefore, the removal of prescriber certification from the RMP is acceptable. It is recommended that the delegate/clinical evaluator considers the proposed PI change from the clinical perspective, and whether advisory committee advice is needed.

Recommendation 20. This is a recommendation for the TGA delegate/clinical evaluator. The provision of 24-hour phone service for patients is included in the approved PI. The sponsor has advised that it will remove this service and submit updated PI following the completion of round 1 evaluation. It is noted that the PI also advises that 'patients must have the ability to access 24-hour emergency care'. This would ensure timely access to urgent medical attention and intervention. Therefore, the removal of 24-hour phone service is acceptable from the RMP perspective. It is recommended that the delegate/clinical evaluator considers the proposed PI change from the clinical perspective, in particular, whether and how much value the 24-hour phone service adds to patient safety outcomes.

The sponsor has provided a response to these (see in Section 6.2).

2. BACKGROUND

- On 1 December 2022, MS Health Pty Ltd submitted updated AU-RMP version 0.4 (dated 24 November 2022; DLP 31 May 2022) for MS-2 Step. The EU-RMP is not available. The sponsor provided revised Education Program material (included as Appendix 1) with this submission. A revised AU-RMP version 4.0 (dated 13 January 2023; DLP 31 May 2022) was provided with the sponsor's response to RMP evaluator's recommendations dated 13 January 2023. On 20 February 2023, the sponsor submitted further changes in AU-RMP version 4.0 (dated 17 February 2023; DLP 31 May 2022) which has been linked to the Category 1, Type J application (PM-2022-05475-1-5). At Round 2, the sponsor submitted updated AU-RMP version 4.1 (dated 5 April 2023; DLP 31 May 2022) with their S31 response dated 6 April 2023.
- MS-2 Step is approved for the medical termination of an intrauterine pregnancy, up to 63 days of gestation, in females of childbearing age.
- The most recently evaluated and approved AU-RMP was version 03 (dated 13 November 2014; DLP 28 April 2013) (R14/1181088).
- The reason for this updated RMP is changes to the summary of safety concerns (SoSC) and changes to the risk minimisation plan. The key changes proposed are as follows:
  - To remove the requirement for pharmacists to be registered to be able to dispense the product.
  - To remove the requirement for prescriber recertification.
  - To remove the requirement for prescribers to complete mandatory training and receive certification to be able to prescribe the product.
  - To remove the requirement for a Sponsor provided 24 hours aftercare service
- This RMP update is linked to the Category 1, Type J application (PM-2022-05475-1-5) that is currently under evaluation due to accompanying changes warranted to the Australian Product Information to support the proposed changes to the risk minimisation plan.
- As the TGA has previously evaluated RMPs for this product, the focus of this review is on the differences between the AU-RMP versions and revisions to the additional risk minimisation materials.

3. CHANGES TO THE SUMMARY OF SAFETY CONCERNS AND PHARMACOVIGILANCE/RISK MINIMISATION ACTIVITIES

At Round 2, the changes to safety concerns and/or activities proposed since the previous RMP evaluation of AU-RMP Version 03 (dated 13 November 2014; DLP 28 April 2013) are presented in the table below (~~Strikethrough~~ text indicates risks that have been removed and **bold** text indicates new/changed risks):

Summary of safety concerns		**Pharmacovigilance**		**Risk Minimisation**	
		Routine	Additional	Routine	Additional
Important identified risks	~~Bleeding~~	~~✓~~	~~–[1]~~	~~✓~~	~~✓[2,3,4,5,6]~~
	Infection, toxic shock syndrome	✓	–[1]	✓	✓[2,3,~~4,5,6~~]
	Method failure	✓	–[1]	✓	✓[2,3,~~4,5,6~~]
	~~Uterine contractions / cramping~~	~~✓~~	~~–[1]~~	~~✓~~	~~✓[3,5,6]~~
	~~Uterine infection (endometritis, pelvic inflammatory disease)~~	~~✓~~	~~–[1]~~	~~✓~~	~~✓[3,5,6]~~
	~~Nausea, vomiting~~	~~✓~~	~~–[1]~~	~~✓~~	~~✓[3,5,6]~~

	~~Diarrhoea~~	~~✓~~	~~–[1]~~	~~✓~~	~~✓[3,5,6]~~
	~~Hypotension~~	~~✓~~	~~–[1]~~	~~✓~~	~~✓[3,5,6]~~
	~~Skin rashes, urticarial~~	~~✓~~	~~–[1]~~	~~✓~~	~~✓[3,5,6]~~
	Cardiac disorders	✓	–[1]	✓	✓[3,~~5,6~~]
Important potential risks	Inadvertent pregnancy exposure and risk of incomplete abortion with severe bleeding	✓	–	✓	✓[3,~~5,6~~]
	Inadvertent pregnancy exposure (risk of malformations)	✓	–	✓	✓[3,~~5,6~~]
	Potential interaction with CYP3A4 inhibitors or inducers	✓	–	✓	~~✓[6]~~
	Potential interaction with products interacting with the glucocorticoid receptor	✓	–	✓	~~✓[6]~~
	~~Severe asthma uncontrolled by treatment~~ **Induced bronchial asthma**	✓	–	✓	~~✓[6]~~
	Effects in lactating women	✓	–	✓	~~✓[6]~~
	Effects in women with impaired liver function	✓	–	✓	~~✓[6]~~
	Effects in women with impaired renal function	✓	–	✓	~~✓[6]~~
	Effects in women with malnutrition	✓	–	✓	~~✓[6]~~
	Incorrect determination of gestational age	✓	–	✓	~~✓[6]~~
	Potential for missed ectopic pregnancy	✓	–	✓	✓[3,~~5,6~~]
	Potential for postnatal developmental delay	✓	–	✓	–
	Potential for off-label use beyond the first trimester	✓	–	✓	~~✓[6]~~
	~~Potential for loss to follow-up~~	~~✓~~	~~–~~	~~✓~~	~~–~~
	~~Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up~~	~~✓~~	~~–~~	~~✓~~	~~✓[6]~~
Missing information	Inherited porphyria	✓	–	–	–
	Theoretical interaction with NSAIDs	✓	–	–	–
	Potential interaction with products interacting with the progesterone receptor	✓	–	–	–
	Use in adolescents	✓	–	–	–
Pharmacological class effect	Risks related to the use of prostaglandin	✓	–	✓	✓[3,~~5,6~~]

[1] ~~Post-marketing surveillance study~~ (completed)
[2] Black box warning
[3] Patient Information and Consent Agreement form
[4] ~~Optional SMS follow-up text message~~
[5] ~~24-hour nurse-after-care call service~~
[6] ~~Physician education~~

A clean SOSC table is provided below:

Summary of safety concerns		**Pharmacovigilance**		**Risk Minimisation**	
		Routine	Additional	Routine	Additional
	Infection, toxic shock syndrome	✓	–	✓	✓[1,2]

Important identified risks	Method failure	✓	–	✓	✓[1,2]
	Cardiac disorders	✓	–	✓	✓[2]
Important potential risks	Inadvertent pregnancy exposure and risk of incomplete abortion with severe bleeding	✓	–	✓	✓[2]
	Inadvertent pregnancy exposure (risk of malformations)	✓	–	✓	✓[2]
	Potential interaction with CYP3A4 inhibitors or inducers	✓	–	✓	–
	Potential interaction with products interacting with the glucocorticoid receptor	✓	–	✓	–
	Induced bronchial asthma	✓	–	✓	–
	Effects in lactating women	✓	–	✓	–
	Effects in women with impaired liver function	✓	–	✓	–
	Effects in women with impaired renal function	✓	–	✓	–
	Effects in women with malnutrition	✓	–	✓	–
	Incorrect determination of gestational age	✓	–	✓	–
	Potential for missed ectopic pregnancy	✓	–	✓	✓[2]
	Potential for postnatal developmental delay	✓	–	✓	–
	Potential for off-label use beyond the first trimester	✓	–	✓	–
Missing information	Inherited porphyria	✓	–	–	–
	Theoretical interaction with NSAIDs	✓	–	–	–
	Potential interaction with products interacting with the progesterone receptor	✓	–	–	–
	Use in adolescents	✓	–	–	–
Pharmacological class effect	Risks related to the use of prostaglandin	✓	–	✓	✓[2]

[1] Black box warning
[2] Patient Information and Consent Agreement

3.1. SUMMARY OF CHANGES TO THE SOSC – INITIAL EVALUATION

In the AU-RMP version 0.4 (dated 24 November 2022; DLP 31 May 2022) for MS-2 Step, the following new safety concerns have been added to the SoSC to align with the Canadian RMP (e004967 (0009-) - Attachment 1 - Canadian RMP) and the PI:

- important identified risk - cardiac disorders
- important potential risk - incorrect determination of gestational age

3.2. RMP EVALUATOR COMMENTS/ RECOMMENDATIONS ON THE SOSC – INITIAL EVALUATION

The Canadian RMP (dated 27 August 2020) was used as the reference RMP in the sponsor's Periodic Benefit-Risk Evaluation Report (PBRER) for mifepristone and misoprostol combipack presentations, covering 01 June 2021 to 31 May 2022 (D22-6031778). The SoSC in the current Canadian RMP:

Identified risk:	Method failure Infection Toxic shock syndrome Cardiac disorders
Potential risk:	Inadvertent risk of pregnancy Induced bronchial asthma Incorrect determination of gestational age Complication arising from the use in undiagnosed ectopic pregnancy
Missing information:	Pregnant and lactating subjects Paediatric patients Geriatric patients Patients with Renal, Hepatic or Cardiac Impairment Off Label use

There are significant differences between the Canadian and Australian RMP.

In the AU-RMP version 0.4 (dated 24 November 2022; DLP 31 May 2022) for MS-2 Step, the below differences with the Canadian RMP (dated 27 August 2020) remain:

- Potential risks: induced bronchial asthma (in contrast with severe asthma uncontrolled by treatment), complication arising from the use in undiagnosed ectopic pregnancy.
- Missing information: patients with renal, hepatic or cardiac impairment.

Potential risk of 'complication arising from the use in undiagnosed ectopic pregnancy' is considered to be captured by 'Potential for missed ectopic pregnancy' included in the AU-RMP. This is satisfactory.

Missing information of 'patients with renal, hepatic or cardiac impairment' is in part captured by potential risks 'Effects in women with impaired liver function' and 'Effects in women with impaired renal function'. Given the classification of cardiac disorders as an important identified risk, and associated warnings in the PI to use with caution in women with risk factors for cardiovascular disease or established cardiovascular disease, this is satisfactory.

Use in pregnant subjects is not listed in the AU-RMP as missing information. This is satisfactory.

The sponsor should be asked to provide reasons on the difference in potential risk of 'induced bronchial asthma' vs 'severe asthma uncontrolled by treatment'.

The sponsor should also be reminded to routinely review the safety concerns in the AU-RMP to ensure it reflects up-to-date safety information. Taking into account the product's reasonable marketing experience (as single ingredient and as combination pack), as well as the fact no additional pharmacovigilance activity is planned to further characterise the risks, the sponsor should evaluate whether any safety concerns can be removed. Further, in the absence of an EU-RMP, any changes to international RMPs should be assessed to determine whether similar updates are warranted in Australia.

The sponsor is requested to provide a description of the process for maintenance of the AU-RMP (e.g. standard operating procedure document).

3.3. Summary of key changes to Safety Specification - Succession 2 & 3 (Round 1)

Changes from AU RMP version 03 to version 4.0	RMP evaluator comment

Removed the following important identified risks: • Bleeding • Contractions / cramping • Uterine infection • Nausea and vomiting • Diarrhoea • Hypotension • Skin rashes / urticaria	This aligns with the Canadian RMP.
Important potential risk "Severe asthma uncontrolled by treatment" changed to "Induced bronchial asthma"	This aligns with the Canadian RMP.

There were no further changes to the safety specification between AU-RMP version 4.0 (dated 13 January 2023; DLP 31 May 2022) and AU-RMP version 4.0 (dated 17 February 2023; DLP 31 May 2022).

The sponsor has noted that AU-RMP also has further potential risks that are not included in the Canadian RMP, or risks that are presented slightly differently.

3.4. RMP Evaluator comments/ recommendations on the SoSC – Succession 2 & 3 (Round 1)

The summary of safety concerns is considered acceptable from an RMP perspective.

It is acknowledged that the sponsor has committed to ensuring that any future changes that are made to Canadian RMP will be assessed to determine whether the same updates are also warranted in Australia.

The updated RMP version 4.0 (dated 17 February 2023) submitted by the sponsor has the same version number with a different date from version 4.0 (dated 13 January 2023). To avoid confusion, for future submissions, the sponsor should update the version number and date for each revision.

3.5. Summary of key changes to Safety Specification – Round 2

Changes from AU RMP version 4.0 to 4.1	RMP evaluator comment
Removed important potential risks 'Potential for loss to follow-up'	This aligns with the Canadian RMP. Given there are no additional pharmacovigilance activities and additional risk minimisation activities to specifically address these safety concerns, and the importance of follow-up is well described in the PI and CMI, this is acceptable.
Removed important potential risks 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up'	This should remain in the SOSC as there are additional considerations to this risk with regards to access to further advice or treatment if follow-up does not occur.

3.6. RMP Evaluator comments/ recommendations on the SoSC – Round 2

The potential risk 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up' should remain in the SOSC as there are additional considerations to this risk with regards to access to further advice or treatment if follow-up does not occur.

Further, it is noted that this safety concern is not discussed in the PSUR, which uses the Canadian RMP as the reference document. It is requested that the sponsor provide an assessment of this safety concern with the PSUR submission expected August 2023. This assessment may serve to support the removal of this safety concern (can be submitted as an RMP update).

4. PHARMACOVIGILANCE PLAN

4.1. Summary of changes to the pharmacovigilance plan – Initial evaluation

The post marketing surveillance study of use of mifepristone/mifepristol for early medical abortion within MSIA clinics is now completed. Section III.2 and Section SIII has been updated to capture this.

4.2. RMP Evaluator comments/ recommendations on pharmacovigilance plan – Initial evaluation

Information regarding the study should be removed from the pharmacovigilance plan in the RMP since final study report/results have been submitted to the TGA for assessment. The study should also be deleted as an additional pharmacovigilance activity in Section V.3 in AU-RMP.

4.3. Summary of changes to the pharmacovigilance plan – Succession 2 & 3 (Round 1)

The completed study has been removed from the pharmacovigilance plan in the updated AU RMP, as requested.

There were no changes to pharmacovigilance plan submitted in Succession 3.

4.4. RMP Evaluator comments/ recommendations on pharmacovigilance plan – Succession 2 & 3 (Round 1)

There are no additional pharmacovigilance activities in the AU RMP. It is noted that the Canadian RMP includes a planned Canadian-specific post-market study:

Safety Concern	Additional activity	Proposed actions/ outcomes	Planned submission date
Planned studies			
Method failure, Infection, toxic shock syndrome, cardiac disorders, Inadvertent risk of pregnancy, induced bronchial asthma, incorrect determination of gestational age, Potential for missed ectopic pregnancy	**Canadian Phase IV study**	**A Phase IV Multi-Centre Prospective Study on the Safety of Combination Mifepristone/Misoprostol for Medical Abortion Under 63 Days Gestation Among Canadian Women** **Primary objective: To determine rate of surgical aspiration, for any reason, within 21 days following medical abortion with combination mifepristone/misoprostol**	**TBD**

The findings from the above study are applicable to Australia and should be included in the AU-RMP. The sponsor should include planned submission dates of study reports.

When available a revised RMP which considers the completed study outcomes should be submitted to the TGA for review.

4.5. Summary of changes to the pharmacovigilance plan – Round 2

The sponsor has included information on the ongoing Canadian Phase IV study in Section III.2 of the AU-RMP, as requested.

4.6. RMP Evaluator comments/ recommendations on pharmacovigilance plan – Round 2

The ongoing Canadian post-market surveillance study should also be added to the tables in Section III.3 (Table 10) and V.3 (Summary of risk minimization measures) as appropriate. Refer to the Canadian RMP to identify the safety concerns that will be addressed by this additional pharmacovigilance activity.

It is acknowledged that the sponsor commits to submitting a revised RMP that considers completed study outcomes to the TGA when available. The sponsor should submit key findings from the study as an accompanying document. The full study report is only required upon TGA's request.

The annotated AU-RMP version 4.1 (dated 5 April 2023) tracks all changes since the approved version 03 (dated 13 November 2014) i.e. marks changes from version 0.4 to the two subsequent versions 4.0 to version 4.1. To avoid confusion and for ease of evaluation, annotated documents should only track the changes made since the last submitted version.

5. RISK MINIMISATION PLAN

5.1. SUMMARY OF CHANGES TO THE RISK MINIMISATION PLAN – INITIAL EVALUATION

The sponsor proposes to remove from the risk minimisation plan:

- the requirement for pharmacist registration to dispense the product
- the requirement for re-certification training for prescribers.

5.2. RMP EVALUATOR COMMENTS/ RECOMMENDATIONS ON THE RISK MINIMISATION PLAN – INITIAL EVALUATION

Detailed evidence/justification to support these proposals have not been provided. The sponsor should provide discussion on:

- additional risk minimisation activities in other countries where MS-2 Step is available compared to Australia
- any safety concerns on the removal of pharmacist registration and prescriber re-certification
- number/percentage of pharmacies registered to dispense MS-2 Step in Australia
- any reports on evaluation of effectiveness of additional risk minimisation activities

Given the reasonable worldwide marketing experience with mifepristone and mifepristol (IBD 28 June 1984 for misoprostol, 29 December 2010 for mifepristone, and MS-2 Step first registered in Australia 04 June 2014), the safety profile is considered well established. Clinical practice and understanding, along with the other additional risk minimisation activities in place, are likely adequate to manage the risks. It is acknowledged that the timeliness of access is essential and corresponds to effectiveness of the product. Final decision on the proposed changes to the risk minimisation plan will be made after review of the sponsor's response.

The sponsor has proposed that 'once registered and certified no re-registration or re-certification is required' for prescribers. It is assumed that this re-certification refers to the periodic renewal of the certificate for the purpose of knowledge maintenance. The sponsor should provide clarification in the RMP on whether and how it plans to inform prescribers of the updated safety information when new evidence becomes available.

The sponsor has stated under 'Restricted Access to MS-2-Step' that the program is to ensure that 'distribution of MS-2-Step is controlled and monitored. With the proposed removal of pharmacist registration, the sponsor should clarify how this is achieved. The sponsor should note, according to the EMA GVP Module XVI, controlled distribution and controlled access programs are different measures that serve different purposes[1].

Further, the sponsor should amend Section V.3 Summary (table) of risk minimisation measures as follows:

[1]EMA Guideline on good pharmacovigilance practices Module XVI, dated 28 March 2017, EMA/204715/2012 Rev 2, https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-xvi-risk-minimisation-measures-selection-tools_en-3.pdf

- Completed post-marketing surveillance study is still listed as an additional pharmacovigilance activity – this should be removed from the table
- 'Special attention in PSURs' was listed as an additional pharmacovigilance activity – this is considered part of routine pharmacovigilance.
- 'Physician education' is not described as an additional risk minimisation activity for potential risks: Potential interaction with CYP3A4 inhibitors or inducers, Potential interaction with products interacting with the glucocorticoid receptor, Severe asthma uncontrolled by treatment, Incorrect determination of gestational age – this should be revised accordingly
- 'Potential for loss to follow up' is not included – this should be added for completeness

5.3. Summary of changes to the risk minimisation plan – Succession 2 & 3

The sponsor has submitted additional changes to the risk minimisation plan in AU-RMP version 4.0 (dated 17 February 2023; DLP 31 May 2022). In summary, the following changes to the risk minimisation plan are proposed (new in **bold**):

- To remove the requirement for pharmacists to be registered to be able to dispense the product.
- To remove the requirement for prescriber recertification.
- **To remove the requirement for prescribers to complete mandatory training and receive certification to be able to prescribe the product.**
- **To remove the requirement for a Sponsor provided 24 hours aftercare service**

As the requirement for prescriber certification and 24-hour phone service are included in the PI, the sponsor has advised that it will remove these and submit the updated PI following the completion of round 1 evaluation[2].

The sponsor states that this would align the MS-2 Step RMP with the expectations of RMPs of the majority of medicines registered with the TGA, and with expectations around prescriber competency for a medicine that has been in-market for many years with hundreds of thousands Australian women having been prescribed MS-2 Step since it was first registered over 8 years ago.

The information in the AU-RMP regarding restricted distribution has been deleted with the proposed removal of mandatory training program and certification for prescribers.

5.4. RMP Evaluator comments/ recommendations on the risk minimisation plan – Succession 2 & 3 (Round 1)

The Sponsor has amended Section V.3 Summary of risk minimisation measures (table) in accordance with the above requested changes. However, further changes are required:

- Identified risk 'Cardiac disorders' is missing and needs to be added

[2] e004967 (0009-) - Cover Letter - 2023-02 Cat 1, Type J, RMP

- Potential risks 'Incorrect determination of gestational age' and 'Potential for loss to follow-up' are missing and need to be added

Additionally, the sponsor should make the below changes to Table 11 in Section V.1:

- Remove 'physician education' as a routine risk minimisation measure as this is considered additional risk minimisation

- Potential risks 'Potential for off-label use beyond the first trimester' and 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up' are missing and need to be added

Misoprostol was first approved in Australia on 7 July 1993, mifepristone on 29 August 2012 and MS-2 Step was registered on 4 June 2014. Given the post-market experience with MS-2 Step in Australia and worldwide, the product's safety profile is well-established. Safety concerns in the SOSC have been removed with this AU-RMP update, which still includes additional potential risks to the Canadian RMP.

Furthermore, it is reasonable to expect that prescribers and dispensers have a level of clinical knowledge of MS-2 Step, or be able to refer to resources available (e.g. the PI) to ensure safe and effective use as like any other medicine. The sponsor will also continue to make the MS-2 Step training materials available to both prescribers and dispensers so that skill levels can be maintained. The patient information and consent form should continue to be implemented.

The sponsor has informed that based on the latest available data in 2020, less than 20% of pharmacists are registered in Australia to dispense MS-2 Step (see Section 6.1, Recommendation 6). As indicated, this presents a patient-safety risk of delayed access to medication, particularly in regional and rural areas as well as for patients whose gestation is approaching the upper limit of MS-2 Step's registered indication.

It is noted that in Australia, there is a government funded service available - healthdirect hotline – which provides 24-hour/7-day health advice from a registered nurse. Moreover, distribution of MS-2 Step will be tracked via general pathways of PBS Authority prescription and PBS dispensing and safety concerns will continue to be monitored by the sponsor under routine pharmacovigilance and reported as necessary as specified in Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements. The sponsor may also be requested to provide a PSUR to the TGA at any time.

The sponsor has pointed out that internationally, in Canada, since 2017 registration of health professionals with Celopharma is no longer required in order to prescribe or dispense Mifeqymiso[3]. The sponsor states no adverse safety signals or additional risk minimisation activities identified in Canada with this change to a broader access regimen. It was noted in the Canadian Monograph for Mifeqymiso[4], it is stated that "*Mifegymiso should be prescribed by*

[3] MIFEGYMISO (mifepristone and misoprostol tablets) - Updates to Product Monograph and Risk Management Plan, accessed 23 February 2023, MIFEGYMISO (mifepristone and misoprostol tablets) - Updates to Product Monograph and Risk Management Plan - Canada.ca
[4] MIFEGYMISO (mifepristone and misoprostol tablets) Canadian Product Monograph, accessed 23 February 2023, 00050659.PDF (hres.ca)

*health professionals with adequate knowledge of medical abortion and/**or** who have completed a Mifegymiso education program*".

The RMP evaluator has noted the need to remove requirements that hinder patient access to reproductive services. The evaluator has also noted different risk mitigation strategies employed by different comparable overseas regulators.

The US FDA has reviewed and finalised the Risk Evaluation and Mitigation Strategies (REMS) for mifepristone on 3 January 2023. The REMS lists 'requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program' as a goal of the REMS[5].

The RMP evaluator has noted that the advice on 24-hour phone service is also provided in the Australian Consumer Medicine Information (CMI). The sponsor should submit the updated CMI to ensure consistent information in the RMP, PI, and CMI.

The requirement for prescriber certification is included in the Australian Product Information (PI). The sponsor has advised that it will remove this requirement and submit the updated PI following the completion of round 1 evaluation. From the RMP perspective, assessing prescriber competencies is more related to clinical practice than to product risk management. Therefore, the removal of prescriber certification from the RMP is acceptable. It is recommended that the delegate/clinical evaluator considers the proposed PI change from the clinical perspective, and whether advisory committee advice is needed.

The provision of 24-hour phone service for patients is included in the PI. The sponsor has advised that it will remove this service and submit updated PI following the completion of round 1 evaluation. It is noted that the PI also advises that 'patients must have the ability to access 24-hour emergency care'. This would ensure timely access to urgent medical attention and intervention. Therefore, the removal of 24-hour phone service is acceptable from the RMP perspective. It is recommended that the delegate/clinical evaluator considers the proposed PI change from the clinical perspective, in particular, whether and how much value the 24-hour phone service adds to patient safety outcomes.

5.5. RMP EVALUATOR COMMENTS/ RECOMMENDATIONS ON THE RISK MINIMISATION PLAN – ROUND 2

At Round 2, the sponsor confirms that the existing standardised training (the Medical Education Program) will still be available for all healthcare practitioners and prescribers and dispensers will be made aware on how to access them via the existing online website (www.ms2step.com.au).

The proposed changes to the risk minimisation plan to remove pharmacist registration, prescriber certification and the Sponsor provided 24 hours aftercare service are considered acceptable from an RMP perspective for the reasons discussed above. The PI and CMI have been updated to reflect the proposed changes to the risk minimisation plan.

As requested at Round 1, the Patient Information and Consent Agreement form and the Educational program materials should be appended to the AU-RMP. The Educational program is still part of the RMP, and the sponsor should provide the educational materials - see TGA RMP guidance Section 5.3. From RMP perspective, the educational materials continue to be provided

[5] US FDA approved REMS for mifepristone, accessed on 24 February 2023, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390

to prescribers and it is our expectation that prescribers will undergo the training. The sponsor needs to include educational materials in track changed version to show any update since the last time RMP was evaluated.

The sponsor is requested to make further changes to the risk minimisation plan, as follows:

- Include potential risk 'incorrect determination of gestational age' in Section V.3 Summary of risk minimization measures (table; page 38) in the AU-RMP
- Add potential risk 'Potential for off-label use beyond the first trimester' to Table 11 in Section V.1 of the AU-RMP
- Append the educational materials and the Patient Information and Consent Agreement form to the AU-RMP
- In Section V.2 Additional Risk Minimisation Measures
    - Under 'Inclusion of Instruction Insert in Composite Pack Carton', remove text relating to the mandatory training program and certification for prescribers:

      "These arrangements are set up and are accessible via the Sponsor's secure healthcare professional website www.ms2step.com.au, or by calling the company directly. The Sponsor may change the restrictions on supply if in the future an effective control mechanism on prescriber access becomes possible via the PBS."
    - Under 'Prescriber Training', specify availability via the website www.ms2step.com.au

5.6. RMP EVALUATOR COMMENTS/ RECOMMENDATIONS OF ADDITIONAL RISK MINIMISATION ACTIVITIES

Additional risk minimisation activities consist of a black box warning, inclusion of CMI and instruction insert in pack, Patient Information and Consent Agreement, and prescriber educational materials (as supportive resources; non-mandatory training).

This is considered sufficient based on the above discussion.

5.7. PRODUCT LABELLING

5.7.1. Product Information

The sponsor should confirm whether the new data from the completed post-market surveillance study study added to Section SIII (Clinical trial exposure) of the AU-RMP version 0.4 (and Section 3.6 of Annex 1.1) will be added to the Australian PI:

> *In an observational cohort study of 15 008 women attending one of 16 Marie Stopes International clinics in Australia for MTOP (gestational age ≤ 63 days) between 1 March 2013 and 30 September 2015, patients were **administered** 200 mg mifepristone orally in-clinic, followed 24- 48 hours later by 800 micrograms of misoprostol buccally, self-administered at home. Method success was defined as complete abortion not requiring surgical intervention. Follow up information was available for 13,078 (87.2%) of the total cohort. Medical abortion was successful in 95.16% (12,445/13,078) of women with follow-up. Higher patient and*

gestational ages were associated (P < 0.001) with a slight increase in method failure. There were 674 serious adverse events (5.15%), mainly due to method failure. Infection (15; 0.11%) and haemorrhage (17; 0.13%) were rare. One death was recorded (<0.01%); however, an association between EMA and cause of death, necrotising pneumonia, was not established.

Moreover, the sponsor should make a minor editorial change (in ***bold***).

Succession 2 update

The sponsor has confirmed in their response that the Australian PI will be updated with the completed post-market surveillance study data as part of the next submitted Category 1, Type J application (see Section 6.1, Recommendation 4).

5.7.2. Consumer Medicine Information

The sponsor should ensure any PI updates are captured in the CMI where applicable.

The CMI along with the instruction insert will be included in the pack.

5.8. Additional Risk Minimisation Materials

The sponsor submitted revised Educational Program material (with tracked changes) with the AU-RMP update submission (as Annex 1; D22-6187939). There were mostly editorial changes to reflect current approved indication and current practices, as well as inclusion of current post marketing data. Of note, the refresher materials have been removed from the package.

In the training manual (Annex 1.1), the sponsor included interim information regarding a pending TGA application to remove PI precautions regarding rhesus alloimmunisation to align with current Australian and International guidelines. It was recommended that the sponsor only incorporate advice that has been approved.

Succession 2&3 (Round 1) update

At Succession 2, the sponsor had submitted an updated training manual with the requested changes with their response.

At Succession 3, the Educational program material has been removed from the AU-RMP with the proposed removal of mandatory training program and certification for prescribers. However, it is noted that the sponsor will continue to provide access to prescriber training to support the education of prescribers. Physician education and Patient Information and Consent Agreement are listed as additional risk minimisation measures in the AU-RMP and these materials should be appended to the AU-RMP. Further, the sponsor should ensure prescribers (and dispensers) are made aware of the availability of MS-2 Step training materials and how to access these.

The sponsor should make the minor editorial change to Section 3.6 of the training manual to amend “administration” to “administered” (see Section 5.5.1).

6. EVALUATION OF SPONSOR RESPONSE

6.1. Reconciliation of recommendations sent 13 December 2022

The sponsor’s response, dated 13 January 2023, can be found on

TRIM D23-5035315

docuBridge e004967 (0008-) - Response - 2023-01 Response to RFI

The sponsor has provided and updated AU-RMP version 4.0 (dated 13 January 2023, DLP 31 May 2022) with their response.

Recommendation 1: The sponsor is requested to provide reasons on the difference in potential risk of 'induced bronchial asthma' vs 'severe asthma uncontrolled by treatment'.
Sponsor's response: The Sponsor proposes to update the potential risk of 'severe asthma uncontrolled by treatment' to 'induced bronchial asthma'. As currently detailed in the AU-RMP, bronchospasm may occur with some prostaglandins and prostaglandin analogues. The possibility should be borne in mind in patients with a history of asthma. *The potential risk 'induced bronchial asthma' is currently included in the Canadian RMP and is targeted for review and safety surveillance as part of the annual PBRER (reports of induced bronchial asthma are identified using a prespecified list of preferred terms in MedDRA version 16.0).* *A copy of the proposed updated AU-RMP has been provided in Module 1.8.*
RMP evaluator comment: The important potential risk of 'severe asthma uncontrolled by treatment' has been replaced with 'induced bronchial asthma' in line with Canadian RMP in the updated AU-RMP. This is acceptable.

Recommendation 2: The sponsor is requested to provide a description of the process for maintenance of the AU-RMP (e.g. standard operating procedure document).

In accordance with the guidance on *Risk management plans for medicines and biologicals* throughout the lifecycle of the product, RMPs must be maintained to incorporate new safety information. Any significant updates are required to be submitted to the TGA for evaluation within a timely manner. In accordance with the *Pharmacovigilance Guidelines*, sponsors should have processes in place (with well-defined responsibilities, requirements and timelines) to ensure they comply with their post-approval commitments.

Further, the sponsor is reminded to routinely review the safety concerns in the AU-RMP to ensure it reflects up-to-date safety information. Taking into account the product's reasonable marketing experience (as single ingredient and as combination pack), as well as the fact no additional pharmacovigilance activity is planned to further characterise the risks, the sponsor should evaluate whether any safety concerns can be removed. Further, in the absence of an EU-RMP, any changes to international RMPs should be assessed to determine whether similar updates are warranted in Australia.

Sponsor's response: The maintenance of the AU-RMP is managed via agreements in place with their supplier (Linepharma International Limited). Specifically, the Safety Data Exchange Agreement (SDEA) held between MS Health Pty Ltd and Linepharma International Limited (supplier)includes the responsibilities relating to the AU-RMP. The SDEA specifies that the supplier coordinates an update to the RMP if a significant safety signal is detected, including immediate notification to MS Health of any significant safety issues. Following the receipt of a notification of a significant safety issue from the supplier, MS Health is then responsible for preparation and maintenance of the AU-RMP including any required submission to TGA (according to TGA guidelines including any specified timelines). MS Health is also responsible for implementation of any applicable risk minimisation measures.

Additionally, s47 *(the service provider) have a standard operating procedure in place for the management of safety information. This dictates that the updated AU RMP be submitted to the TGA in accordance with the TGA RMP guidelines.*

Further to the above, the Sponsor has reviewed the safety concerns listed within the AU-RMP and proposes to remove those that have a low risk in regard to the seriousness of the safety concern, a low risk to the individual patient and have minimal impact on public health. The following identified risks have therefore been removed as part of this response:

- *Bleeding*
- *Contractions / cramping*
- *Uterine infection*
- *Nausea and vomiting*
- *Diarrhoea*
- *Hypotension*
- *Skin rashes / urticaria*

A clean and annotated copy of the proposed AU-RMP has been provided in Module 1.8.

In the absence of the EU-RMP, the Sponsor confirms that the safety concerns that are listed within the AU-RMP and the changes proposed above, align with those detailed in the Canadian RMP (although it is noted that the AU RMP still includes additional potential risks over and above those that are included in the Canadian RMP, or presents these slightly differently). A copy of the Canadian RMP has been provided as Attachment 1 to this response. An assurance is provided that any future changes that are made to Canadian RMP with be assessed to determine whether the same updates are also warranted in Australia (as per the processes defined above).

RMP evaluator comment: The sponsor's commitment to assess future changes made to the Canadian RMP to determine whether similar updates are warranted in Australia is acknowledged. The sponsor's proposal to remove the above important identified risks is consistent with the Canadian RMP and is acceptable.

Recommendation 3: The sponsor should remove information regarding the completed post-market surveillance study from the pharmacovigilance plan in the RMP as final study report/results have been submitted to the TGA for assessment. The study should also be deleted as an additional pharmacovigilance activity in Section V.3 in AU-RMP.
Sponsor's response: The sponsor has removed the information regarding the completed post-market surveillance study from the pharmacovigilance plan in the RMP. The study has also been deleted as an additional pharmacovigilance activity in Sections III.2 and V.3 of the RMP.
RMP evaluator comment: The AU RMP has been updated as requested.
Recommendation 4: The sponsor should confirm whether the data from the completed post-market surveillance study added to Section SIII (Clinical trial exposure) of the AU-RMP version 0.4 (and Section 3.6 of Annex 1.1) will be added to the Australian PI.
Sponsor's response: The sponsor confirms that they propose to update the Australian PI with the completed postmarket surveillance study data as part of the next submitted Category 1, Type J application
RMP evaluator comment: Noted. This is acceptable.
Recommendation 5: The sponsor should make the following minor editorial change (in **bold**): *In an observational cohort study of 15 008 women attending one of 16 Marie Stopes International clinics in Australia for MTOP (gestational age ≤ 63 days) between 1 March 2013 and 30 September 2015, patients were **administered** 200 mg mifepristone orally in-clinic, followed 24- 48 hours later by 800 micrograms of misoprostol buccally, self-administered at home. Method success was defined as complete abortion not requiring surgical intervention. Follow up information was available for 13,078 (87.2%) of the total cohort. Medical abortion was successful in 95.16% (12,445/13,078) of women with follow-up. Higher patient and gestational ages were associated (P < 0.001) with a slight increase in method failure. There were 674 serious adverse events (5.15%), mainly due to method failure. Infection (15; 0.11%) and haemorrhage (17; 0.13%) were rare. One death was recorded (<0.01%); however, an association between EMA and cause of death, necrotising pneumonia, was not established.*
Sponsor's response: The sponsor has updated the RMP in accordance with the requested minor editorial amendment. A copy of the updated RMP has been provided in Module 1.8.
RMP evaluator comment: The AU RMP has been updated as requested.

Recommendation 6: To support the proposals to remove requirements for prescriber recertification training and pharmacist registration, the sponsor should provide justification/discussion on:

- additional risk minimisation activities in other countries where MS-2 Step is available compared to Australia
- any safety concerns on the removal of pharmacist registration and prescriber re-certification
- number/percentage of pharmacies registered to dispense MS-2 Step in Australia
- any reports on evaluation of effectiveness of additional risk minimisation activities

Sponsor's response: As of December 2022, there are 5,472 pharmacists registered to provide MS-2 Step® to Australian patients. The most recent Dept of Health data (Allied Health factsheets) reports a total of 32,904 pharmacists registered in Australia in 2020 (more recent data not available); indicating only ~17% of pharmacists are currently registered to dispense MS-2 Step to patients.
The challenge of having less than 20% of pharmacists registered to dispense MS-2 Step presents a risk from a patient-safety perspective of delayed access to medication. This is especially so for patients in either regional and remote settings where there may not be an easily accessible registered pharmacist; as well as for patients whose gestation is approaching the upper limit of MS-2 Step's registered indication and for whom timely access to MToP is even more critical. MS Health will continue to make the MS-2 Step training materials available to both prescribers and dispensers so that skill levels can be maintained, but removal of these specific requirements (prescriber recertification, dispenser registration) is expected to improve the ability of patients to receive timely access to their medication.
MS Health notes that within the Canadian setting, since 2017 patients seeking a medical termination of pregnancy are dispensed an identically configured Mifepristone + Misoprostol composite pack by pharmacists who are not required to register prior to dispensing; or physicians who need to recertify. There have been no adverse safety signals or additional risk minimisation activities identified in Canada with this change to a broader access regimen.

RMP evaluator comment: Noted. Considering the proposed removal of mandatory training program and certification of prescribers and dispensers, the sponsor should ensure prescribers and dispensers are aware of the availability of MS-2 Step training materials and how to access these.

Recommendation 7: The sponsor has proposed that 'once registered and certified no re-registration or recertification is required' for prescribers. It is assumed that this re-certification refers to the periodic renewal of the certificate for the purpose of knowledge maintenance. The sponsor should provide clarification in the AU-RMP on whether and how it plans to inform prescribers of the updated safety information when new evidence becomes available.

Sponsor's response: The Sponsor confirms that re-certification refers to the periodic renewal of the certificate for the purpose of knowledge maintenance.
The MS-2 Step composite pack product has been available in Australia for over 8 years (registered 4/6/2014, marketed 1/2/2015). The pack components (Mifepristone + Misoprostol) have been registered for the Medical Termination of Pregnancy in Australia (and globally) prior to this. The product's characteristics, safety and AE profile are relatively well understood. There is no proposed change in the patient population as part of this application and as such, it is unlikely that a significant change to the product's existing safety profile is going to be encountered.
It is noted that prescribing Medical Practitioner's must remain up-to-date on changes to the safety profile for any product that they prescribe. This information is communicated to prescribers via PI updates and notices on the TGA website (as appropriate). In the event of a significant change to the product safety profile and a need to rapidly disseminate information to prescribers, MS Health would utilise the channels mentioned above and also utilise the MS-2 Step prescriber database (which is being proposed to remain in place). MS Health proposes to continue to utilise the standard channels used for other registered medicines when providing updated information to prescribers.

RMP evaluator comment: The sponsor's response is acceptable.

Recommendation 8: The sponsor has stated under 'Restricted Access to MS-2-Step' that the program is to ensure that "distribution of MS-2-Step is controlled and monitored". With the proposed removal of pharmacist registration, the sponsor should clarify how this is achieved. The sponsor should note, according to the EMA GVP Module XVI, controlled distribution and controlled access programs are different measures that serve different purposes.

Sponsor's response: The European Medicines Agency (EMA) guidance; Guideline on good pharmacovigilance practices (GVP), Module XVI, Section XVI.B.2.2 states the following:

"Since a controlled access programme has large implications for all stakeholders, the use of such a programme should be limited and should be guided by a clear therapeutic need for the product based on its demonstrated benefit"

The sponsor's proposed RMP amendments i.e. removing the need for prescriber recertification and removing the need for dispenser registration, is endeavouring to minimise impacts on patients who may otherwise struggle to access their medication in a timely manner. MS Health proposes to continue providing prescriber education and maintain the database of certified prescribers to act as a control on any potential product misuse or abuse.

In addition to this, MS Health highlights the fact that it is the responsibility of the prescriber to ensure that they are compliant with relevant requirements to provide any therapeutic product e.g. they have completed any relevant training and have the required knowledge to prescribe the therapeutic product in question. With respect to the MS-2 Step product, an additional extra level of control is provided during the PBS-script approval process. The majority of MS-2 Step scripts are PBS-scripts; the approval process requires the prescriber to affirm that they are certified to prescribe.

NB: this need to affirm certification exists regardless of whether the product is designated Authority Required or Streamlined Authority.

Given the above, it is unlikely for additional restricted access controls to be required and MS Health highlights the fact that the impetus for removing the requirement for dispenser registration is to improve patient access. Especially those patients located in rural and/or remote settings; and those later in their gestation and for who the timely access to medication is critical (and can be more challenging).

Within this context, the term "Restricted Access to MS-2 Step" (compared to the EMA GVP Module XVI definition, as provided below for ease of reference) may be inappropriate and appears to be a carryover from the preceding RMP document. The sponsor proposes amending this to "Restricted Distribution of MS-2 Step" as the product will continue to be distributed through controlled pharmaceutical supply chains; thus minimising the potential for product misuse or abuse.

EMA GVP Definitions

XVI.B.2.3.1. Controlled distribution system A controlled distribution system refers to the set of measures implemented to ensure that the stages of the distribution chain of a medicinal product are tracked up to the prescription and/or pharmacy dispensing the product. Orders and shipments of product from a single or multiple identified distribution points facilitate traceability of the product. For instance, this sort of measures could be considered for those products controlled in each country under the respective national legislations to prevent misuse and abuse of medicines.

XVI.B.2.2. Controlled access programme A controlled access programme consists of interventions seeking to control access to a medicinal product beyond the level of control ensured by routine risk minimisation measures, i.e. the legal status. Since a controlled access programme has large implications for all stakeholders, the use of such a programme should be limited and should be guided by a clear therapeutic need for the product based on its demonstrated benefit (e.g. it treats a serious disease without alternative therapies; it treats patients who have failed on existing therapies), the nature of the associated risk (e.g. risk is lifethreatening), and the likelihood that this risk can be managed by such a programme. Therefore, controlled access should only be considered as a tool for minimising an important risk with significant public health or individual patient impact for a product with clearly demonstrated benefits but which would not otherwise be available without a programme where patient access is contingent on fulfilling one or more requirements prior to a product being prescribed or dispensed in order to assure its safe use.

Examples of requirements that need to be fulfilled before the product is prescribed and/or dispensed and/or used in a controlled access programme are listed below (they may be included individually or in combination): • specific testing and/or examination of the patient to ensure compliance with strictly defined clinical criteria; • prescriber, dispenser and/or patient documenting their receipt and understanding of information on the serious risk of the product; • explicit procedures for systematic patient follow-up through enrolment in a specific data collection system e.g. patient registry; • medicines made available for dispensing only by pharmacies that are registered and approved to dispense the product. On occasions, a requirement to test or to monitor a patient in a specific way can also be used as a controlled access tool. For example,

monitoring of the patient's health status, laboratory values or other characteristic prior to and/or during treatment, e.g. electrocardiogram, liver function tests, regular blood tests, pregnancy tests (which can be part of a pregnancy prevention programme). Measures should be put in place to ensure that monitoring takes place according to the SmPC where this is critical to risk-benefit balance of the product.

RMP evaluator comment: The section regarding restricted distribution has been removed with the proposed removal of mandatory training program and certification for prescribers.

Recommendation 9: The sponsor should amend Section V.3 Summary (table) of risk minimisation measures as follows:

- Completed post-marketing surveillance study is still listed as an additional pharmacovigilance activity – this should be removed from the table
- 'Special attention in PSURs' was listed as an additional pharmacovigilance activity – this is considered part of routine pharmacovigilance.
- 'Physician education' is not described as an additional risk minimisation activity for potential risks: Potential interaction with CYP3A4 inhibitors or inducers, Potential interaction with products interacting with the glucocorticoid receptor, Severe asthma uncontrolled by treatment, Incorrect determination of gestational age – this should be revised accordingly
- 'Potential for loss to follow up' is not included – this should be added for completeness

Sponsor's response: The Sponsor has amended Section V.3 Summary (table) of risk minimisation measures in accordance with the above requested changes and in other sections as applicable. A copy of the update AU RMP has been provided in Module 1.8.

RMP evaluator comment: Further changes to the table in Section V.3 are required:

- **Identified risk 'Cardiac disorders' is missing and needs to be added**
- **Potential risks 'Incorrect determination of gestational age' and 'Potential for loss to follow-up' are missing and need to be added**

Additionally, the sponsor should make the below changes to Table 11 in Section V.1:

- **Remove 'physician education' as a routine risk minimisation measure.**
- **Potential risks 'Potential for off-label use beyond the first trimester' and 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up' are missing and need to be added**

Recommendation 10: In the revised training manual (Annex 1.1), the sponsor has included interim information regarding a pending TGA application to remove PI precautions regarding rhesus alloimmunisation to align with current Australian and International guidelines. The sponsor should note, the content of additional risk minimisation materials, including training manual should always align with the approved PI and CMI. Updates to training materials should occur concurrently with, or following TGA approved PI changes.

Sponsor's response: The reference to the TGA application to remove PI precautions regarding rhesus alloimmunisation has been removed from the training manual Annex 1.1. An updated training manual (Annex 1.1) has been provided in Module 1.8.

RMP evaluator comment: Reference to interim information regarding the pending TGA application (PM-2022-03010-1-5) has been removed from the training manual as requested.

Recommendation 11: The most recently evaluated AU-RMP was version 03 (dated 13 November 2014; DLP 28 April 2013). MS Health Pty Ltd has submitted updated AU-RMP version 0.4 (dated 24 November 2022; DLP 31 May 2022) for MS-2 Step, noting that the EU-RMP is not available. Chronologically, going from Version 03 to 0.4 is confusing. The sponsor should consider amending the proposed version number.
Sponsor's response: The applicant inadvertently included 0.4 as the next sequential version. To avoid any further confusion (and subsequent errors), the version number has been updated to 4.0.
RMP evaluator comment: Noted. The sponsor has submitted an updated AU-RMP version number 4.0.

6.2. RECONCILIATION OF ROUND 1 RECOMMENDATIONS – DATED 27 FEBRUARY 2023

The sponsor's response after Succession 3 evaluation, dated 6 April 2023, can be found on

TRIM D23-5289076

docuBridge e004967 (0012-) - Response - 2023-04 Response to S31 Request, MS3

The sponsor has provided and updated AU-RMP version 4.1 (dated 5 April 2023, DLP 31 May 2022) with their response.

Recommendation 12: The sponsor has submitted the updated RMP version 4.0 (dated 17 February 2023). This RMP has the same version number with a different date from version 4.0 (dated 13 January 2023). To avoid confusion, for future submissions, the sponsor should update the version number and date for each revision.
Sponsor's response: To avoid further confusion, the version number of the RMP has been updated along with the date for each new revision.
RMP evaluator comment: It is noted the sponsor has submitted an updated AU-RMP version 4.1 (dated 5 April 2023, DLP 31 May 2022) with this response.
Recommendation 13: The findings from the Canadian Phase IV study are applicable to Australia and should be included in the AU-RMP as an additional pharmacovigilance activity. The sponsor should include planned submission dates of study reports. When available a revised RMP which considers the completed study outcomes should be submitted to the TGA for review.
Sponsor's response: The Canadian Phase IV study has been included in Section III.2 of the proposed RMP. The proposed study to determine the effectiveness and safety of combination mifepristone/misoprostol for medical abortion under 63 days gestation among 3,000 Canadian women (the MiMAC study) is currently ongoing and is estimated to be completed in Q1 2024 with the final study report currently planned to be available in Q4 2024. *Once the study has been completed, the sponsor provides the assurance that the study reports together with a revised RMP (which considers the completed study outcome) will be submitted to the TGA. The submission is planned for Q4 2024 / Q1 2025.*
RMP evaluator comment: The sponsor has included information on the Canadian Phase IV study in Section III.2 of the AU-RMP, as requested. This additional pharmacovigilance activity should also be added to the tables in Section III.3 and V.3 as appropriate. It is acknowledged that the sponsor commits to submitting a revised RMP that considers completed study outcomes to the TGA when available. The sponsor should submit key findings from the study as an accompanying document. The full study report is only required upon TGA's request.

Recommendation 14: Further changes to Section V.3 Summary (table) of risk minimisation measures of the AU-RMP, are required:

- Identified risk 'Cardiac disorders' is missing and needs to be added
- Potential risks 'Incorrect determination of gestational age' and 'Potential for loss to follow-up' are missing and need to be added

Sponsor's response: The Sponsor notes that the identified risk 'cardiac disorders' was added to the previously submitted version of the RMP. Section V.3 has been updated further to include the missing potential risk 'incorrect determination of gestational age'.
The Sponsor proposes to remove the potential risk 'potential for loss to follow-up'. This will align with the current Canadian RMP and will bring the potential risks in line with other prescription products with a similar risk profile.
The current Product Information and Consumer Medicines Information includes the requirement for prescribers to ensure that upon discharge from the treatment centre, all women should be provided with appropriate medications as necessary and be fully counselled regarding the likely signs and symptoms she may experience and have direct access to the treatment centre by telephone or local access. Further to this they will receive precise instruction as to whom they should contact and where to go in the event of problems emerging. This will ensure that if a patient does not participate in a follow up visit, they possess the information they need about where to go for further advice or treatment.
A copy of the updated annotated (with the recent changes highlighted with a blue comment) and clean RMP has been provided in Module 1.8.

RMP evaluator comment: The table in Section *V.3 Summary of risk minimization measures* (from page 38) in the AU-RMP does not include the missing potential risk 'incorrect determination of gestational age' as stated. This should be addressed by the sponsor. It is noted the sponsor has added information on 'incorrect determination of gestational age' to Table 5 in Section VII.3.1.
The sponsor's proposal to remove the potential risk 'Potential for loss to follow-up' is acceptable from an RMP perspective, given:

- this will align with the current Canadian RMP
- there are no additional pharmacovigilance activities or additional risk minimisation measures proposed to specifically address potential loss to follow-up
- the importance of follow-up examination 14 to 21 days after taking mifepristone to ensure termination is complete and that there are no complications is well described (as a "must") in the PI/CMI black box warnings.

However, it was noted the sponsor has also removed 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up'. This should remain in the SOSC as there are additional considerations to this risk with regards to access to further advice or treatment if follow-up does not occur. It is noted that this safety concern is not discussed in the PSUR, which uses the Canadian RMP as the reference document. It is requested that the sponsor provide an assessment of this safety concern with the PSUR submission expected August 2023. This assessment may serve to support the removal of this safety concern (can be submitted as an RMP update).

Recommendation 15: Changes to Table 11 in Section V.1 of the AU-RMP are required:

- Remove 'physician education' as a routine risk minimisation measure as this is considered additional risk minimisation.
- Potential risks 'Potential for off-label use beyond the first trimester' and 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up' are missing and need to be added

Sponsor's response: The Sponsor has updated Table 11 in Section V.1 of the RMP to remove physician education as a routine risk minimisation measure and to include the following potential risks:

- *Potential for off-label use beyond the first trimester*

As proposed in Recommendation 14 above, the potential risk for loss to follow up is proposed to be removed.
A copy of the updated annotated and clean RMP has been provided in Module 1.8.

RMP evaluator comment: As per comments above, the removal of the potential risks relating to loss to follow-up from the summary of safety concerns is acceptable.
The Sponsor has updated Table 11 in Section V.1 of the AU-RMP to remove physician education as a routine risk minimisation measure as requested. However, 'Potential for off-label use beyond the first trimester' has not been added as a potential risk as stated.

Recommendation 16: The Educational program material has been removed from the AU-RMP with the proposed removal of mandatory training program and certification for prescribers. However, it is noted that the sponsor will continue to provide access to prescriber training to support the education of prescribers. Physician education and Patient Information and Consent Agreement form are listed as additional risk minimisation measures in the AU-RMP and these materials should be appended to the AU-RMP. Further, the sponsor should ensure prescribers (and dispensers) are made aware of the availability of MS-2 Step training materials and how to access these.

Sponsor's response: The sponsor confirms that prescribers and dispenses will continue to be made aware of the availability of the MS-2 Step training materials and how to access them.

RMP evaluator comment: Noted. The Patient Information and Consent Agreement form is listed as an additional risk minimisation measure in the AU-RMP and the Educational program material will continue to be supplied - these materials should be appended to the AU-RMP.
The TGA requires that copies of Australian educational materials to be provided in Annex 3 of the Australia Specific Annex. Materials should be provided with content and intended layout, including images and graphic presentations of information. For digital additional risk minimisation tools, provide content and images of the onscreen layout of the information, and/or the login details or access codes to enable the TGA to evaluate the safety content in the format in which it is provided to the end user. In the absence of an ASA, the same requirement applies to the Australian RMP.
Additionally, the following revisions to V.2 Additional Risk Minimisation Measures are requested:

- Under 'Inclusion of Instruction Insert in Composite Pack Carton' remove text relating to the mandatory training program and certification for prescribers:

  "These arrangements are set up and are accessible via the Sponsor's secure healthcare professional website www.ms2step.com.au, or by calling the company directly. The Sponsor may change the restrictions on supply if in the future an effective control mechanism on prescriber access becomes possible via the PBS."
- Under 'Prescriber Training', specify availability via the website www.ms2step.com.au**.**

Recommendation 17: In Section 3.6 of the training manual provided in Succession 2, the sponsor should make the minor editorial change of "administration" to "administered"

Sponsor's response: In accordance with the response to Question 1 above, the Sponsor is proposing to remove the Medical Education Program from the RMP and therefore the training manual will not be provided as an attachment. The Sponsor however provides an assurance that the minor editorial change will be made to the training manual that will be available for all healthcare practitioners that prescribe MS-2 Step via the existing online website (www.ms2step.com.au).

RMP evaluator comment: As per the response above, the educational material will need to be provided as an attachment to the AU-RMP.

Recommendation 18: The advice on 24-hour phone service is also provided in the Consumer Medicine Information (CMI). The sponsor should submit the updated CMI to ensure consistent information in the RMP, Product Information (PI), and CMI.

Sponsor's response: The Consumer Medicine Information (CMI) and Product Information (PI) have been updated to remove the reference to the 24-hour phone service. A copy of the revised annotated and clean CMI and PI have been provided in Module 1.3.2 and 1.3.1 respectively.

RMP evaluator comment: Reference to the 24-hour phone service has been removed from the CMI and PI as requested.

Recommendation 19: This is a recommendation for the TGA delegate/clinical evaluator. The requirement for prescriber certification is included in the approved PI. The sponsor has advised that it will remove this requirement and submit the updated PI following the completion of round 1 evaluation. From the RMP perspective, assessing prescriber competencies is more related to clinical practice than to product risk management. Therefore, the removal of prescriber certification from the RMP is acceptable. It is recommended that the delegate/clinical evaluator considers the proposed PI change from the clinical perspective, and whether advisory committee advice is needed.
Sponsor's response: The Sponsor notes that this recommendation is for the TGA delegate / clinical evaluator. However, as previously proposed, the sponsor has updated the PI and CMI to remove the prescriber certification and has provided a copy of the annotated and clean CMI and PI in Module 1.3.2 and 1.3.1 respectively.
RMP evaluator comment: Noted.
Recommendation 20: This is a recommendation for the TGA delegate/clinical evaluator. The provision of 24-hour phone service for patients is included in the approved PI. The sponsor has advised that it will remove this service and submit updated PI following the completion of round 1 evaluation. It is noted that the PI also advises that 'patients must have the ability to access 24-hour emergency care'. This would ensure timely access to urgent medical attention and intervention. Therefore, the removal of 24-hour phone service is acceptable from the RMP perspective. It is recommended that the delegate/clinical evaluator considers the proposed PI change from the clinical perspective, in particular, whether and how much value the 24-hour phone service adds to patient safety outcomes.
Sponsor's response: As above, the Sponsor notes that this recommendation is for the TGA delegate / clinical evaluator. However, as previously proposed (and in accordance with the response to Question 19 above), the sponsor has updated the PI and CMI to remove the provision of the 24-hour phone service. A copy of the revised annotated and clean CMI and PI has been provided in Module 1.3.2 and 1.3.1 respectively.
RMP evaluator comment: Noted.

APPENDIX 1 – LIST OF ACRONYMS

AE	Adverse Event
ACM	Advisory Committee on Medicines
AU-RMP	Australian Risk Management Plan
CMI	Consumer Medicine Information
DLP	Data Lock Point
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
MHRA	Medicines & Healthcare Products Regulatory Agency
PI	Product Information
PMAB	Prescription Medicines Authorisation Branch
RMP	Risk Management Plan
SOSC	Summary of Safety Concerns
TGA	Therapeutic Goods Administration

Australian Government
Department of Health
Therapeutic Goods Administration

Risk Management Plan Evaluation Report

Mifepristone/ Misoprostol (MS-2-Step)

Submission No: PM-2022-05475-1-5

Sponsor: MS Health Pty Ltd

Updated RMP received: 01 December 2022

Sponsor's Response received: 13 January 2023

Succession 3 Report (round 1 for PM-2022-05475-1-5): 27 February 2023

Round 2 Report: 20 April 2023

Round 3 Report: 15 May 2023

TGA Health Safety Regulation

RISK MANAGEMENT PLAN EVALUATION REPORT

Submission type:	PI update (corresponding to RMP updates)
Sponsor:	MS Health Pty Ltd
Generic name:	**Mifepristone/ Misoprostol**
Trade name:	**MS-2-STEP**
Submission No; eSubmission ID:	PM-2022-05475-1-5; e004967
RMP file No:	2013/020378
TRIM reference:	D22-6199891
AU-RMP: *(EU-RMP not available)*	Initial - Version 0.4; dated 24 November 2022; DLP 31 May 2022 e004967 (0006-) - Risk management plan - Clean D22-6187939 Succession 2 - AU-RMP version 4.0 (dated 13 January 2023, DLP 31 May 2022) D23-5035315 Succession 3/Round 1 - AU-RMP version 4.0 (dated 17 February 2023, DLP 31 May 2022) D23-5140670 Round 2 – AU-RMP version 4.1 (dated 5 April 2023, DLP 31 May 2022) Round 3 - AU-RMP version 4.2 (dated 9 May 2023; DLP 31 May 2022)
Last evaluated AU-RMP:	Version 03; dated 13 November 2014; DLP 28 April 2013 R14/1181088
Date finalised:	15 May 2023 [Round 3/pre-ACM]
Referral to ACM:	To be considered by ACM on 1-2 June 2023 as part of the submission
Reason(s) for update:	New safety concern added Removed safety concern Pharmacovigilance milestone met Ceased risk minimisation activity Other:

SUMMARY

- On 1 December 2022, MS Health Pty Ltd submitted updated AU-RMP version 0.4 (dated 24 November 2022; DLP 31 May 2022) for MS-2 Step. The EU-RMP is not available. A revised AU-RMP version 4.0 (dated 13 January 2023; DLP 31 May 2022) was provided with the sponsor's response to RMP evaluator's recommendations dated 13 January 2023. On 20 February 2023, the sponsor submitted further changes in AU-RMP version 4.0 (dated 17 February 2023; DLP 31 May 2022) which has been linked to the Category 1, Type J application (PM-2022-05475-1-5). At Round 2, the sponsor submitted updated AU-RMP version 4.1 (dated 5 April 2023; DLP 31 May 2022) with their S31 response dated 6 April 2023. At Round 3, the sponsor provided an updated AU-RMP version 4.2 (dated 9 May 2023; DLP 31 May 2022) to address recommendations from Round 2.
- MS-2 Step is approved for the medical termination of an intrauterine pregnancy, up to 63 days of gestation, in females of childbearing age.
- The most recently evaluated and approved AU-RMP was version 03 (dated 13 November 2014; DLP 28 April 2013) (R14/1181088).
- The reason for this updated RMP is changes to the summary of safety concerns (SoSC) and changes to the risk minimisation plan. The key changes proposed for risk minimisation activities are as follows:
    - To remove the requirement for pharmacists to be registered to be able to dispense the product.
    - To remove the need for prescribers to complete mandatory training and receive certification to be able to prescribe the product and to remove the requirement for recertification training.
    - To remove the requirement for a Sponsor provided 24 hours aftercare service
- As the TGA has previously evaluated RMPs for this product, the focus of this review is on the differences between the AU-RMP versions and revisions to the additional risk minimisation materials.
- The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below:

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Infection, toxic shock syndrome	✓	–	✓	✓1,2
	Method failure	✓	–	✓	✓1,2
	Cardiac disorders	✓	–	✓	✓2
Important potential risks	Inadvertent pregnancy exposure and risk of incomplete abortion with severe bleeding	✓	–	✓	✓2
	Inadvertent pregnancy exposure (risk of malformations)	✓	–	✓	✓2
	Potential interaction with CYP3A4 inhibitors or inducers	✓	–	✓	–
	Potential interaction with products interacting with the glucocorticoid receptor	✓	–	✓	–
	Induced bronchial asthma	✓	–	✓	–
	Effects in lactating women	✓	–	✓	–
	Effects in women with impaired liver function	✓	–	✓	–
	Effects in women with impaired renal function	✓	–	✓	–

	Effects in women with malnutrition	✓	–	✓	–
	Incorrect determination of gestational age	✓	–	✓	–
	Potential for missed ectopic pregnancy	✓	–	✓	✓[2]
	Potential for postnatal developmental delay	✓	–	✓	–
	Potential for off-label use beyond the first trimester	✓	–	✓	–
	Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up	✓	–	✓	–
Missing information	Inherited porphyria	✓	–	–	–
	Theoretical interaction with NSAIDs	✓	–	–	–
	Potential interaction with products interacting with the progesterone receptor	✓	–	–	–
	Use in adolescents	✓	–	–	–
Pharmacological class effect	Risks related to the use of prostaglandin	✓	–	✓	✓[2]

[1] Black box warning
[2] Patient Information and Consent Agreement form

- The sponsor has updated the summary of safety concerns in line with recommendations by the RMP evaluator as well as to reflect up-to-date safety information for MS-2 Step. The summary of safety concerns is acceptable from an RMP perspective.
- The completed post marketing surveillance study has been removed from the pharmacovigilance plan. Routine pharmacovigilance is proposed for all safety concerns. There is one additional pharmacovigilance activity – an ongoing Canadian post-market surveillance study on the effectiveness and safety of combination mifepristone/misoprostol for medical abortion under 63 days gestation. The pharmacovigilance plan is acceptable from an RMP perspective.
- The sponsor proposes to remove from the risk minimisation plan the requirements for prescriber certification, pharmacist registration and a Sponsor-provided 24 hours aftercare service. Additional risk minimisation activities will consist of a black box warning, inclusion of CMI and instruction insert in pack, and Patient Information and Consent Agreement form. The sponsor will continue to make educational materials available as support to prescribers and dispensers. The proposed risk minimisation plan aligns with that in Canada. The RMP evaluator has noted the post-market experience with MS-2 Step, its well-established safety profile, and existing safety frameworks in place. The RMP evaluator has also noted the importance of timely access of this medicine in terms of patient-safety and the need to remove requirements that hinder patient access to reproductive services. The proposed changes to the risk minimisation plan are acceptable from an RMP perspective. Referral to ACM for advice on the changes to risk minimisation activities has been sought.

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1. OUTCOME OF THE EVALUATION

1.1. RECOMMENDATIONS TO THE SPONSOR – ROUND 3

The updated AU-RMP version 4.2 (dated 9 May 2023; DLP 31 May 2022) has been considered.

The recommendations made in the initial evaluation and Round 1, along with consideration of the sponsor response, are located in Section 6.1 and 6.2 respectively.

The recommendations made in Round 2, along with consideration of the sponsor response, are located in Section 7.1.

The sponsor has accepted all recommendations made by the RMP evaluator. There are no new or outstanding recommendations for the sponsor.

The delegate has sought ACM advice regarding the removal of the requirement for prescriber certification and the removal of 24-hour phone service for patients.

1.2. WORDING FOR CONDITIONS OF REGISTRATION

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> *The MS-2 STEP Australian Risk Management Plan (AU-RMP) (version 4.2, dated 9 May 2023, data lock point 31 May 2022), included with submission PM-2022-05475-1-5, to be revised to the satisfaction of the TGA, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*

As there will be substantial changes to the risk minimisation measures, routine submission of PSURs is requested. The following wording is recommended for the PSUR requirement:

> *An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).*
>
> *Reports are to be provided in line with the current published list of EU reference dates* ***no less frequently than annually*** *until the period covered by such reports is not less than three years from the date of this approval letter.*
>
> *The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII- periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.*

1.3. ADVICE TO THE DELEGATE

Recommendations 19 and 20 from Round 1 are for the TGA delegate/clinical evaluator:

Recommendation 19. This is a recommendation for the TGA delegate/clinical evaluator. The requirement for prescriber certification is included in the approved PI. The sponsor has advised that it will remove this requirement and submit the updated PI following the completion of round 1 evaluation. From the RMP perspective, assessing prescriber competencies is more related to clinical practice than to product risk management. Therefore, the removal of prescriber certification from the RMP is acceptable. It is recommended that the delegate/clinical evaluator considers the proposed PI change from the clinical perspective, and whether advisory committee advice is needed.

Recommendation 20. This is a recommendation for the TGA delegate/clinical evaluator. The provision of 24-hour phone service for patients is included in the approved PI. The sponsor has advised that it will remove this service and submit updated PI following the completion of round 1 evaluation. It is noted that the PI also advises that 'patients must have the ability to access 24-hour emergency care'. This would ensure timely access to urgent medical attention and intervention. Therefore, the removal of 24-hour phone service is acceptable from the RMP perspective. It is recommended that the delegate/clinical evaluator considers the proposed PI change from the clinical perspective, in particular, whether and how much value the 24-hour phone service adds to patient safety outcomes.

The sponsor has provided a response to these (see in Section 6.2).

2. BACKGROUND

- On 1 December 2022, MS Health Pty Ltd submitted updated AU-RMP version 0.4 (dated 24 November 2022; DLP 31 May 2022) for MS-2 Step. The EU-RMP is not available. The sponsor provided revised Education Program material (included as Appendix 1) with this submission. A revised AU-RMP version 4.0 (dated 13 January 2023; DLP 31 May 2022) was provided with the sponsor's response to RMP evaluator's recommendations dated 13 January 2023. On 20 February 2023, the sponsor submitted further changes in AU-RMP version 4.0 (dated 17 February 2023; DLP 31 May 2022) which has been linked to the Category 1, Type J application (PM-2022-05475-1-5). At Round 2, the sponsor submitted updated AU-RMP version 4.1 (dated 5 April 2023; DLP 31 May 2022) with their S31 response dated 6 April 2023. At Round 3, the sponsor provided an updated AU-RMP version 4.2 (dated 9 May 2023; DLP 31 May 2022) to address recommendations from Round 2.
- MS-2 Step is approved for the medical termination of an intrauterine pregnancy, up to 63 days of gestation, in females of childbearing age.
- The most recently evaluated and approved AU-RMP was version 03 (dated 13 November 2014; DLP 28 April 2013) (R14/1181088).
- The reason for this updated RMP is changes to the summary of safety concerns (SoSC) and changes to the risk minimisation plan. The key changes proposed are as follows:
  - To remove the requirement for pharmacists to be registered to be able to dispense the product.
  - To remove the need for prescribers to complete mandatory training and receive certification to be able to prescribe the product and to remove the requirement for recertification training.
  - To remove the requirement for a Sponsor provided 24 hours aftercare service
- This RMP update is linked to the Category 1, Type J application (PM-2022-05475-1-5) that is currently under evaluation due to accompanying changes warranted to the Australian Product Information to support the proposed changes to the risk minimisation plan.
- As the TGA has previously evaluated RMPs for this product, the focus of this review is on the differences between the AU-RMP versions and revisions to the additional risk minimisation materials.

3. CHANGES TO THE SUMMARY OF SAFETY CONCERNS AND PHARMACOVIGILANCE/RISK MINIMISATION ACTIVITIES

At Round 3, the changes to safety concerns and/or activities proposed since the previous RMP evaluation of AU-RMP Version 03 (dated 13 November 2014; DLP 28 April 2013) are presented in the table below (~~Strikethrough~~ text indicates risks that have been removed and **bold** text indicates new/changed risks):

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	~~Bleeding~~	~~✓~~	~~1~~	~~✓~~	~~✓2,3,4,5,6~~
	Infection, toxic shock syndrome	✓	1	✓	✓2,3~~,4, 5,6~~
	Method failure	✓	1	✓	✓2,3~~,4, 5,6~~
	~~Uterine contractions / cramping~~	~~✓~~	~~1~~	~~✓~~	~~✓3,5,6~~

	~~Uterine infection (endometritis, pelvic inflammatory disease)~~	~~✓~~	~~–[1]~~	~~✓~~	~~✓[3,5,6]~~
	~~Nausea, vomiting~~	~~✓~~	~~–[1]~~	~~✓~~	~~✓[3,5,6]~~
	~~Diarrhoea~~	~~✓~~	~~–[1]~~	~~✓~~	~~✓[3,5,6]~~
	~~Hypotension~~	~~✓~~	~~–[1]~~	~~✓~~	~~✓[3,5,6]~~
	~~Skin rashes, urticarial~~	~~✓~~	~~–[1]~~	~~✓~~	~~✓[3,5,6]~~
	Cardiac disorders	✓	–[1]	✓	✓[3,~~5,6~~]
Important potential risks	Inadvertent pregnancy exposure and risk of incomplete abortion with severe bleeding	✓	–	✓	✓[3,~~5,6~~]
	Inadvertent pregnancy exposure (risk of malformations)	✓	–	✓	✓[3,~~5,6~~]
	Potential interaction with CYP3A4 inhibitors or inducers	✓	–	✓	~~✓[6]~~
	Potential interaction with products interacting with the glucocorticoid receptor	✓	–	✓	~~✓[6]~~
	~~Severe asthma uncontrolled by treatment~~ **Induced bronchial asthma**	✓	–	✓	~~✓[6]~~
	Effects in lactating women	✓	–	✓	~~✓[6]~~
	Effects in women with impaired liver function	✓	–	✓	~~✓[6]~~
	Effects in women with impaired renal function	✓	–	✓	~~✓[6]~~
	Effects in women with malnutrition	✓	–	✓	~~✓[6]~~
	Incorrect determination of gestational age	✓	–	✓	~~✓[6]~~
	Potential for missed ectopic pregnancy	✓	–	✓	✓[3,~~5,6~~]
	Potential for postnatal developmental delay	✓	–	✓	–
	Potential for off-label use beyond the first trimester	✓	–	✓	~~✓[6]~~
	~~Potential for loss to follow-up~~	~~✓~~	~~–~~	~~✓~~	~~–~~
	Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up	✓	–	✓	–
Missing information	Inherited porphyria	✓	–	–	–
	Theoretical interaction with NSAIDs	✓	–	–	–
	Potential interaction with products interacting with the progesterone receptor	✓	–	–	–
	Use in adolescents	✓	–	–	–
Pharmacological class effect	Risks related to the use of prostaglandin	✓	–	✓	✓[3,~~5,6~~]

[1] ~~Post-marketing surveillance study~~ (completed)
[2] Black box warning
[3] Patient Information and Consent Agreement form
[4] ~~Optional SMS follow-up text message~~
[5] ~~24-hour nurse after-care call service~~
[6] ~~Physician education~~

A clean SOSC table is provided below:

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Infection, toxic shock syndrome	✓	–	✓	✓[1,2]
	Method failure	✓	–	✓	✓[1,2]
	Cardiac disorders	✓	–	✓	✓[2]
Important potential risks	Inadvertent pregnancy exposure and risk of incomplete abortion with severe bleeding	✓	–	✓	✓[2]
	Inadvertent pregnancy exposure (risk of malformations)	✓	–	✓	✓[2]
	Potential interaction with CYP3A4 inhibitors or inducers	✓	–	✓	–
	Potential interaction with products interacting with the glucocorticoid receptor	✓	–	✓	–
	Induced bronchial asthma	✓	–	✓	–
	Effects in lactating women	✓	–	✓	–
	Effects in women with impaired liver function	✓	–	✓	–
	Effects in women with impaired renal function	✓	–	✓	–
	Effects in women with malnutrition	✓	–	✓	–
	Incorrect determination of gestational age	✓	–	✓	–
	Potential for missed ectopic pregnancy	✓	–	✓	✓[2]
	Potential for postnatal developmental delay	✓	–	✓	–
	Potential for off-label use beyond the first trimester	✓	–	✓	–
	Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up	✓	–	✓	–
Missing information	Inherited porphyria	✓	–	–	–
	Theoretical interaction with NSAIDs	✓	–	–	–
	Potential interaction with products interacting with the progesterone receptor	✓	–	–	–
	Use in adolescents	✓	–	–	–
Pharmacological class effect	Risks related to the use of prostaglandin	✓	–	✓	✓[2]

[1] Black box warning
[2] Patient Information and Consent Agreement

3.1. SUMMARY OF CHANGES TO THE SOSC – INITIAL EVALUATION

In the AU-RMP version 0.4 (dated 24 November 2022; DLP 31 May 2022) for MS-2 Step, the following new safety concerns have been added to the SoSC to align with the Canadian RMP (e004967 (0009-) - Attachment 1 - Canadian RMP) and the PI:

- important identified risk - cardiac disorders
- important potential risk - incorrect determination of gestational age

3.2. RMP EVALUATOR COMMENTS/ RECOMMENDATIONS ON THE SOSC – INITIAL EVALUATION

The Canadian RMP (dated 27 August 2020) was used as the reference RMP in the sponsor's Periodic Benefit-Risk Evaluation Report (PBRER) for mifepristone and misoprostol combipack presentations, covering 01 June 2021 to 31 May 2022 (D22-6031778). The SoSC in the current Canadian RMP:

Identified risk:	Method failure Infection Toxic shock syndrome Cardiac disorders
Potential risk:	Inadvertent risk of pregnancy Induced bronchial asthma Incorrect determination of gestational age Complication arising from the use in undiagnosed ectopic pregnancy
Missing information:	Pregnant and lactating subjects Paediatric patients Geriatric patients Patients with Renal, Hepatic or Cardiac Impairment Off Label use

There are significant differences between the Canadian and Australian RMP.

In the AU-RMP version 0.4 (dated 24 November 2022; DLP 31 May 2022) for MS-2 Step, the below differences with the Canadian RMP (dated 27 August 2020) remain:

- Potential risks: induced bronchial asthma (in contrast with severe asthma uncontrolled by treatment), complication arising from the use in undiagnosed ectopic pregnancy.
- Missing information: patients with renal, hepatic or cardiac impairment.

Potential risk of 'complication arising from the use in undiagnosed ectopic pregnancy' is considered to be captured by 'Potential for missed ectopic pregnancy' included in the AU-RMP. This is satisfactory.

Missing information of 'patients with renal, hepatic or cardiac impairment' is in part captured by potential risks 'Effects in women with impaired liver function' and 'Effects in women with impaired renal function'. Given the classification of cardiac disorders as an important identified risk, and associated warnings in the PI to use with caution in women with risk factors for cardiovascular disease or established cardiovascular disease, this is satisfactory.

Use in pregnant subjects is not listed in the AU-RMP as missing information. This is satisfactory.

The sponsor should be asked to provide reasons on the difference in potential risk of 'induced bronchial asthma' vs 'severe asthma uncontrolled by treatment'.

The sponsor should also be reminded to routinely review the safety concerns in the AU-RMP to ensure it reflects up-to-date safety information. Taking into account the product's reasonable marketing experience (as single ingredient and as combination pack), as well as the fact no additional pharmacovigilance activity is planned to further characterise the risks, the sponsor should evaluate whether any safety concerns can be removed. Further, in the absence of an EU-RMP, any changes to international RMPs should be assessed to determine whether similar updates are warranted in Australia.

The sponsor is requested to provide a description of the process for maintenance of the AU-RMP (e.g. standard operating procedure document).

3.3. Summary of key changes to Safety Specification - Succession 2 & 3 (Round 1)

Changes from AU RMP version 03 to version 4.0	RMP evaluator comment
Removed the following important identified risks: • Bleeding • Contractions / cramping • Uterine infection • Nausea and vomiting • Diarrhoea • Hypotension • Skin rashes / urticaria	This aligns with the Canadian RMP.
Important potential risk "Severe asthma uncontrolled by treatment" changed to "Induced bronchial asthma"	This aligns with the Canadian RMP.

There were no further changes to the safety specification between AU-RMP version 4.0 (dated 13 January 2023; DLP 31 May 2022) and AU-RMP version 4.0 (dated 17 February 2023; DLP 31 May 2022).

The sponsor has noted that AU-RMP also has further potential risks that are not included in the Canadian RMP, or risks that are presented slightly differently.

3.4. RMP Evaluator comments/ recommendations on the SoSC – Succession 2 & 3 (Round 1)

The summary of safety concerns is considered acceptable from an RMP perspective.

It is acknowledged that the sponsor has committed to ensuring that any future changes that are made to Canadian RMP will be assessed to determine whether the same updates are also warranted in Australia.

The updated RMP version 4.0 (dated 17 February 2023) submitted by the sponsor has the same version number with a different date from version 4.0 (dated 13 January 2023). To avoid confusion, for future submissions, the sponsor should update the version number and date for each revision.

3.5. Summary of key changes to Safety Specification – Round 2

Changes from AU RMP version 4.0 to 4.1	RMP evaluator comment
Removed important potential risks 'Potential for loss to follow-up'	This aligns with the Canadian RMP. Given there are no additional pharmacovigilance activities and additional risk minimisation activities to specifically address these safety concerns, and the importance of follow-up is well described in the PI and CMI, this is acceptable.
Removed important potential risks 'Potential safety risks in vulnerable groups including women in	This should remain in the SOSC as there are additional considerations to this risk with regards

regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up'	to access to further advice or treatment if follow-up does not occur.

3.6. RMP Evaluator comments/ recommendations on the SoSC – Round 2

The potential risk 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up' should remain in the SOSC as there are additional considerations to this risk with regards to access to further advice or treatment if follow-up does not occur.

Further, it is noted that this safety concern is not discussed in the PSUR, which uses the Canadian RMP as the reference document. It is requested that the sponsor provide an assessment of this safety concern with the PSUR submission expected August 2023. This assessment may serve to support the removal of this safety concern (can be submitted as an RMP update).

3.7. RMP Evaluator comments/ recommendations on the SoSC – Round 3

The Sponsor has amended the RMP to reinsert the potential risk 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up'. Additionally, the Sponsor provides and assurance that an assessment of this safety concern will be provided with the next PSUR submission which is expected in August.

The summary of safety concerns is considered acceptable from an RMP perspective.

4. PHARMACOVIGILANCE PLAN

4.1. Summary of changes to the pharmacovigilance plan – Initial evaluation

The post marketing surveillance study of use of mifepristone/mifepristol for early medical abortion within MSIA clinics is now completed. Section III.2 and Section SIII has been updated to capture this.

4.2. RMP Evaluator comments/ recommendations on pharmacovigilance plan – Initial evaluation

Information regarding the study should be removed from the pharmacovigilance plan in the RMP since final study report/results have been submitted to the TGA for assessment. The study should also be deleted as an additional pharmacovigilance activity in Section V.3 in AU-RMP.

4.3. Summary of changes to the pharmacovigilance plan – Succession 2 & 3 (Round 1)

The completed study has been removed from the pharmacovigilance plan in the updated AU RMP, as requested.

There were no changes to pharmacovigilance plan submitted in Succession 3.

4.4. RMP Evaluator comments/ recommendations on pharmacovigilance plan – Succession 2 & 3 (Round 1)

There are no additional pharmacovigilance activities in the AU RMP. It is noted that the Canadian RMP includes a planned Canadian-specific post-market study:

Safety Concern	Additional activity	Proposed actions/ outcomes	Planned submission date
		Planned studies	
Method failure, Infection, toxic shock syndrome, cardiac disorders, Inadvertent risk of pregnancy, induced bronchial asthma, incorrect determination of gestational age, Potential for missed ectopic pregnancy	**Canadian Phase IV study**	**A Phase IV Multi-Centre Prospective Study on the Safety of Combination Mifepristone/Misoprostol for Medical Abortion Under 63 Days Gestation Among Canadian Women** **Primary objective: To determine rate of surgical aspiration, for any reason, within 21 days following medical abortion with combination mifepristone/misoprostol**	**TBD**

The findings from the above study are applicable to Australia and should be included in the AU-RMP. The sponsor should include planned submission dates of study reports.

When available a revised RMP which considers the completed study outcomes should be submitted to the TGA for review.

4.5. Summary of changes to the pharmacovigilance plan – Round 2

The sponsor has included information on the ongoing Canadian Phase IV study in Section III.2 of the AU-RMP, as requested.

4.6. RMP Evaluator comments/ recommendations on pharmacovigilance plan – Round 2

The ongoing Canadian post-market surveillance study should also be added to the tables in Section III.3 (Table 10) and V.3 (Summary of risk minimization measures) as appropriate. Refer to the Canadian RMP to identify the safety concerns that will be addressed by this additional pharmacovigilance activity.

It is acknowledged that the sponsor commits to submitting a revised RMP that considers completed study outcomes to the TGA when available. The sponsor should submit key findings from the study as an accompanying document. The full study report is only required upon TGA's request.

The annotated AU-RMP version 4.1 (dated 5 April 2023) tracks all changes since the approved version 03 (dated 13 November 2014) i.e. marks changes from version 0.4 to the two

subsequent versions 4.0 to version 4.1. To avoid confusion and for ease of evaluation, annotated documents should only track the changes made since the last submitted version.

4.7. RMP EVALUATOR COMMENTS/ RECOMMENDATIONS ON PHARMACOVIGILANCE PLAN – ROUND 3

The sponsor has amended the RMP to include the Canadian post-market surveillance study in Sections V.3. The sponsor has not included this study in Section III.3, table 10, as this study is not an imposed or required additional pharmacovigilance activity. It is noted that the study details are included in the previous section III.2. This is acceptable.

The sponsor will provide key findings from the Canadian postmarket surveillance study as an accompanying document when available.

The pharmacovigilance plan is considered acceptable from an RMP perspective.

5. RISK MINIMISATION PLAN

5.1. SUMMARY OF CHANGES TO THE RISK MINIMISATION PLAN – INITIAL EVALUATION

The sponsor proposes to remove from the risk minimisation plan:

- the requirement for pharmacist registration to dispense the product
- the requirement for re-certification training for prescribers.

5.2. RMP EVALUATOR COMMENTS/ RECOMMENDATIONS ON THE RISK MINIMISATION PLAN – INITIAL EVALUATION

Detailed evidence/justification to support these proposals have not been provided. The sponsor should provide discussion on:

- additional risk minimisation activities in other countries where MS-2 Step is available compared to Australia
- any safety concerns on the removal of pharmacist registration and prescriber re-certification
- number/percentage of pharmacies registered to dispense MS-2 Step in Australia
- any reports on evaluation of effectiveness of additional risk minimisation activities

Given the reasonable worldwide marketing experience with mifepristone and mifepristol (IBD 28 June 1984 for misoprostol, 29 December 2010 for mifepristone, and MS-2 Step first registered in Australia 04 June 2014), the safety profile is considered well established. Clinical practice and understanding, along with the other additional risk minimisation activities in place, are likely adequate to manage the risks. It is acknowledged that the timeliness of access is essential and corresponds to effectiveness of the product. Final decision on the proposed changes to the risk minimisation plan will be made after review of the sponsor's response.

The sponsor has proposed that 'once registered and certified no re-registration or re-certification is required' for prescribers. It is assumed that this re-certification refers to the periodic renewal of the certificate for the purpose of knowledge maintenance. The sponsor

should provide clarification in the RMP on whether and how it plans to inform prescribers of the updated safety information when new evidence becomes available.

The sponsor has stated under 'Restricted Access to MS-2-Step' that the program is to ensure that 'distribution of MS-2-Step is controlled and monitored. With the proposed removal of pharmacist registration, the sponsor should clarify how this is achieved. The sponsor should note, according to the EMA GVP Module XVI, controlled distribution and controlled access programs are different measures that serve different purposes[1].

Further, the sponsor should amend Section V.3 Summary (table) of risk minimisation measures as follows:

- Completed post-marketing surveillance study is still listed as an additional pharmacovigilance activity – this should be removed from the table
- 'Special attention in PSURs' was listed as an additional pharmacovigilance activity – this is considered part of routine pharmacovigilance.
- 'Physician education' is not described as an additional risk minimisation activity for potential risks: Potential interaction with CYP3A4 inhibitors or inducers, Potential interaction with products interacting with the glucocorticoid receptor, Severe asthma uncontrolled by treatment, Incorrect determination of gestational age – this should be revised accordingly
- 'Potential for loss to follow up' is not included – this should be added for completeness

5.3. SUMMARY OF CHANGES TO THE RISK MINIMISATION PLAN – SUCCESSION 2 & 3

The sponsor has submitted additional changes to the risk minimisation plan in AU-RMP version 4.0 (dated 17 February 2023; DLP 31 May 2022). In summary, the following changes to the risk minimisation plan are proposed (new in **bold**):

- To remove the requirement for pharmacists to be registered to be able to dispense the product.
- To remove the requirement for prescriber recertification.
- **To remove the requirement for prescribers to complete mandatory training and receive certification to be able to prescribe the product.**
- **To remove the requirement for a Sponsor provided 24 hours aftercare service**

As the requirement for prescriber certification and 24-hour phone service are included in the PI, the sponsor has advised that it will remove these and submit the updated PI following the completion of round 1 evaluation[2].

The sponsor states that this would align the MS-2 Step RMP with the expectations of RMPs of the majority of medicines registered with the TGA, and with expectations around prescriber competency for a medicine that has been in-market for many years with hundreds of thousands

[1]EMA Guideline on good pharmacovigilance practices Module XVI, dated 28 March 2017, EMA/204715/2012 Rev 2, https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-xvi-risk-minimisation-measures-selection-tools_en-3.pdf
[2] e004967 (0009-) - Cover Letter - 2023-02 Cat 1, Type J, RMP

Australian women having been prescribed MS-2 Step since it was first registered over 8 years ago.

The information in the AU-RMP regarding restricted distribution has been deleted with the proposed removal of mandatory training program and certification for prescribers.

5.4. RMP EVALUATOR COMMENTS/ RECOMMENDATIONS ON THE RISK MINIMISATION PLAN – SUCCESSION 2 & 3 (ROUND 1)

The Sponsor has amended Section V.3 Summary of risk minimisation measures (table) in accordance with the above requested changes. However, further changes are required:

- Identified risk 'Cardiac disorders' is missing and needs to be added
- Potential risks 'Incorrect determination of gestational age' and 'Potential for loss to follow-up' are missing and need to be added

Additionally, the sponsor should make the below changes to Table 11 in Section V.1:

- Remove 'physician education' as a routine risk minimisation measure as this is considered additional risk minimisation
- Potential risks 'Potential for off-label use beyond the first trimester' and 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up' are missing and need to be added

Misoprostol was first approved in Australia on 7 July 1993, mifepristone on 29 August 2012 and MS-2 Step was registered on 4 June 2014. Given the post-market experience with MS-2 Step in Australia and worldwide, the product's safety profile is well-established. Safety concerns in the SOSC have been removed with this AU-RMP update, which still includes additional potential risks to the Canadian RMP.

Furthermore, it is reasonable to expect that prescribers and dispensers have a level of clinical knowledge of MS-2 Step, or be able to refer to resources available (e.g. the PI) to ensure safe and effective use as like any other medicine. The sponsor will also continue to make the MS-2 Step training materials available to both prescribers and dispensers so that skill levels can be maintained. The patient information and consent form should continue to be implemented.

The sponsor has informed that based on the latest available data in 2020, less than 20% of pharmacists are registered in Australia to dispense MS-2 Step (see Section 6.1, Recommendation 6). As indicated, this presents a patient-safety risk of delayed access to medication, particularly in regional and rural areas as well as for patients whose gestation is approaching the upper limit of MS-2 Step's registered indication.

It is noted that in Australia, there is a government funded service available - healthdirect hotline – which provides 24-hour/7-day health advice from a registered nurse. Moreover, distribution of MS-2 Step will be tracked via general pathways of PBS Authority prescription and PBS dispensing and safety concerns will continue to be monitored by the sponsor under routine pharmacovigilance and reported as necessary as specified in Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements. The sponsor may also be requested to provide a PSUR to the TGA at any time.

The sponsor has pointed out that internationally, in Canada, since 2017 registration of health professionals with Celopharma is no longer required in order to prescribe or dispense Mifeqymiso[3]. The sponsor states no adverse safety signals or additional risk minimisation activities identified in Canada with this change to a broader access regimen. It was noted in the Canadian Monograph for Mifeqymiso[4], it is stated that "*Mifegymiso should be prescribed by health professionals with adequate knowledge of medical abortion and/**or** who have completed a Mifegymiso education program*".

The RMP evaluator has noted the need to remove requirements that hinder patient access to reproductive services. The evaluator has also noted different risk mitigation strategies employed by different comparable overseas regulators.

The US FDA has reviewed and finalised the Risk Evaluation and Mitigation Strategies (REMS) for mifepristone on 3 January 2023. The REMS lists 'requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program' as a goal of the REMS[5].

The RMP evaluator has noted that the advice on 24-hour phone service is also provided in the Australian Consumer Medicine Information (CMI). The sponsor should submit the updated CMI to ensure consistent information in the RMP, PI, and CMI.

The requirement for prescriber certification is included in the Australian Product Information (PI). The sponsor has advised that it will remove this requirement and submit the updated PI following the completion of round 1 evaluation. From the RMP perspective, assessing prescriber competencies is more related to clinical practice than to product risk management. Therefore, the removal of prescriber certification from the RMP is acceptable. It is recommended that the delegate/clinical evaluator considers the proposed PI change from the clinical perspective, and whether advisory committee advice is needed.

The provision of 24-hour phone service for patients is included in the PI. The sponsor has advised that it will remove this service and submit updated PI following the completion of round 1 evaluation. It is noted that the PI also advises that 'patients must have the ability to access 24-hour emergency care'. This would ensure timely access to urgent medical attention and intervention. Therefore, the removal of 24-hour phone service is acceptable from the RMP perspective. It is recommended that the delegate/clinical evaluator considers the proposed PI change from the clinical perspective, in particular, whether and how much value the 24-hour phone service adds to patient safety outcomes.

5.5. RMP EVALUATOR COMMENTS/ RECOMMENDATIONS ON THE RISK MINIMISATION PLAN – ROUND 2

At Round 2, the sponsor confirms that the existing standardised training (the Medical Education Program) will still be available for all healthcare practitioners and prescribers and

[3] MIFEGYMISO (mifepristone and misoprostol tablets) - Updates to Product Monograph and Risk Management Plan, accessed 23 February 2023, MIFEGYMISO (mifepristone and misoprostol tablets) - Updates to Product Monograph and Risk Management Plan - Canada.ca
[4] MIFEGYMISO (mifepristone and misoprostol tablets) Canadian Product Monograph, accessed 23 February 2023, 00050659.PDF (hres.ca)
[5] US FDA approved REMS for mifepristone, accessed on 24 February 2023, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390

dispensers will be made aware on how to access them via the existing online website (www.ms2step.com.au).

The proposed changes to the risk minimisation plan to remove pharmacist registration, prescriber certification and the Sponsor provided 24 hours aftercare service are considered acceptable from an RMP perspective for the reasons discussed above. The PI and CMI have been updated to reflect the proposed changes to the risk minimisation plan.

As requested at Round 1, the Patient Information and Consent Agreement form and the Educational program materials should be appended to the AU-RMP. The Educational program is still part of the RMP, and the sponsor should provide the educational materials - see TGA RMP guidance Section 5.3. From RMP perspective, the educational materials continue to be provided to prescribers and it is our expectation that prescribers will undergo the training. The sponsor needs to include educational materials in track changed version to show any update since the last time RMP was evaluated.

The sponsor is requested to make further changes to the risk minimisation plan, as follows:

- Include potential risk 'incorrect determination of gestational age' in Section V.3 Summary of risk minimization measures (table; page 38) in the AU-RMP
- Add potential risk 'Potential for off-label use beyond the first trimester' to Table 11 in Section V.1 of the AU-RMP
- Append the educational materials and the Patient Information and Consent Agreement form to the AU-RMP
- In Section V.2 Additional Risk Minimisation Measures
    - Under 'Inclusion of Instruction Insert in Composite Pack Carton', remove text relating to the mandatory training program and certification for prescribers:

      "These arrangements are set up and are accessible via the Sponsor's secure healthcare professional website www.ms2step.com.au, or by calling the company directly. The Sponsor may change the restrictions on supply if in the future an effective control mechanism on prescriber access becomes possible via the PBS."
    - Under 'Prescriber Training', specify availability via the website www.ms2step.com.au

5.6. RMP Evaluator comments/ recommendations on the risk minimisation plan – Round 2

The Sponsor has satisfactorily amended the RMP in accordance with the above requested changes including appending the Educational Program materials and Patient Information Sheet - Consent form to the AU-RMP.

The delegate has sought ACM advice regarding the removal of the requirement for prescriber certification and the removal of 24-hour phone service for patients.

5.7. RMP EVALUATOR COMMENTS/ RECOMMENDATIONS OF ADDITIONAL RISK MINIMISATION ACTIVITIES

Additional risk minimisation activities consist of a black box warning, inclusion of CMI and instruction insert in pack, Patient Information and Consent Agreement, and prescriber educational materials (as supportive resources; non-mandatory training).

This is considered sufficient based on the above discussion from an RMP perspective.

5.8. PRODUCT LABELLING

5.8.1. Product Information

The sponsor should confirm whether the new data from the completed post-market surveillance study study added to Section SIII (Clinical trial exposure) of the AU-RMP version 0.4 (and Section 3.6 of Annex 1.1) will be added to the Australian PI:

> *In an observational cohort study of 15 008 women attending one of 16 Marie Stopes International clinics in Australia for MTOP (gestational age ≤ 63 days) between 1 March 2013 and 30 September 2015, patients were **administered** 200 mg mifepristone orally in-clinic, followed 24- 48 hours later by 800 micrograms of misoprostol buccally, self-administered at home. Method success was defined as complete abortion not requiring surgical intervention. Follow up information was available for 13,078 (87.2%) of the total cohort. Medical abortion was successful in 95.16% (12,445/13,078) of women with follow-up. Higher patient and gestational ages were associated (P < 0.001) with a slight increase in method failure. There were 674 serious adverse events (5.15%), mainly due to method failure. Infection (15; 0.11%) and haemorrhage (17; 0.13%) were rare. One death was recorded (<0.01%); however, an association between EMA and cause of death, necrotising pneumonia, was not established.*

Moreover, the sponsor should make a minor editorial change (in ***bold***).

Succession 2 update

The sponsor has confirmed in their response that the Australian PI will be updated with the completed post-market surveillance study data as part of the next submitted Category 1, Type J application (see Section 6.1, Recommendation 4).

5.8.2. Consumer Medicine Information

The sponsor should ensure any PI updates are captured in the CMI where applicable.

The CMI along with the instruction insert will be included in the pack.

5.9. ADDITIONAL RISK MINIMISATION MATERIALS

The sponsor submitted revised Educational Program material (with tracked changes) with the AU-RMP update submission (as Annex 1; D22-6187939). There were mostly editorial changes to reflect current approved indication and current practices, as well as inclusion of current post marketing data. Of note, the refresher materials have been removed from the package.

In the training manual (Annex 1.1), the sponsor included interim information regarding a pending TGA application to remove PI precautions regarding rhesus alloimmunisation to align

with current Australian and International guidelines. It was recommended that the sponsor only incorporate advice that has been approved.

Succession 2&3 (Round 1) update

At Succession 2, the sponsor had submitted an updated training manual with the requested changes with their response.

At Succession 3, the Educational program material has been removed from the AU-RMP with the proposed removal of mandatory training program and certification for prescribers. However, it is noted that the sponsor will continue to provide access to prescriber training to support the education of prescribers. Physician education and Patient Information and Consent Agreement are listed as additional risk minimisation measures in the AU-RMP and these materials should be appended to the AU-RMP. Further, the sponsor should ensure prescribers (and dispensers) are made aware of the availability of MS-2 Step training materials and how to access these.

The sponsor should make the minor editorial change to Section 3.6 of the training manual to amend "administration" to "administered" (see Section 5.5.1).

Round 3 update

The Educational Program materials and Patient Information Sheet - Consent form has been appended to the AU-RMP. The training manual and slide deck has been edited to remove references to prescriber certification and the 24-hour aftercare service. This is acceptable.

6. EVALUATION OF SPONSOR RESPONSE

6.1. RECONCILIATION OF RECOMMENDATIONS SENT 13 DECEMBER 2022

The sponsor's response, dated 13 January 2023, can be found on

TRIM D23-5035315

docuBridge e004967 (0008-) - Response - 2023-01 Response to RFI

The sponsor has provided and updated AU-RMP version 4.0 (dated 13 January 2023, DLP 31 May 2022) with their response.

Recommendation 1: The sponsor is requested to provide reasons on the difference in potential risk of 'induced bronchial asthma' vs 'severe asthma uncontrolled by treatment'.
Sponsor's response: The Sponsor proposes to update the potential risk of 'severe asthma uncontrolled by treatment' to 'induced bronchial asthma'. As currently detailed in the AU-RMP, bronchospasm may occur with some prostaglandins and prostaglandin analogues. The possibility should be borne in mind in patients with a history of asthma. *The potential risk 'induced bronchial asthma' is currently included in the Canadian RMP and is targeted for review and safety surveillance as part of the annual PBRER (reports of induced bronchial asthma are identified using a prespecified list of preferred terms in MedDRA version 16.0).* *A copy of the proposed updated AU-RMP has been provided in Module 1.8.*
RMP evaluator comment: The important potential risk of 'severe asthma uncontrolled by treatment' has been replaced with 'induced bronchial asthma' in line with Canadian RMP in the updated AU-RMP. This is acceptable.

Recommendation 2: The sponsor is requested to provide a description of the process for maintenance of the AU-RMP (e.g. standard operating procedure document).

In accordance with the guidance on *Risk management plans for medicines and biologicals* throughout the lifecycle of the product, RMPs must be maintained to incorporate new safety information. Any significant updates are required to be submitted to the TGA for evaluation within a timely manner. In accordance with the *Pharmacovigilance Guidelines*, sponsors should have processes in place (with well-defined responsibilities, requirements and timelines) to ensure they comply with their post-approval commitments.

Further, the sponsor is reminded to routinely review the safety concerns in the AU-RMP to ensure it reflects up-to-date safety information. Taking into account the product's reasonable marketing experience (as single ingredient and as combination pack), as well as the fact no additional pharmacovigilance activity is planned to further characterise the risks, the sponsor should evaluate whether any safety concerns can be removed. Further, in the absence of an EU-RMP, any changes to international RMPs should be assessed to determine whether similar updates are warranted in Australia.

Sponsor's response: The maintenance of the AU-RMP is managed via agreements in place with their supplier (Linepharma International Limited). Specifically, the Safety Data Exchange Agreement (SDEA) held between MS Health Pty Ltd and Linepharma International Limited (supplier)includes the responsibilities relating to the AU-RMP. The SDEA specifies that the supplier coordinates an update to the RMP if a significant safety signal is detected, including immediate notification to MS Health of any significant safety issues. Following the receipt of a notification of a significant safety issue from the supplier, MS Health is then responsible for preparation and maintenance of the AU-RMP including any required submission to TGA (according to TGA guidelines including any specified timelines). MS Health is also responsible for implementation of any applicable risk minimisation measures.

Additionally, s47 *(the service provider) have a standard operating procedure in place for the management of safety information. This dictates that the updated AU RMP be submitted to the TGA in accordance with the TGA RMP guidelines.*

Further to the above, the Sponsor has reviewed the safety concerns listed within the AU-RMP and proposes to remove those that have a low risk in regard to the seriousness of the safety concern, a low risk to the individual patient and have minimal impact on public health. The following identified risks have therefore been removed as part of this response:

- *Bleeding*
- *Contractions / cramping*
- *Uterine infection*
- *Nausea and vomiting*
- *Diarrhoea*
- *Hypotension*
- *Skin rashes / urticaria*

A clean and annotated copy of the proposed AU-RMP has been provided in Module 1.8.

In the absence of the EU-RMP, the Sponsor confirms that the safety concerns that are listed within the AU-RMP and the changes proposed above, align with those detailed in the Canadian RMP (although it is noted that the AU RMP still includes additional potential risks over and above those that are included in the Canadian RMP, or presents these slightly differently). A copy of the Canadian RMP has been provided as Attachment 1 to this response. An assurance is provided that any future changes that are made to Canadian RMP with be assessed to determine whether the same updates are also warranted in Australia (as per the processes defined above).

RMP evaluator comment: The sponsor's commitment to assess future changes made to the Canadian RMP to determine whether similar updates are warranted in Australia is acknowledged. The sponsor's proposal to remove the above important identified risks is consistent with the Canadian RMP and is acceptable.

Recommendation 3: The sponsor should remove information regarding the completed post-market surveillance study from the pharmacovigilance plan in the RMP as final study report/results have been submitted to the TGA for assessment. The study should also be deleted as an additional pharmacovigilance activity in Section V.3 in AU-RMP.
Sponsor's response: The sponsor has removed the information regarding the completed post-market surveillance study from the pharmacovigilance plan in the RMP. The study has also been deleted as an additional pharmacovigilance activity in Sections III.2 and V.3 of the RMP.
RMP evaluator comment: The AU RMP has been updated as requested.
Recommendation 4: The sponsor should confirm whether the data from the completed post-market surveillance study added to Section SIII (Clinical trial exposure) of the AU-RMP version 0.4 (and Section 3.6 of Annex 1.1) will be added to the Australian PI.
Sponsor's response: The sponsor confirms that they propose to update the Australian PI with the completed postmarket surveillance study data as part of the next submitted Category 1, Type J application
RMP evaluator comment: Noted. This is acceptable.
Recommendation 5: The sponsor should make the following minor editorial change (in **bold**): *In an observational cohort study of 15 008 women attending one of 16 Marie Stopes International clinics in Australia for MTOP (gestational age ≤ 63 days) between 1 March 2013 and 30 September 2015, patients were **administered** 200 mg mifepristone orally in-clinic, followed 24- 48 hours later by 800 micrograms of misoprostol buccally, self-administered at home. Method success was defined as complete abortion not requiring surgical intervention. Follow up information was available for 13,078 (87.2%) of the total cohort. Medical abortion was successful in 95.16% (12,445/13,078) of women with follow-up. Higher patient and gestational ages were associated (P < 0.001) with a slight increase in method failure. There were 674 serious adverse events (5.15%), mainly due to method failure. Infection (15; 0.11%) and haemorrhage (17; 0.13%) were rare. One death was recorded (<0.01%); however, an association between EMA and cause of death, necrotising pneumonia, was not established.*
Sponsor's response: The sponsor has updated the RMP in accordance with the requested minor editorial amendment. A copy of the updated RMP has been provided in Module 1.8.
RMP evaluator comment: The AU RMP has been updated as requested.

Recommendation 6: To support the proposals to remove requirements for prescriber recertification training and pharmacist registration, the sponsor should provide justification/discussion on:

- additional risk minimisation activities in other countries where MS-2 Step is available compared to Australia
- any safety concerns on the removal of pharmacist registration and prescriber re-certification
- number/percentage of pharmacies registered to dispense MS-2 Step in Australia
- any reports on evaluation of effectiveness of additional risk minimisation activities

Sponsor's response: As of December 2022, there are 5,472 pharmacists registered to provide MS-2 Step® to Australian patients. The most recent Dept of Health data (Allied Health factsheets) reports a total of 32,904 pharmacists registered in Australia in 2020 (more recent data not available); indicating only ~17% of pharmacists are currently registered to dispense MS-2 Step to patients.
The challenge of having less than 20% of pharmacists registered to dispense MS-2 Step presents a risk from a patient-safety perspective of delayed access to medication. This is especially so for patients in either regional and remote settings where there may not be an easily accessible registered pharmacist; as well as for patients whose gestation is approaching the upper limit of MS-2 Step's registered indication and for whom timely access to MToP is even more critical. MS Health will continue to make the MS-2 Step training materials available to both prescribers and dispensers so that skill levels can be maintained, but removal of these specific requirements (prescriber recertification, dispenser registration) is expected to improve the ability of patients to receive timely access to their medication.
MS Health notes that within the Canadian setting, since 2017 patients seeking a medical termination of pregnancy are dispensed an identically configured Mifepristone + Misoprostol composite pack by pharmacists who are not required to register prior to dispensing; or physicians who need to recertify. There have been no adverse safety signals or additional risk minimisation activities identified in Canada with this change to a broader access regimen.

RMP evaluator comment: Noted. Considering the proposed removal of mandatory training program and certification of prescribers and dispensers, the sponsor should ensure prescribers and dispensers are aware of the availability of MS-2 Step training materials and how to access these.

Recommendation 7: The sponsor has proposed that 'once registered and certified no re-registration or recertification is required' for prescribers. It is assumed that this re-certification refers to the periodic renewal of the certificate for the purpose of knowledge maintenance. The sponsor should provide clarification in the AU-RMP on whether and how it plans to inform prescribers of the updated safety information when new evidence becomes available.

Sponsor's response: The Sponsor confirms that re-certification refers to the periodic renewal of the certificate for the purpose of knowledge maintenance.
The MS-2 Step composite pack product has been available in Australia for over 8 years (registered 4/6/2014, marketed 1/2/2015). The pack components (Mifepristone + Misoprostol) have been registered for the Medical Termination of Pregnancy in Australia (and globally) prior to this. The product's characteristics, safety and AE profile are relatively well understood. There is no proposed change in the patient population as part of this application and as such, it is unlikely that a significant change to the product's existing safety profile is going to be encountered.
It is noted that prescribing Medical Practitioner's must remain up-to-date on changes to the safety profile for any product that they prescribe. This information is communicated to prescribers via PI updates and notices on the TGA website (as appropriate). In the event of a significant change to the product safety profile and a need to rapidly disseminate information to prescribers, MS Health would utilise the channels mentioned above and also utilise the MS-2 Step prescriber database (which is being proposed to remain in place). MS Health proposes to continue to utilise the standard channels used for other registered medicines when providing updated information to prescribers.

RMP evaluator comment: The sponsor's response is acceptable.

Recommendation 8: The sponsor has stated under 'Restricted Access to MS-2-Step' that the program is to ensure that "distribution of MS-2-Step is controlled and monitored". With the proposed removal of pharmacist registration, the sponsor should clarify how this is achieved. The sponsor should note, according to the EMA GVP Module XVI, controlled distribution and controlled access programs are different measures that serve different purposes.

Sponsor's response: The European Medicines Agency (EMA) guidance; Guideline on good pharmacovigilance practices (GVP), Module XVI, Section XVI.B.2.2 states the following:

"Since a controlled access programme has large implications for all stakeholders, the use of such a programme should be limited and should be guided by a clear therapeutic need for the product based on its demonstrated benefit"

The sponsor's proposed RMP amendments i.e. removing the need for prescriber recertification and removing the need for dispenser registration, is endeavouring to minimise impacts on patients who may otherwise struggle to access their medication in a timely manner. MS Health proposes to continue providing prescriber education and maintain the database of certified prescribers to act as a control on any potential product misuse or abuse.

In addition to this, MS Health highlights the fact that it is the responsibility of the prescriber to ensure that they are compliant with relevant requirements to provide any therapeutic product e.g. they have completed any relevant training and have the required knowledge to prescribe the therapeutic product in question. With respect to the MS-2 Step product, an additional extra level of control is provided during the PBS-script approval process. The majority of MS-2 Step scripts are PBS-scripts; the approval process requires the prescriber to affirm that they are certified to prescribe.

NB: this need to affirm certification exists regardless of whether the product is designated Authority Required or Streamlined Authority.

Given the above, it is unlikely for additional restricted access controls to be required and MS Health highlights the fact that the impetus for removing the requirement for dispenser registration is to improve patient access. Especially those patients located in rural and/or remote settings; and those later in their gestation and for who the timely access to medication is critical (and can be more challenging).

Within this context, the term "Restricted Access to MS-2 Step" (compared to the EMA GVP Module XVI definition, as provided below for ease of reference) may be inappropriate and appears to be a carryover from the preceding RMP document. The sponsor proposes amending this to "Restricted Distribution of MS-2 Step" as the product will continue to be distributed through controlled pharmaceutical supply chains; thus minimising the potential for product misuse or abuse.

EMA GVP Definitions

XVI.B.2.3.1. Controlled distribution system A controlled distribution system refers to the set of measures implemented to ensure that the stages of the distribution chain of a medicinal product are tracked up to the prescription and/or pharmacy dispensing the product. Orders and shipments of product from a single or multiple identified distribution points facilitate traceability of the product. For instance, this sort of measures could be considered for those products controlled in each country under the respective national legislations to prevent misuse and abuse of medicines.

XVI.B.2.2. Controlled access programme A controlled access programme consists of interventions seeking to control access to a medicinal product beyond the level of control ensured by routine risk minimisation measures, i.e. the legal status. Since a controlled access programme has large implications for all stakeholders, the use of such a programme should be limited and should be guided by a clear therapeutic need for the product based on its demonstrated benefit (e.g. it treats a serious disease without alternative therapies; it treats patients who have failed on existing therapies), the nature of the associated risk (e.g. risk is lifethreatening), and the likelihood that this risk can be managed by such a programme. Therefore, controlled access should only be considered as a tool for minimising an important risk with significant public health or individual patient impact for a product with clearly demonstrated benefits but which would not otherwise be available without a programme where patient access is contingent on fulfilling one or more requirements prior to a product being prescribed or dispensed in order to assure its safe use.

Examples of requirements that need to be fulfilled before the product is prescribed and/or dispensed and/or used in a controlled access programme are listed below (they may be included individually or in combination): • specific testing and/or examination of the patient to ensure compliance with strictly defined clinical criteria; • prescriber, dispenser and/or patient documenting their receipt and understanding of information on the serious risk of the product; • explicit procedures for systematic patient follow-up through enrolment in a specific data collection system e.g. patient registry; • medicines made available for dispensing only by pharmacies that are registered and approved to dispense the product. On occasions, a requirement to test or to monitor a patient in a specific way can also be used as a controlled access tool. For example,

monitoring of the patient's health status, laboratory values or other characteristic prior to and/or during treatment, e.g. electrocardiogram, liver function tests, regular blood tests, pregnancy tests (which can be part of a pregnancy prevention programme). Measures should be put in place to ensure that monitoring takes place according to the SmPC where this is critical to risk-benefit balance of the product.

RMP evaluator comment: The section regarding restricted distribution has been removed with the proposed removal of mandatory training program and certification for prescribers.

Recommendation 9: The sponsor should amend Section V.3 Summary (table) of risk minimisation measures as follows:

- Completed post-marketing surveillance study is still listed as an additional pharmacovigilance activity – this should be removed from the table
- 'Special attention in PSURs' was listed as an additional pharmacovigilance activity – this is considered part of routine pharmacovigilance.
- 'Physician education' is not described as an additional risk minimisation activity for potential risks: Potential interaction with CYP3A4 inhibitors or inducers, Potential interaction with products interacting with the glucocorticoid receptor, Severe asthma uncontrolled by treatment, Incorrect determination of gestational age – this should be revised accordingly
- 'Potential for loss to follow up' is not included – this should be added for completeness

Sponsor's response: The Sponsor has amended Section V.3 Summary (table) of risk minimisation measures in accordance with the above requested changes and in other sections as applicable. A copy of the update AU RMP has been provided in Module 1.8.

RMP evaluator comment: Further changes to the table in Section V.3 are required:

- **Identified risk 'Cardiac disorders' is missing and needs to be added**
- **Potential risks 'Incorrect determination of gestational age' and 'Potential for loss to follow-up' are missing and need to be added**

Additionally, the sponsor should make the below changes to Table 11 in Section V.1:

- **Remove 'physician education' as a routine risk minimisation measure.**
- **Potential risks 'Potential for off-label use beyond the first trimester' and 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up' are missing and need to be added**

Recommendation 10: In the revised training manual (Annex 1.1), the sponsor has included interim information regarding a pending TGA application to remove PI precautions regarding rhesus alloimmunisation to align with current Australian and International guidelines. The sponsor should note, the content of additional risk minimisation materials, including training manual should always align with the approved PI and CMI. Updates to training materials should occur concurrently with, or following TGA approved PI changes.

Sponsor's response: The reference to the TGA application to remove PI precautions regarding rhesus alloimmunisation has been removed from the training manual Annex 1.1. An updated training manual (Annex 1.1) has been provided in Module 1.8.

RMP evaluator comment: Reference to interim information regarding the pending TGA application (PM-2022-03010-1-5) has been removed from the training manual as requested.

Recommendation 11: The most recently evaluated AU-RMP was version 03 (dated 13 November 2014; DLP 28 April 2013). MS Health Pty Ltd has submitted updated AU-RMP version 0.4 (dated 24 November 2022; DLP 31 May 2022) for MS-2 Step, noting that the EU-RMP is not available. Chronologically, going from Version 03 to 0.4 is confusing. The sponsor should consider amending the proposed version number.
Sponsor's response: The applicant inadvertently included 0.4 as the next sequential version. To avoid any further confusion (and subsequent errors), the version number has been updated to 4.0.
RMP evaluator comment: Noted. The sponsor has submitted an updated AU-RMP version number 4.0.

6.2. Reconciliation of Round 1 recommendations – dated 27 February 2023

The sponsor's response after Succession 3 evaluation, dated 6 April 2023, can be found on

TRIM D23-5289076

docuBridge e004967 (0012-) - Response - 2023-04 Response to S31 Request, MS3

The sponsor has provided and updated AU-RMP version 4.1 (dated 5 April 2023, DLP 31 May 2022) with their response.

Recommendation 12: The sponsor has submitted the updated RMP version 4.0 (dated 17 February 2023). This RMP has the same version number with a different date from version 4.0 (dated 13 January 2023). To avoid confusion, for future submissions, the sponsor should update the version number and date for each revision.
Sponsor's response: To avoid further confusion, the version number of the RMP has been updated along with the date for each new revision.
RMP evaluator comment: It is noted the sponsor has submitted an updated AU-RMP version 4.1 (dated 5 April 2023, DLP 31 May 2022) with this response.
Recommendation 13: The findings from the Canadian Phase IV study are applicable to Australia and should be included in the AU-RMP as an additional pharmacovigilance activity. The sponsor should include planned submission dates of study reports. When available a revised RMP which considers the completed study outcomes should be submitted to the TGA for review.
Sponsor's response: The Canadian Phase IV study has been included in Section III.2 of the proposed RMP. The proposed study to determine the effectiveness and safety of combination mifepristone/misoprostol for medical abortion under 63 days gestation among 3,000 Canadian women (the MiMAC study) is currently ongoing and is estimated to be completed in Q1 2024 with the final study report currently planned to be available in Q4 2024. *Once the study has been completed, the sponsor provides the assurance that the study reports together with a revised RMP (which considers the completed study outcome) will be submitted to the TGA. The submission is planned for Q4 2024 / Q1 2025.*
RMP evaluator comment: The sponsor has included information on the Canadian Phase IV study in Section III.2 of the AU-RMP, as requested. This additional pharmacovigilance activity should also be added to the tables in Section III.3 and V.3 as appropriate. It is acknowledged that the sponsor commits to submitting a revised RMP that considers completed study outcomes to the TGA when available. The sponsor should submit key findings from the study as an accompanying document. The full study report is only required upon TGA's request.

Recommendation 14: Further changes to Section V.3 Summary (table) of risk minimisation measures of the AU-RMP, are required:

- Identified risk 'Cardiac disorders' is missing and needs to be added
- Potential risks 'Incorrect determination of gestational age' and 'Potential for loss to follow-up' are missing and need to be added

Sponsor's response: The Sponsor notes that the identified risk 'cardiac disorders' was added to the previously submitted version of the RMP. Section V.3 has been updated further to include the missing potential risk 'incorrect determination of gestational age'.
The Sponsor proposes to remove the potential risk 'potential for loss to follow-up'. This will align with the current Canadian RMP and will bring the potential risks in line with other prescription products with a similar risk profile.
The current Product Information and Consumer Medicines Information includes the requirement for prescribers to ensure that upon discharge from the treatment centre, all women should be provided with appropriate medications as necessary and be fully counselled regarding the likely signs and symptoms she may experience and have direct access to the treatment centre by telephone or local access. Further to this they will receive precise instruction as to whom they should contact and where to go in the event of problems emerging. This will ensure that if a patient does not participate in a follow up visit, they possess the information they need about where to go for further advice or treatment.
A copy of the updated annotated (with the recent changes highlighted with a blue comment) and clean RMP has been provided in Module 1.8.

RMP evaluator comment: The table in Section *V.3 Summary of risk minimization measures* (from page 38) in the AU-RMP does not include the missing potential risk 'incorrect determination of gestational age' as stated. This should be addressed by the sponsor. It is noted the sponsor has added information on 'incorrect determination of gestational age' to Table 5 in Section VII.3.1.
The sponsor's proposal to remove the potential risk 'Potential for loss to follow-up' is acceptable from an RMP perspective, given:

- this will align with the current Canadian RMP
- there are no additional pharmacovigilance activities or additional risk minimisation measures proposed to specifically address potential loss to follow-up
- the importance of follow-up examination 14 to 21 days after taking mifepristone to ensure termination is complete and that there are no complications is well described (as a "must") in the PI/CMI black box warnings.

However, it was noted the sponsor has also removed 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up'. This should remain in the SOSC as there are additional considerations to this risk with regards to access to further advice or treatment if follow-up does not occur. It is noted that this safety concern is not discussed in the PSUR, which uses the Canadian RMP as the reference document. It is requested that the sponsor provide an assessment of this safety concern with the PSUR submission expected August 2023. This assessment may serve to support the removal of this safety concern (can be submitted as an RMP update).

Recommendation 15: Changes to Table 11 in Section V.1 of the AU-RMP are required:

- Remove 'physician education' as a routine risk minimisation measure as this is considered additional risk minimisation.
- Potential risks 'Potential for off-label use beyond the first trimester' and 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up' are missing and need to be added

Sponsor's response: The Sponsor has updated Table 11 in Section V.1 of the RMP to remove physician education as a routine risk minimisation measure and to include the following potential risks:

- *Potential for off-label use beyond the first trimester*

As proposed in Recommendation 14 above, the potential risk for loss to follow up is proposed to be removed.
A copy of the updated annotated and clean RMP has been provided in Module 1.8.

RMP evaluator comment: As per comments above, the removal of the potential risks relating to loss to follow-up from the summary of safety concerns is acceptable.
The Sponsor has updated Table 11 in Section V.1 of the AU-RMP to remove physician education as a routine risk minimisation measure as requested. However, 'Potential for off-label use beyond the first trimester' has not been added as a potential risk as stated.

Recommendation 16: The Educational program material has been removed from the AU-RMP with the proposed removal of mandatory training program and certification for prescribers. However, it is noted that the sponsor will continue to provide access to prescriber training to support the education of prescribers. Physician education and Patient Information and Consent Agreement form are listed as additional risk minimisation measures in the AU-RMP and these materials should be appended to the AU-RMP. Further, the sponsor should ensure prescribers (and dispensers) are made aware of the availability of MS-2 Step training materials and how to access these.

Sponsor's response: The sponsor confirms that prescribers and dispenses will continue to be made aware of the availability of the MS-2 Step training materials and how to access them.

RMP evaluator comment: Noted. The Patient Information and Consent Agreement form is listed as an additional risk minimisation measure in the AU-RMP and the Educational program material will continue to be supplied - these materials should be appended to the AU-RMP.
The TGA requires that copies of Australian educational materials to be provided in Annex 3 of the Australia Specific Annex. Materials should be provided with content and intended layout, including images and graphic presentations of information. For digital additional risk minimisation tools, provide content and images of the onscreen layout of the information, and/or the login details or access codes to enable the TGA to evaluate the safety content in the format in which it is provided to the end user. In the absence of an ASA, the same requirement applies to the Australian RMP.
Additionally, the following revisions to V.2 Additional Risk Minimisation Measures are requested:

- Under 'Inclusion of Instruction Insert in Composite Pack Carton' remove text relating to the mandatory training program and certification for prescribers:

  "These arrangements are set up and are accessible via the Sponsor's secure healthcare professional website www.ms2step.com.au, or by calling the company directly. The Sponsor may change the restrictions on supply if in the future an effective control mechanism on prescriber access becomes possible via the PBS."
- Under 'Prescriber Training', specify availability via the website www.ms2step.com.au.

Recommendation 17: In Section 3.6 of the training manual provided in Succession 2, the sponsor should make the minor editorial change of "administration" to "administered"

Sponsor's response: In accordance with the response to Question 1 above, the Sponsor is proposing to remove the Medical Education Program from the RMP and therefore the training manual will not be provided as an attachment. The Sponsor however provides an assurance that the minor editorial change will be made to the training manual that will be available for all healthcare practitioners that prescribe MS-2 Step via the existing online website (www.ms2step.com.au).

RMP evaluator comment: As per the response above, the educational material will need to be provided as an attachment to the AU-RMP.

Recommendation 18: The advice on 24-hour phone service is also provided in the Consumer Medicine Information (CMI). The sponsor should submit the updated CMI to ensure consistent information in the RMP, Product Information (PI), and CMI.

Sponsor's response: The Consumer Medicine Information (CMI) and Product Information (PI) have been updated to remove the reference to the 24-hour phone service. A copy of the revised annotated and clean CMI and PI have been provided in Module 1.3.2 and 1.3.1 respectively.

RMP evaluator comment: Reference to the 24-hour phone service has been removed from the CMI and PI as requested.

Recommendation 19: This is a recommendation for the TGA delegate/clinical evaluator. The requirement for prescriber certification is included in the approved PI. The sponsor has advised that it will remove this requirement and submit the updated PI following the completion of round 1 evaluation. From the RMP perspective, assessing prescriber competencies is more related to clinical practice than to product risk management. Therefore, the removal of prescriber certification from the RMP is acceptable. It is recommended that the delegate/clinical evaluator considers the proposed PI change from the clinical perspective, and whether advisory committee advice is needed.
Sponsor's response: The Sponsor notes that this recommendation is for the TGA delegate / clinical evaluator. However, as previously proposed, the sponsor has updated the PI and CMI to remove the prescriber certification and has provided a copy of the annotated and clean CMI and PI in Module 1.3.2 and 1.3.1 respectively.
RMP evaluator comment: Noted.
Recommendation 20: This is a recommendation for the TGA delegate/clinical evaluator. The provision of 24-hour phone service for patients is included in the approved PI. The sponsor has advised that it will remove this service and submit updated PI following the completion of round 1 evaluation. It is noted that the PI also advises that 'patients must have the ability to access 24-hour emergency care'. This would ensure timely access to urgent medical attention and intervention. Therefore, the removal of 24-hour phone service is acceptable from the RMP perspective. It is recommended that the delegate/clinical evaluator considers the proposed PI change from the clinical perspective, in particular, whether and how much value the 24-hour phone service adds to patient safety outcomes.
Sponsor's response: As above, the Sponsor notes that this recommendation is for the TGA delegate / clinical evaluator. However, as previously proposed (and in accordance with the response to Question 19 above), the sponsor has updated the PI and CMI to remove the provision of the 24-hour phone service. A copy of the revised annotated and clean CMI and PI has been provided in Module 1.3.2 and 1.3.1 respectively.
RMP evaluator comment: Noted.

7. ROUND 3 EVALUATION

7.1. RECONCILIATION OF ROUND 2 RECOMMENDATIONS

The sponsor's response after Round 2 evaluation, dated 10 May 2023, can be found on docuBridge:

e004967 (0014-) - Response - 2023-05 Response to S31 Request - RMP Round 2 Evaluation Report

The sponsor has provided and updated AU-RMP version 4.2 (dated 9 May 2023; DLP 31 May 2022) with their response.

Outstanding Recommendation 13: The ongoing Canadian post-market surveillance study should also be added to the tables in Section III.3 (Table 10) and V.3 (Summary of risk minimization measures) as appropriate. Refer to the Canadian RMP to identify the safety concerns that will be addressed by this additional pharmacovigilance activity. It is acknowledged that the sponsor commits to submitting a revised RMP that considers completed study outcomes to the TGA when available. The sponsor should submit key findings from the study as an accompanying document. The full study report is only required upon TGA's request.
Sponsor's response: The Sponsor has amended the RMP to include the Canadian post-market surveillance study in Sections V.3. As this study is not an imposed or required additional pharmacovigilance activity, the inclusion of this study in Section III.3, table 10, is not applicable. It is noted that the study details are included in the previous section III.2. *The Sponsor acknowledges the TGA request to submit the key findings from the Canadian postmarket surveillance study and confirms that this will be provided as an accompanying document to the revised RMP. A copy of the updated annotated and clean RMP has been provided in Module 1.8.*
RMP evaluator comment: The sponsor's response and amendments to the RMP are acceptable.
Outstanding Recommendation 14: The potential risk 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up' should remain in the SOSC as there are additional considerations to this risk with regards to access to further advice or treatment if follow-up does not occur. Further, it is noted that this safety concern is not discussed in the PSUR, which uses the Canadian RMP as the reference document. It is requested that the sponsor provide an assessment of this safety concern with the PSUR submission expected August 2023. This assessment may serve to support the removal of this safety concern (can be submitted as an RMP update).
Sponsor's response: The Sponsor has amended the RMP to reinsert the potential risk 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up'. Additionally, the Sponsor provides and assurance that an assessment of this safety concern will be provided with the next PSUR submission which is expected in August.
RMP evaluator comment: This is acceptable.
Recommendation 21: The annotated AU-RMP version 4.1 (dated 5 April 2023) tracks all changes since the approved version 03 (dated 13 November 2014) i.e. marks changes from version 0.4 to the two subsequent versions 4.0 to version 4.1. To avoid confusion and for ease of evaluation, annotated documents should only track the changes made since the last submitted version.
Sponsor's response: *The Sponsor acknowledges the TGA's request to only track the changes made since the last submitted version and ensures that this process will be followed for future revisions.*
RMP evaluator comment: The sponsor's response is noted.

Recommendation 22: The sponsor should make the following changes to the risk minimisation plan:

- Include potential risk 'incorrect determination of gestational age' in Section V.3 Summary of risk minimization measures (table; page 38) in the AU-RMP
- Add potential risk 'Potential for off-label use beyond the first trimester' to Table 11 in Section V.1 of the AU-RMP
- Append the Educational Program materials and Patient Information and Consent Agreement form to the AU-RMP
- In Section V.2 Additional Risk Minimisation Measures
    - Under 'Inclusion of Instruction Insert in Composite Pack Carton', remove text relating to the mandatory training program and certification for prescribers:
      "These arrangements are set up and are accessible via the Sponsor's secure healthcare professional website www.ms2step.com.au, or by calling the company directly. The Sponsor may change the restrictions on supply if in the future an effective control mechanism on prescriber access becomes possible via the PBS."
    - Under 'Prescriber Training', specify availability via the website www.ms2step.com.au

Sponsor's response: The Sponsor has amended the RMP in accordance with the above requested changes including appending the Educational Program materials and Patient Information Sheet - Consent form to the AU-RMP. A copy of the amended RMP has been included in Module 1.8.

RMP evaluator comment: The AU-RMP has been amended as requested, this is acceptable. The educational materials and consent form have been reviewed and considered satisfactory.

APPENDIX 1 – LIST OF ACRONYMS

AE	Adverse Event
ACM	Advisory Committee on Medicines
AU-RMP	Australian Risk Management Plan
CMI	Consumer Medicine Information
DLP	Data Lock Point
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
MHRA	Medicines & Healthcare Products Regulatory Agency
PI	Product Information
PMAB	Prescription Medicines Authorisation Branch
RMP	Risk Management Plan
SOSC	Summary of Safety Concerns
TGA	Therapeutic Goods Administration

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Delegate's overview

Active ingredient(s): Mifepristone and misoprostol

Proprietary product name: [MS-2 Step composite pack]

Sponsor: [s47 [redacted] on behalf of MS Health Pty Ltd]

Submission number: [PM-2022-05475-1-5]

eID [e004967]

07 May 2023

TGA Health Safety Regulation

Submission information

Submission number	PM-2022-05475-1-5
Active ingredient(s)	Mifepristone and misoprostol
Product name	MS-2 Step composite pack
Strengths/dose form	MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet blister; GyMiso misoprostol 200 microgram tablet blister
Sponsor	s47 [redacted] on behalf of MS Health Pty Ltd
Description of the submission/proposed indication	This is a Category 1, Type J application (variation to the register entry resulting in a change of product information requiring evaluation of clinical, non-clinical or bioequivalence data) to update the PI for MS-2 Step composite pack. Section 4.2 of the current PI advises MS-2 Step can only be prescribed by doctors with the appropriate qualifications and certified training. The Sponsor proposes to amend 'medical practitioner' in the boxed warning and 'doctors' in Section 4.2 of the PI to 'healthcare practitioners' as well as remove the requirement for prescriber certification. Removal of 24-hour phone service for patients is also proposed.
Summary of data	It is a Literature Based Submission. The main evidence provided to support the proposed change is from 3 studies, including data for approximately 1800 women receiving MToP up to 63 days gestation and approximately 1100 women receiving MToP up to 8 weeks gestation. Overall, the evidence provided supports the proposed changes to the boxed warning of the MS-2 Step PI to amend '*medical practitioner*' to '*healthcare practitioner*' and to amend '*doctors with the appropriate qualifications and certified training*' in Section 4.2 to '*healthcare practitioners with the appropriate qualifications and certified training*' given the Sponsor proposes to maintain the existing standardised training for prescribers. However, subsequent submission by the sponsor to the Risk Management Section, to remove the requirement for prescriber certification from the PI as part of the updated RMP provided to TGA (dated 17th February 2023). The proposed removal of prescriber certification from the PI does potentially bring into question the Sponsor's justification for the proposed changes to the PI as the Clinical Expert's assertion regarding a minimum baseline of education irrespective of training background would

	not hold if the requirement for prescriber certification is removed. The proposed changes to the boxed warning and Section 4.2 give rise to inconsistencies in the PI which have not been addressed: • Section 4.2 Dose and method of administration: The Sponsor states in the Cover letter the application proposes to amend the reference to 'doctors' in Section 4.2 to 'healthcare practitioners'. However Section 4.2 includes the text '*When MS-2 Step fails to cause termination of intra-uterine pregnancy, the patient should return to the treating doctor for assessment and discussion of treatment options, which may include pregnancy termination by surgery*.' This text is not consistent with the proposed changes advising patients receiving these medications are followed up by a healthcare practitioner, preferably the prescriber. • Section 4.4 Special warnings and precautions for use: Section 4.4 includes information regarding particular co-morbidities as follows: *Take special care in case of suspected acute adrenal failure. In case of suspected acute adrenal failure, dexamethasone administration is recommended (please refer to the dexamethasone Product Information).* *Due to the antiglucocorticoid activity of mifepristone, the efficacy of long-term corticosteroid therapy, including inhaled corticosteroids in asthmatic patients, may be decreased during the 3 to 4 days following intake of mifepristone. Therapy should be adjusted.* Patients with these medical comorbidities may require additional medical management such as adjustment of inhaled corticosteroid (ICS) therapy for asthma patients for example, that may be outside the scope of practice of non-physician healthcare providers. The Sponsor has not specifically addressed how patients with relevant medical comorbidities as described in the PI will be managed by non-physician healthcare providers. • Section 4.4 Special warnings and precautions for use and Section 4.8 Adverse effects (undesirable effects): Section 4.4 includes text regarding cases of serious bacterial infection, including very rare cases of fatal septic shock, with statements in the 'Infection' subsection specifically referring to 'doctors' as follows: - *'Treating doctors evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event.'* This text is not consistent with the proposed changes advising patients receiving these medications are followed up by a healthcare practitioner, preferably the prescriber.

	It would seem appropriate all healthcare providers would need to be aware of this risk. - *'These symptoms, even without a fever, may indicate Clostridium sordellii infection. Strong consideration should be given to obtaining a complete blood count in these patients. Significant leukocytosis with a marked left shift and haemo-concentration may be indicative of sepsis. Doctors should consider immediately initiating treatment with antibiotics that includes coverage of anaerobic bacteria such as Clostridium sordellii.'* This text is also included in Section 4.8 of the PI. These statements refer to clinical management of a potentially serious infection/possible sepsis including initiation of appropriate antibiotic therapy. As aforementioned, it is not clear whether this is within the scope of practice of non-physician healthcare providers. • Section 4.6 Fertility, pregnancy and lactation: Section 4.6 includes the following text*:* *'To avoid the potential exposure of a subsequent pregnancy to MS-2 Step it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after administration of MS-2 Step.'* This is considered important safety information. It is not clear whether prescription of reliable contraceptive methods is within the scope of practice for all healthcare providers for whom expanded prescriber eligibility is proposed (acknowledging different state/territory legislation), and therefore if some patients may need to be referred to a different healthcare provider. 'Return to fertility' is included in the 'Serious warnings and precautions' box in the Canadian Mifegymiso product monograph [2]. These outstanding issues may require appropriate risk minimisation strategies such as updates to the educational materials.
Preliminary view	At this stage I am inclined to hear the discussion and deliberation of the ACM members on training requirements before making my final decision.
Outstanding issues	Removal of prescriber certification and training requirement. Although the sponsor will continue to make educational materials available as support to prescribers and dispensers. Removal of 24-hour phone service for the patients. Inconsistencies noted in Sections 4.2, 4.4, 4.6 and 4.8 of the MS-2 Step composite pack PI with the proposed expansion of prescriber eligibility as discussed above and in Section 4.1.2 of clinical evaluation report.

Request for ACM advice

ACM meeting number: 39 **Date (of meeting): 1st / 2nd June 2023**

Summary of issue/s for advice	Clinical Impact of removal of prescriber certification and training requirement. Clinical Impact of removal of 24-hour phone service for the patients. Inconsistencies noted in Sections 4.2, 4.4, 4.6 and 4.8 of the MS-2 Step composite pack PI with the proposed expansion of prescriber eligibility as discussed above and in Section 4.1.2 of clinical evaluation report.
Advice sought	1. Please provide your advice on the proposed changes by the sponsor in the PI / RMP a. Boxed warning of the MS-2 Step PI to amend '*medical practitioner*' to '*healthcare practitioner*' b. Removal of the requirement for prescriber certification from the PI as part of the updated RMP. c. Removal of 24-hour phone service for patients. d. Inconsistencies noted in Sections 4.2, 4.4, 4.6 and 4.8 of the MS-2 Step composite pack PI with the proposed expansion of prescriber eligibility.

s22 [redacted]

Delegate of the Secretary under regulation 35A of the Therapeutic Goods Regulations 1990

08 May 2023

Date

Body of overview

Introduction

Mifepristone belongs to the Pharmacotherapeutic group: Other sex hormone and modulator of the reproductive function/antiprogestogen, ATC code GO3XB01.

Misoprostol belongs to the Pharmacotherapeutic group: Other gynaecological medicines – prostaglandins, ATC code G02AD06.

Mifepristone is a synthetic steroid with an antiprogestational action as a result of competition with progesterone at the progesterone receptors. In women at doses of greater than or equal to 1 mg/kg, mifepristone antagonises the endometrial and myometrial effects of progesterone. During pregnancy it sensitises the myometrium to the contraction inducing action of prostaglandins. Misoprostol is a synthetic analogue of prostaglandin E1. At the recommended dosages, misoprostol induces contractions of the smooth muscle fibres in the myometrium and relaxation of the uterine cervix. In the event of an early termination of pregnancy, the combination of a prostaglandin analogue used in a sequential regimen after mifepristone leads to an increase in the success rate and accelerates the expulsion of the conceptus.

The approved indication is [1]:

MS-2 Step is indicated in females of childbearing age for the medical termination of an intrauterine pregnancy, up to 63 days of gestation.

It is recommended that the duration of pregnancy (i.e., up to 63 days gestation) be confirmed by ultrasound. In the event that an ultrasound is not possible, extra caution should be exercised.

Ultrasound is also useful to exclude ectopic pregnancy.

Currently the MS-2 Step PI defines MS-2 Step can only be prescribed by doctors with the appropriate qualifications and certified training, with the subsequent post administration follow up to be conducted by a medical practitioner, preferably the prescriber. Therefore, access to early medical abortion (as indicated up to 63 days of gestation) is restricted to where a certified medical practitioner is located.

To ensure timely access to patients, and to ensure that the product is prescribed by the persons authorised by state and territory legislation, the application proposes to amend the black box warning from referencing 'medical practitioner' to 'healthcare practitioner', and for the reference to 'doctors' in section 4.2 to be amended to 'healthcare practitioners'.

Regulatory History

The individual components of MS-2 Step, Mifepristone Linepharma (mifepristone 200 mg tablet) and GyMiso (misoprostol 200 microgram tablet) were registered in Australia on 29th August 2012 for medical termination of developing intrauterine pregnancy up to 49 days gestation as follows:

Mifepristone Linepharma (AUST R 175671):

Medical termination of a developing intra-uterine pregnancy. In sequential combination with a prostaglandin analogue up to 49 days of gestation; and preparation for the action of registered prostaglandin analogues that are indicated for the termination of pregnancy for medical reasons beyond the first trimester.

GyMiso (AUST R 188015):

GyMiso is indicated in females of childbearing age for the medical termination of a developing intrauterine pregnancy in sequential combination with a mifepristone 200 mg tablet, up to 49 days of gestation.

MS-2 Step composite pack containing Mifepristone Linepharma (mifepristone) 200 mg tablet and GyMiso (misoprostol) 200 microgram tablets was registered on 4th June 2014 (Submission PM-2013-01037-1-5). As part of this submission, the indication was extended to the medical termination of a developing intrauterine pregnancy from 49 days up to 63 days gestation.

Following registration of MS-2 Step composite pack, the Sponsor withdrew the GyMiso mono product from the market, and removed the indication for medical termination of pregnancy up to 49 days for the Mifepristone Linepharma mono product (Submission PM-2014-03311-1-5).

MS-2 Step combination pack is not registered in other countries/regions.

The combination product Mifegymiso (mifepristone 200 mg tablet and misoprostol 200 microgram tablet combination pack, Linepharma International Limited) is approved in Canada for a comparable indication to MS-2 Step composite pack [2]:

'*Mifegymiso (mifepristone tablet/misoprostol tablets) is indicated for:*

• *medical termination of a developing intra-uterine pregnancy with a gestational age up to 63 days as measured from the first day of the Last Menstrual Period (LMP) in a presumed 28-day cycle.*

Mifegymiso is not intended for routine use as a contraceptive.'

Mifegymiso should be prescribed by health professionals with adequate knowledge of medical abortion and/or who have completed a Mifegymiso education program.

Mifepristone is registered in the USA, UK and various countries in Europe. In the USA, Mifeprex (mifepristone) is only available through the mifepristone risk evaluation and mitigation strategy (REMS) Program

Proposed MS-2 Step PI change
Boxed warning It is very important that all patients receiving these medications are followed up by a ~~medical~~ healthcare practitioner, preferably the prescriber, to ensure that the medication has been effective. Even if no adverse events have occurred all patients must receive follow-up 14 to 21 days after taking mifepristone. Read the Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE carefully.
4.2 Dose and method of administration MS-2 Step is indicated for medical termination of intrauterine pregnancy, up to 63 days of gestation. The method of administration is as follows: Mifepristone: 200 mg of mifepristone (1 tablet containing 200 mg) orally, followed 36 to 48 hours later by the administration of GyMiso®.

GyMiso®: 800 micrograms of misoprostol (4 tablets, each tablet containing 200 micrograms) buccally, i.e: kept between the cheek and the gum for 30 minutes before any fragments being swallowed with water.

When MS-2 Step fails to cause termination of intra-uterine pregnancy, the patient should return to the treating doctor for assessment and discussion of treatment options, which may include pregnancy termination by surgery.

No dosage adjustment of misoprostol or mifepristone is necessary with renal or hepatic insufficiency when administered at the recommended doses.

There are no data available on the effect of food intake on the absorption of mifepristone or misoprostol. MS-2 Step should be taken 2 hours before or 2 hours after a meal.

Refer also to 4.3 CONTRAINDICATIONS, and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

MS-2 Step should only be prescribed by healthcare practitioners ~~doctors~~ with the appropriate qualifications ~~and certified training~~. Ectopic pregnancy should be excluded, an intrauterine device (IUD) (if present) must be removed, consent must be obtained and patients must have the ability to access 24-hour emergency care if and when required for incomplete abortion or bleeding.

Risk Management Plan (RMP) evaluation

RMP evaluator recommendations regarding condition/s of registration

- On 1 December 2022, MS Health Pty Ltd submitted updated AU-RMP version 0.4 (dated 24 November 2022; DLP 31 May 2022) for MS-2 Step. The EU-RMP is not available. A revised AU-RMP version 4.0 (dated 13 January 2023; DLP 31 May 2022) was provided with the sponsor's response to RMP evaluator's recommendations dated 13 January 2023. On 20 February 2023, the sponsor submitted further changes in AU-RMP version 4.0 (dated 17 February 2023; DLP 31 May 2022) which has been linked to the Category 1, Type J application (PM-2022-05475-1-5). At Round 2, the sponsor submitted updated AU-RMP version 4.1 (dated 5 April 2023; DLP 31 May 2022) with their S31 response dated 6 April 2023.
- MS-2 Step is approved for the medical termination of an intrauterine pregnancy, up to 63 days of gestation, in females of childbearing age.
- The most recently evaluated and approved AU-RMP was version 03 (dated 13 November 2014; DLP 28 April 2013) (R14/1181088).
- The reason for this updated RMP is changes to the summary of safety concerns (SoSC) and changes to the risk minimisation plan. The key changes proposed for risk minimisation activities are as follows:
    - To remove the requirement for pharmacists to be registered to be able to dispense the product.
    - To remove the requirement for prescriber recertification.
    - To remove the need for prescribers to complete mandatory training and receive certification to be able to prescribe the product.
    - To remove the requirement for a Sponsor provided 24 hours aftercare service
- As the TGA has previously evaluated RMPs for this product, the focus of this review is on the differences between the AU-RMP versions and revisions to the additional risk minimisation materials.
- The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below:

Summary of safety concerns	Pharmacovigilance	Risk Minimisation

		Routine	Additional	Routine	Additional
Important identified risks	Infection, toxic shock syndrome	✓	–	✓	✓[1,2]
	Method failure	✓	–	✓	✓[1,2]
	Cardiac disorders	✓	–	✓	✓[2]
Important potential risks	Inadvertent pregnancy exposure and risk of incomplete abortion with severe bleeding	✓	–	✓	✓[2]
	Inadvertent pregnancy exposure (risk of malformations)	✓	–	✓	✓[2]
	Potential interaction with CYP3A4 inhibitors or inducers	✓	–	✓	–
	Potential interaction with products interacting with the glucocorticoid receptor	✓	–	✓	–
	Induced bronchial asthma	✓	–	✓	–
	Effects in lactating women	✓	–	✓	–
	Effects in women with impaired liver function	✓	–	✓	–
	Effects in women with impaired renal function	✓	–	✓	–
	Effects in women with malnutrition	✓	–	✓	–
	Incorrect determination of gestational age	✓	–	✓	–
	Potential for missed ectopic pregnancy	✓	–	✓	✓[2]
	Potential for postnatal developmental delay	✓	–	✓	–
	Potential for off-label use beyond the first trimester	✓	–	✓	–
Missing information	Inherited porphyria	✓	–	–	–
	Theoretical interaction with NSAIDs	✓	–	–	–
	Potential interaction with products interacting with the progesterone receptor	✓	–	–	–
	Use in adolescents	✓	–	–	–
Pharmacological class effect	Risks related to the use of prostaglandin	✓	–	✓	✓[2]

[1] Black box warning

[2] Patient Information and Consent Agreement form

- The sponsor has updated the summary of safety concerns in line with recommendations by the RMP evaluator as well as to reflect up-to-date safety information for MS-2 Step. At

Round 2, the sponsor has proposed to remove potential risk 'Potential for loss to follow-up' and this is acceptable from an RMP perspective. However, the sponsor has also removed potential risk 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up', which is not supported as there are additional considerations to this risk with regards to access to further advice or treatment if follow-up does not occur.

- The completed post marketing surveillance study has been removed from the pharmacovigilance plan. Routine pharmacovigilance is proposed for all safety concerns. There is one additional pharmacovigilance activity – an ongoing Canadian post-market surveillance study on the effectiveness and safety of combination mifepristone/misoprostol for medical abortion under 63 days gestation. Further changes to the pharmacovigilance plan in the AU-RMP is recommended.

- The sponsor proposes to remove from the risk minimisation plan the requirements for prescriber certification, pharmacist registration and a Sponsor-provided 24 hours aftercare service. Additional risk minimisation activities will consist of a black box warning, inclusion of CMI and instruction insert in pack, and Patient Information and Consent Agreement form. The sponsor will continue to make educational materials available as support to prescribers and dispensers. The proposed risk minimisation plan aligns with that in Canada and the UK. The RMP evaluator has noted the post-market experience with MS-2 Step, its well-established safety profile, and existing safety frameworks in place. The RMP evaluator has also noted the importance of timely access of this medicine in terms of patient-safety and the need to remove requirements that hinder patient access to reproductive services. The proposed changes to the risk minimisation plan are acceptable from an RMP perspective. Further changes to the risk minimisation plan are recommended. The sponsor is also requested to include a copy of the Educational Program materials and Patient Information and Consent Agreement form in the appendix of the AU-RMP.

The MS-2 STEP Australian Risk Management Plan (AU-RMP) (version 4.1, dated 5 April 2023, data lock point 31 May 2022), included with submission PM-2022-05475-1-5, to be revised to the satisfaction of the TGA, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Discussion

The main evidence provided to support the proposed change is from 3 studies, including data for approximately 1800 women receiving MToP up to 63 days gestation [5, 6] and approximately 1100 women receiving MToP up to 8 weeks gestation [7].

The Kopp Kallner *et al*. [5] study is considered most relevant to use in Australia. This study was conducted in a high-resource setting with ultrasound as part of the protocol, whereas the studies by Warriner *et al*. [6] and Jejeebhoy *et al*. [7] were conducted in low-resource settings. Neither of the latter 2 studies included ultrasound assessment per study protocol, nor was hCG testing utilised in the Warriner study. This does not generally align with the Australian MS-2 Step PI [1], which recommends confirmation of pregnancy duration by ultrasound in the indication, and lists 'pregnancy not confirmed by an ultrasound or biological test such as urine or serum HCG' as a contraindication. Furthermore, the study population and dose of misoprostol used in the Jejeebhoy *et al*. [7] study differs from approved use in Australia.

Although the Warriner *et al*. and Jejeebhoy *et al*. studies [6, 7] are less applicable to the Australian setting, overall there were no safety concerns with provision of MToP by MLPs identified in any

of the 3 studies, with effectiveness outcomes comparable for MLPs and doctors. The risk of failure was comparable for MToP performed by MLPs and doctors in all studies and is a known risk described in the MS-2 Step PI [1]. There were no serious adverse events reported. The reasons for complications were provided by Kopp Kallner *et al*. [5] and noted to be consistent with the safety profile of MToP with mifepristone/misoprostol.

There was variability in provider experience across the 3 studies. Nurse-midwives experienced in MToP were recruited in the Kopp Kallner *et al*. [5] study with additional early pregnancy ultrasound training provided. All providers underwent MToP training in the Warriner *et al*. and Jejeebhoy *et al*. studies [6, 7]. The importance of education with regard to the MToP process was endorsed by the Clinical Expert who reiterated *'MS Health proposes to continue providing the same (existing) standardised training for all potential prescribers (as detailed in the current approved Australian RMP) and doing so will ensure a minimum baseline of education regardless of training background',* stating further *'The PI amendments proposed by MS Health simply enable individual jurisdictions to make decisions appropriate for their population'.*

Broadening the prescriber eligibility to include non-physician prescribers (in accordance with individual state and territory requirements) is consistent with established practice in Canada and the USA, noting the USA has REMS program requirements for all prescribers [3].

Overall, the evidence provided supports the proposed changes to the boxed warning of the MS-2 Step PI to amend '*medical practitioner'* to '*healthcare practitioner'* and to amend '*doctors with the appropriate qualifications and certified training'* in Section 4.2 to '*healthcare practitioners with the appropriate qualifications and certified training*' given the Sponsor proposes to maintain the existing standardised training for prescribers.

However, the Sponsor has subsequently submitted proposal to remove the mandatory requirement for prescriber certification from the PI as part of the updated RMP provided to TGA (dated 17th February 2023). The proposed removal of prescriber certification from the PI does potentially bring into question the Sponsor's justification for the proposed changes to the PI as the Clinical Expert's assertion regarding a minimum baseline of education irrespective of training background would not hold if the requirement for prescriber certification is removed. In their S31 response they do however emphasis that the existing standardised training (the Medical Education Program) will still be available for all healthcare practitioners that prescribe MS-2 Step via the existing online website (www.ms2step.com.au). The change proposed in the most recent submitted update to the RMP was to remove the mandatory aspect of the training and the subsequent certification.

But the justification provided by the Clinical Expert in the Clinical Overview Addendum to expand prescriber eligibility to include non-physician prescribers (in accordance with individual state and territory requirements) included assurance the existing standardised training for all potential prescribers as per current approved Australian RMP (i.e. mandatory practitioner training and certification) would be maintained, and was supported by data provided in the dossier. As noted in the clinical evaluation report, all the providers underwent MToP training in the Warriner *et al*. and Jejeebhoy *et al*. studies (including certification in the Warriner *et al*. study) [6, 7], and the Kopp Kallner study [5] recruited nurse-midwives experienced in MToP who received additional ultrasound training. The proposed removal of '*and certified training*' from the proposed PI provided with the Section 31 response does not align with the Clinical Expert's assertion that '*a minimum baseline of education regardless of training background will continue to be provided*' and data included in the submission to support the proposed expansion of prescriber eligibility.

Conclusions

The evidence provided in the submission support the proposed changes to the boxed warning to amend 'medical practitioner' to 'healthcare practitioner' and to amend 'doctors with the appropriate qualifications and certified training' in Section 4.2 to 'healthcare practitioners with

the appropriate qualifications and certified training' (in accordance with individual state and territory requirements) on the basis the existing standardised training for all potential prescribers is maintained.

However, the sponsor's proposal to remove 'certified training' from the PI has created uncertainty regarding the risk of expanding prescriber eligibility and removing the requirement for certified training.

Attachments for ACM

Number	Document name	Location/ID	ACM attachment
1	Clinical Evaluation Report	D23-5339936	☐
2	RMP	D22-6199891	☐
3	Annotated PI	e004967 (0012-) - Product Information - Annotated	☐

References

1. Australian MS-2 Step PI. Available at TGA PI/CMI repository. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent=&id=CP-2014-PI-01965-1&d=20230222172310101

2. Canadian Mifegymiso Product Monograph (date of revision 17th June 2022). Provided in Module 5.4 (e004967 (0007-) - Canada SmPC)

3. US Mifeprex Product Label. Revised 01/2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020687Orig1s025Lbl.pdf

4. WHO Abortion Care Guideline 2022. Geneva: World Health Organization; 2022. Provided in Module 5.4 (e004967 (0007-) - WHO - Abort Care guidelines - 2022)

5. Kopp Kallner H, Gomperts R, Salomonsson E, Johansson M, Marions L, Gemzell-Danielsson K. The efficacy, safety and acceptability of medical termination of pregnancy provided by standard care by doctors or by nurse-midwives: a randomised controlled equivalence trial. *BJOG*. 2015;122:510-517. Provided in Module 5.4 (e004967 (0007-) - Kopp-Kallner 2014).

6. Warriner IK, Wang D, Huong NTM, Thapa K, Tamang A, Shah I *et al*. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomised controlled equivalence trial in Nepal. *Lancet*. 2011;377:1155-1161. Provided in Module 5.4 (e004967 (0007-) - Warriner 2011)

7. Jejeebhoy SJ, Kalyanwala S, Mundle S, Tank J, Zavier AJF, Kumar R *et al*. feasibility of expanding the medication abortion provider baser in India to include ayurvedic physicians and nurses. *Int Perspect Sex Reprod Health*. 2012;38:133-142. Provided in Module 5.4 (e004967 (0007-) - Jejeebhoy 2012)

8. Barnard S, Kim C, Park MH, Ngo TD. Doctors or mid-level providers for abortion. *Cochrane Database of Systematic Reviews* 2015, Issue 7. Art. No.: CD011242. DOI: 10.1002/14651858.CD011242.pub2. Provided in Module 5.4 (e004967 (0007-) - Barnard 2015)

9. Regulatory Decision Summary – Mifegymiso - Health Canada. https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detail.php?linkID=RDS00032

10. Regulatory Decision Summary – Mifegymiso - Health Canada. https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detail.php?linkID=RDS00294

11. Schummers L, Darling EK, Dunn S, McGrail K, Gayowsky A, Law MR *et al*. Abortion safety and use with normally prescribed mifepristone in Canada. *N Engl J Med*. 2022;386:57-67. Provided in Module 5.4 (e004967 (0007-) - Schummers 2022)

12. Schummers L, Darling EK, Dunn S, McGrail K, Gayowsky A, Law MR *et al*. Abortion safety and use with normally prescribed mifepristone in Canada. *N Engl J Med*. 2022;386:57-67. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7489974/

13. Berer M. Provision of abortion by mid-level providers: international policy, practice and perspectives. *Bull World Health Organ*. 2009;87:58-63. Provided in module 5.4 (e004967 (0007-) - Berer 2009)

14. UK SPC Mifepristone Linepharma 200 mg tablet (revised 27/10/22). https://mhraproducts4853.blob.core.windows.net/docs/72e81b0722b04c4d065babba78a7be4e0dbe89fb

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Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Advisory Committee on Medicines Minutes

Item 2.13
Mifepristone and misoprostol

Proprietary Product Name: MS-2 Step composite pack

Sponsor: s47 [redacted] on behalf of MS Health Pty Ltd

June 2023

Contents

Submission details

Submission details	
Type of submission:	Type J (Variation to the register entry resulting in a change of product information requiring evaluation of clinical, non-clinical or bioequivalence data)
Product name(s):	MS-2 Step composite pack
Active ingredient(s):	Mifepristone and misoprostol
Submission number:	PM-2022-05475-1-5
Approved strength(s) / dose form(s):	MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet blister; GyMiso misoprostol 200 microgram tablet blister
Initial indication proposed by the sponsor:	Section 4.2 of the current PI advises MS-2 Step can only be prescribed by doctors with the appropriate qualifications and certified training. The Sponsor proposes to amend 'medical practitioner' in the boxed warning and 'doctors' in Section 4.2 of the PI to 'healthcare practitioners' as well as remove the requirement for prescriber certification. Removal of 24-hour phone service for patients is also proposed.

Documents submitted for ACM consideration

The ACM considered the following documentation:

A1 Delegates Summary and Request for ACM Advice
A2 Sponsors Application Letter
M5 Clinical Evaluation Report
R1 Risk Management Plan (RMP) Evaluation Report
A3 Sponsors Response to Delegates Overview (Cover Letter)
A3a Sponsors Response to Delegates Overview
A3c Adverse Reactions Update
A3d Sponsors Comments on PI
A3e Sponsors Comments on Foreign PI
A3f PSUR for the period 1 June 2021 to 31 May 2022
C1 Product Information – annotated
C1 Product Information – clean
C1a Consumer Medicines Information – clean – MS-2Step GyMiso
C1a Consumer Medicines Information – clean – Ms-2Step Mifepristone Linepharma

Delegate's Overview

Delegate's summary of issues

The Delegate identified the following in their request for ACM advice:

Clinical Impact of removal of prescriber certification and training requirement.

Clinical Impact of removal of 24-hour phone service for the patients.

Inconsistencies noted in Sections 4.2, 4.4, 4.6 and 4.8 of the MS-2 Step composite pack PI with the proposed expansion of prescriber eligibility as discussed above and in Section 4.1.2 of clinical evaluation report.

Delegate's preliminary view

The delegate has no reason to say, at this time, that the application should not be approved for the proposed PI change. However, the final decision will only be taken after the ACM meeting.

Advice sought by Delegate of the Secretary of Department of Health and Aged Care

1. Please provide your advice on the proposed changes by the sponsor in the PI / RMP

a) Boxed warning of the MS-2 Step PI to amend 'medical practitioner' to 'healthcare practitioner'

b) Removal of the requirement for prescriber certification from the PI as part of the updated RMP.

c) Removal of 24-hour phone service for patients.

d) Inconsistencies noted in Sections 4.2, 4.4, 4.6 and 4.8 of the MS-2 Step composite pack PI with the proposed expansion of prescriber eligibility.

ACM discussion

An invited expert in the field of women's health (GP) was involved in the discussion for this item.

General comments

The ACM noted that this application seeks to amend the PI for MS-2 Step. Broadly the application seeks to

- Change prescribing from medical practitioner to healthcare practitioner
- Remove the requirement for prescriber certification
- Remove the sponsor managed 24-hour phone service for patients

The combination of mifepristone and misoprostol (MS2-Step composite pack) was first registered in Australia as a combination in August 2012. The ACM noted that the MS2-Step composite pack is not registered in other countries, however Mifegymiso (mifepristone 200 mg and misoprostol 200 micrograms) is registered in Canada and has comparable indications to MS2-Step.

The ACM noted that in Australia termination of pregnancy can occur via medical termination of pregnancy (MTOP) or surgical termination of pregnancy (SToP). The ACM noted that there are legislative variations between States and Territories in respect to termination of pregnancy services.

Safety

The ACM discussed the three key studies (Kopp Kallner et al. (2014), Warriner et al. (2011), and Jejeebhoy et al. (2012)) provided by the sponsor in support of this application.

The ACM noted that the Kopp Kallner et al. (2014) study appeared the most relevant to the Australia context. Within this study the WHO protocol was followed and all women received an ultrasound prior to treatment. Within the doctor prescribed arm, 34 doctors prescribed treatment to 583 women. While in the nurse-midwife arm, 2 nurses prescribed treatment to 597 patients. Outcomes were comparable within both arms.

The ACM also considered the Canadian experience (Schummers et al. 2022) using Mifegymiso. The ACM noted that Regulations were amended in May 2017 and November 2017, together removing the requirement for:

- Pharmacist registration
- Healthcare profession registration
- Mandatory training
- Removing the limitation on an eligible prescriber from 'physician' to be 'authorised health professional' leaving the authority for authorising health professional with the provincial licensing bodies.

ACM advice to the Delegate

The ACM advised the following in response to the Delegate's specific request for advice:

1. Please provide your advice on the proposed changes by the sponsor in the PI / RMP

a) Boxed warning of the MS-2 Step PI to amend 'medical practitioner' to 'healthcare practitioner'

The ACM acknowledged that the healthcare and evidentiary landscape related to medical termination of pregnancy (MTOP) has changed since MS-2 Step was originally registered in Australia (2012). The ACM noted the widespread promulgation of comprehensive guidelines and educational resources for the use of MS-2 Step in Australia. The ACM also noted international changes to the regulation of MTOP with the use of a broader range of health professional prescribers including nurse led models. The ACM also acknowledged the importance of improving access to pregnancy termination services and reducing stigma.

The ACM considered the impacts of broadening the prescribing group to healthcare practitioners within the Australian context. The ACM commented that there are instances where the PI outlines which medical specialist should prescribe, manage and/or supervise treatment. However, the ACM noted that currently for the majority of products, the prescribing requirements are defined by scope of practice and jurisdictional regulatory arrangements, with no recommendations about the prescriber included in the PI. The ACM discussed the term healthcare practitioner and noted the AHPRA list of health practitioners. The ACM did not consider it appropriate for all health practitioners as per the AHPRA list to be able to prescribe MS-2 Step (or other prescription medicines). The ACM acknowledged that there are additional checks and balances beyond the wording of the PI that control prescribing, for example medicine scheduling. However, the ACM noted that changing the

boxed warning (and associated parts of the PI) to state healthcare practitioners may inadvertently assume the PI is supportive of all healthcare practitioners prescribing MS-2 Step. The ACM suggested that some additional wording such as 'healthcare practitioners with an appropriate scope of practice' or 'authorised healthcare practitioners' (as per Canada) may be appropriate. However, prior to coming to a final position the ACM requested additional clarification regarding the wider eligibility criteria for healthcare practitioners prescribing and/or authorisation, including further information on scope of practice and jurisdictional arrangements and consideration of PIs where prescribing information is included.

b) Removal of the requirement for prescriber certification from the PI as part of the updated RMP.

The ACM was supportive of the removal of the requirement for prescriber certification from the PI and as part of the updated RMP. The ACM noted that good guidance and training material is now widely available.

The ACM advised that the phrase *with the appropriate qualifications and training* should remain within the Dose and Method of Administration section of the PI. The ACM noted the obligation on the prescriber to ensure they have the relevant skill, capability and undertake the appropriate due diligence and clinical assessment prior to prescribing the medication.

c) Removal of 24-hour phone service for patients.

The ACM noted that limited information on the use of the 24-hour phone service for patients was provided in the dossier and advised that this information would be helpful to determine whether it is appropriate to remove this service.

The ACM recommended that prior to a decision on removal of the 24-hour phone service for patients the sponsor be requested to provide information on utility of the service.

d) Inconsistencies noted in Sections 4.2, 4.4, 4.6 and 4.8 of the MS-2 Step composite pack PI with the proposed expansion of prescriber eligibility.

The ACM advised that consideration of these inconsistencies would be discussed following a recommendation on the proposed expansion of prescriber eligibility.

ACM conclusion

The ACM advised that additional information is required to allow the ACM to appropriately consider this application and provide an overall benefit risk outcome.

The ACM requested the following information be gathered:

- Clarification on the eligibility criteria for prescribing should MS2-Step prescribing to broadened to healthcare practitioners
- Sponsor to provide information on the utility of the 24-hour phone service

Ratified and sent to the sponsor on 21 June 2023.

Therapeutic Goods Administration

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COVER SHEET

Active ingredient:	Mifepristone and misoprostol
Trade name:	**MS-2 Step**
Sponsor:	s47 [redacted] on behalf of MS Health Pty Ltd
Submission number:	PM-2022-05475-1-5
Form and strength:	MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet blister; GyMiso misoprostol 200 microgram tablet blister

Papers presented for consideration

A1 Delegates Summary and Request for ACM Advice
A2 Sponsors Application Letter
M5 Clinical Evaluation Report
R1 Risk Management Plan (RMP) Evaluation Report

Sponsor response documents

A3 A3_Sponsors Response to Delegates Overview (Cover Letter)
A3a A3a_Sponsors Response to Delegates Overview
A3c A3c_Adverse Reactions Update
A3d A3d_Sponsors Comments on Pl
A3e A3e_Sponsors Comments on Foreign Pl
A3f A3f_PSUR for the period- 1 June 2021 to 31 May 2022 -

Product information documents

C1 C1_Product Information - annotated
C1 C1_Product Information - clean
C1a C1a_Consumer Medicines Information – clean – MS-2Step GyMiso
C1a C1a_Consumer Medicines Information – clean – MS-2Step Mifepristone Linepharma

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Department of Health and Aged Care
Therapeutic Goods Administration

Delegate's overview

Active ingredient(s): Mifepristone and misoprostol

Proprietary product name: [MS-2 Step composite pack] [redacted]

Sponsor: [s47 [redacted] on behalf of MS Health Pty Ltd]

Submission number: [PM-2022-05475-1-5]

eID [e004967]

07 May 2023

TGA Health Safety Regulation

Submission information

Submission number	PM-2022-05475-1-5
Active ingredient(s)	Mifepristone and misoprostol
Product name	MS-2 Step composite pack
Strengths/dose form	MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet blister; GyMiso misoprostol 200 microgram tablet blister
Sponsor	s47 [redacted] on behalf of MS Health Pty Ltd
Description of the submission/proposed indication	This is a Category 1, Type J application (variation to the register entry resulting in a change of product information requiring evaluation of clinical, non-clinical or bioequivalence data) to update the PI for MS-2 Step composite pack. Section 4.2 of the current PI advises MS-2 Step can only be prescribed by doctors with the appropriate qualifications and certified training. The Sponsor proposes to amend 'medical practitioner' in the boxed warning and 'doctors' in Section 4.2 of the PI to 'healthcare practitioners' as well as remove the requirement for prescriber certification. Removal of 24-hour phone service for patients is also proposed.
Summary of data	It is a Literature Based Submission. The main evidence provided to support the proposed change is from 3 studies, including data for approximately 1800 women receiving MToP up to 63 days gestation and approximately 1100 women receiving MToP up to 8 weeks gestation. Overall, the evidence provided supports the proposed changes to the boxed warning of the MS-2 Step PI to amend '*medical practitioner*' to '*healthcare practitioner*' and to amend '*doctors with the appropriate qualifications and certified training*' in Section 4.2 to '*healthcare practitioners with the appropriate qualifications and certified training*' given the Sponsor proposes to maintain the existing standardised training for prescribers. However, subsequent submission by the sponsor to the Risk Management Section, to remove the requirement for prescriber certification from the PI as part of the updated RMP provided to TGA (dated 17th February 2023). The proposed removal of prescriber certification from the PI does potentially bring into question the Sponsor's justification for the proposed changes to the PI as the Clinical Expert's assertion regarding a minimum baseline of education irrespective of training background would

	not hold if the requirement for prescriber certification is removed. The proposed changes to the boxed warning and Section 4.2 give rise to inconsistencies in the PI which have not been addressed: • Section 4.2 Dose and method of administration: The Sponsor states in the Cover letter the application proposes to amend the reference to 'doctors' in Section 4.2 to 'healthcare practitioners'. However Section 4.2 includes the text '*When MS-2 Step fails to cause termination of intra-uterine pregnancy, the patient should return to the treating doctor for assessment and discussion of treatment options, which may include pregnancy termination by surgery*.' This text is not consistent with the proposed changes advising patients receiving these medications are followed up by a healthcare practitioner, preferably the prescriber. • Section 4.4 Special warnings and precautions for use: Section 4.4 includes information regarding particular co-morbidities as follows: *Take special care in case of suspected acute adrenal failure. In case of suspected acute adrenal failure, dexamethasone administration is recommended (please refer to the dexamethasone Product Information).* *Due to the antiglucocorticoid activity of mifepristone, the efficacy of long-term corticosteroid therapy, including inhaled corticosteroids in asthmatic patients, may be decreased during the 3 to 4 days following intake of mifepristone. Therapy should be adjusted.* Patients with these medical comorbidities may require additional medical management such as adjustment of inhaled corticosteroid (ICS) therapy for asthma patients for example, that may be outside the scope of practice of non-physician healthcare providers. The Sponsor has not specifically addressed how patients with relevant medical comorbidities as described in the PI will be managed by non-physician healthcare providers. • Section 4.4 Special warnings and precautions for use and Section 4.8 Adverse effects (undesirable effects): Section 4.4 includes text regarding cases of serious bacterial infection, including very rare cases of fatal septic shock, with statements in the 'Infection' subsection specifically referring to 'doctors' as follows: - *'Treating doctors evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event.'* This text is not consistent with the proposed changes advising patients receiving these medications are followed up by a healthcare practitioner, preferably the prescriber.

	It would seem appropriate all healthcare providers would need to be aware of this risk. - *'These symptoms, even without a fever, may indicate Clostridium sordellii infection. Strong consideration should be given to obtaining a complete blood count in these patients. Significant leukocytosis with a marked left shift and haemo-concentration may be indicative of sepsis. Doctors should consider immediately initiating treatment with antibiotics that includes coverage of anaerobic bacteria such as Clostridium sordellii.'* This text is also included in Section 4.8 of the PI. These statements refer to clinical management of a potentially serious infection/possible sepsis including initiation of appropriate antibiotic therapy. As aforementioned, it is not clear whether this is within the scope of practice of non-physician healthcare providers. • Section 4.6 Fertility, pregnancy and lactation: Section 4.6 includes the following text*:* *'To avoid the potential exposure of a subsequent pregnancy to MS-2 Step it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after administration of MS-2 Step.'* This is considered important safety information. It is not clear whether prescription of reliable contraceptive methods is within the scope of practice for all healthcare providers for whom expanded prescriber eligibility is proposed (acknowledging different state/territory legislation), and therefore if some patients may need to be referred to a different healthcare provider. 'Return to fertility' is included in the 'Serious warnings and precautions' box in the Canadian Mifegymiso product monograph [2]. These outstanding issues may require appropriate risk minimisation strategies such as updates to the educational materials.
Preliminary view	At this stage I am inclined to hear the discussion and deliberation of the ACM members on training requirements before making my final decision.
Outstanding issues	Removal of prescriber certification and training requirement. Although the sponsor will continue to make educational materials available as support to prescribers and dispensers. Removal of 24-hour phone service for the patients. Inconsistencies noted in Sections 4.2, 4.4, 4.6 and 4.8 of the MS-2 Step composite pack PI with the proposed expansion of prescriber eligibility as discussed above and in Section 4.1.2 of clinical evaluation report.

Request for ACM advice

ACM meeting number: 39 **Date (of meeting): 1st / 2nd June 2023**

Summary of issue/s for advice	Clinical Impact of removal of prescriber certification and training requirement. Clinical Impact of removal of 24-hour phone service for the patients. Inconsistencies noted in Sections 4.2, 4.4, 4.6 and 4.8 of the MS-2 Step composite pack PI with the proposed expansion of prescriber eligibility as discussed above and in Section 4.1.2 of clinical evaluation report.
Advice sought	1. Please provide your advice on the proposed changes by the sponsor in the PI / RMP a. Boxed warning of the MS-2 Step PI to amend '*medical practitioner*' to '*healthcare practitioner*' b. Removal of the requirement for prescriber certification from the PI as part of the updated RMP. c. Removal of 24-hour phone service for patients. d. Inconsistencies noted in Sections 4.2, 4.4, 4.6 and 4.8 of the MS-2 Step composite pack PI with the proposed expansion of prescriber eligibility.

s22 [redacted]

Delegate of the Secretary under regulation 35A of the Therapeutic Goods Regulations 1990

08 May 2023

Date

Body of overview

Introduction

Mifepristone belongs to the Pharmacotherapeutic group: Other sex hormone and modulator of the reproductive function/antiprogestogen, ATC code GO3XB01.

Misoprostol belongs to the Pharmacotherapeutic group: Other gynaecological medicines – prostaglandins, ATC code G02AD06.

Mifepristone is a synthetic steroid with an antiprogestational action as a result of competition with progesterone at the progesterone receptors. In women at doses of greater than or equal to 1 mg/kg, mifepristone antagonises the endometrial and myometrial effects of progesterone. During pregnancy it sensitises the myometrium to the contraction inducing action of prostaglandins. Misoprostol is a synthetic analogue of prostaglandin E1. At the recommended dosages, misoprostol induces contractions of the smooth muscle fibres in the myometrium and relaxation of the uterine cervix. In the event of an early termination of pregnancy, the combination of a prostaglandin analogue used in a sequential regimen after mifepristone leads to an increase in the success rate and accelerates the expulsion of the conceptus.

The approved indication is [1]:

MS-2 Step is indicated in females of childbearing age for the medical termination of an intrauterine pregnancy, up to 63 days of gestation.

It is recommended that the duration of pregnancy (i.e., up to 63 days gestation) be confirmed by ultrasound. In the event that an ultrasound is not possible, extra caution should be exercised.

Ultrasound is also useful to exclude ectopic pregnancy.

Currently the MS-2 Step PI defines MS-2 Step can only be prescribed by doctors with the appropriate qualifications and certified training, with the subsequent post administration follow up to be conducted by a medical practitioner, preferably the prescriber. Therefore, access to early medical abortion (as indicated up to 63 days of gestation) is restricted to where a certified medical practitioner is located.

To ensure timely access to patients, and to ensure that the product is prescribed by the persons authorised by state and territory legislation, the application proposes to amend the black box warning from referencing 'medical practitioner' to 'healthcare practitioner', and for the reference to 'doctors' in section 4.2 to be amended to 'healthcare practitioners'.

Regulatory History

The individual components of MS-2 Step, Mifepristone Linepharma (mifepristone 200 mg tablet) and GyMiso (misoprostol 200 microgram tablet) were registered in Australia on 29th August 2012 for medical termination of developing intrauterine pregnancy up to 49 days gestation as follows:

Mifepristone Linepharma (AUST R 175671):

Medical termination of a developing intra-uterine pregnancy. In sequential combination with a prostaglandin analogue up to 49 days of gestation; and preparation for the action of registered prostaglandin analogues that are indicated for the termination of pregnancy for medical reasons beyond the first trimester.

GyMiso (AUST R 188015):

GyMiso is indicated in females of childbearing age for the medical termination of a developing intrauterine pregnancy in sequential combination with a mifepristone 200 mg tablet, up to 49 days of gestation.

MS-2 Step composite pack containing Mifepristone Linepharma (mifepristone) 200 mg tablet and GyMiso (misoprostol) 200 microgram tablets was registered on 4th June 2014 (Submission PM-2013-01037-1-5). As part of this submission, the indication was extended to the medical termination of a developing intrauterine pregnancy from 49 days up to 63 days gestation.

Following registration of MS-2 Step composite pack, the Sponsor withdrew the GyMiso mono product from the market, and removed the indication for medical termination of pregnancy up to 49 days for the Mifepristone Linepharma mono product (Submission PM-2014-03311-1-5).

MS-2 Step combination pack is not registered in other countries/regions.

The combination product Mifegymiso (mifepristone 200 mg tablet and misoprostol 200 microgram tablet combination pack, Linepharma International Limited) is approved in Canada for a comparable indication to MS-2 Step composite pack [2]:

'*Mifegymiso (mifepristone tablet/misoprostol tablets) is indicated for:*

• *medical termination of a developing intra-uterine pregnancy with a gestational age up to 63 days as measured from the first day of the Last Menstrual Period (LMP) in a presumed 28-day cycle.*

Mifegymiso is not intended for routine use as a contraceptive.'

Mifegymiso should be prescribed by health professionals with adequate knowledge of medical abortion and/or who have completed a Mifegymiso education program.

Mifepristone is registered in the USA, UK and various countries in Europe. In the USA, Mifeprex (mifepristone) is only available through the mifepristone risk evaluation and mitigation strategy (REMS) Program

Proposed MS-2 Step PI change
Boxed warning It is very important that all patients receiving these medications are followed up by a ~~medical~~ healthcare practitioner, preferably the prescriber, to ensure that the medication has been effective. Even if no adverse events have occurred all patients must receive follow-up 14 to 21 days after taking mifepristone. Read the Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE carefully.
4.2 Dose and method of administration MS-2 Step is indicated for medical termination of intrauterine pregnancy, up to 63 days of gestation. The method of administration is as follows: Mifepristone: 200 mg of mifepristone (1 tablet containing 200 mg) orally, followed 36 to 48 hours later by the administration of GyMiso®.

GyMiso®: 800 micrograms of misoprostol (4 tablets, each tablet containing 200 micrograms) buccally, i.e: kept between the cheek and the gum for 30 minutes before any fragments being swallowed with water.

When MS-2 Step fails to cause termination of intra-uterine pregnancy, the patient should return to the treating doctor for assessment and discussion of treatment options, which may include pregnancy termination by surgery.

No dosage adjustment of misoprostol or mifepristone is necessary with renal or hepatic insufficiency when administered at the recommended doses.

There are no data available on the effect of food intake on the absorption of mifepristone or misoprostol. MS-2 Step should be taken 2 hours before or 2 hours after a meal.

Refer also to 4.3 CONTRAINDICATIONS, and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

MS-2 Step should only be prescribed by healthcare practitioners ~~doctors~~ with the appropriate qualifications ~~and certified training~~. Ectopic pregnancy should be excluded, an intrauterine device (IUD) (if present) must be removed, consent must be obtained and patients must have the ability to access 24-hour emergency care if and when required for incomplete abortion or bleeding.

Risk Management Plan (RMP) evaluation

RMP evaluator recommendations regarding condition/s of registration

- On 1 December 2022, MS Health Pty Ltd submitted updated AU-RMP version 0.4 (dated 24 November 2022; DLP 31 May 2022) for MS-2 Step. The EU-RMP is not available. A revised AU-RMP version 4.0 (dated 13 January 2023; DLP 31 May 2022) was provided with the sponsor's response to RMP evaluator's recommendations dated 13 January 2023. On 20 February 2023, the sponsor submitted further changes in AU-RMP version 4.0 (dated 17 February 2023; DLP 31 May 2022) which has been linked to the Category 1, Type J application (PM-2022-05475-1-5). At Round 2, the sponsor submitted updated AU-RMP version 4.1 (dated 5 April 2023; DLP 31 May 2022) with their S31 response dated 6 April 2023.
- MS-2 Step is approved for the medical termination of an intrauterine pregnancy, up to 63 days of gestation, in females of childbearing age.
- The most recently evaluated and approved AU-RMP was version 03 (dated 13 November 2014; DLP 28 April 2013) (R14/1181088).
- The reason for this updated RMP is changes to the summary of safety concerns (SoSC) and changes to the risk minimisation plan. The key changes proposed for risk minimisation activities are as follows:
    - To remove the requirement for pharmacists to be registered to be able to dispense the product.
    - To remove the requirement for prescriber recertification.
    - To remove the need for prescribers to complete mandatory training and receive certification to be able to prescribe the product.
    - To remove the requirement for a Sponsor provided 24 hours aftercare service
- As the TGA has previously evaluated RMPs for this product, the focus of this review is on the differences between the AU-RMP versions and revisions to the additional risk minimisation materials.
- The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below:

Summary of safety concerns	Pharmacovigilance	Risk Minimisation

		Routine	Additional	Routine	Additional
Important identified risks	Infection, toxic shock syndrome	✓	–	✓	✓[1,2]
	Method failure	✓	–	✓	✓[1,2]
	Cardiac disorders	✓	–	✓	✓[2]
Important potential risks	Inadvertent pregnancy exposure and risk of incomplete abortion with severe bleeding	✓	–	✓	✓[2]
	Inadvertent pregnancy exposure (risk of malformations)	✓	–	✓	✓[2]
	Potential interaction with CYP3A4 inhibitors or inducers	✓	–	✓	–
	Potential interaction with products interacting with the glucocorticoid receptor	✓	–	✓	–
	Induced bronchial asthma	✓	–	✓	–
	Effects in lactating women	✓	–	✓	–
	Effects in women with impaired liver function	✓	–	✓	–
	Effects in women with impaired renal function	✓	–	✓	–
	Effects in women with malnutrition	✓	–	✓	–
	Incorrect determination of gestational age	✓	–	✓	–
	Potential for missed ectopic pregnancy	✓	–	✓	✓[2]
	Potential for postnatal developmental delay	✓	–	✓	–
	Potential for off-label use beyond the first trimester	✓	–	✓	–
Missing information	Inherited porphyria	✓	–	–	–
	Theoretical interaction with NSAIDs	✓	–	–	–
	Potential interaction with products interacting with the progesterone receptor	✓	–	–	–
	Use in adolescents	✓	–	–	–
Pharmacological class effect	Risks related to the use of prostaglandin	✓	–	✓	✓[2]

[1] Black box warning

[2] Patient Information and Consent Agreement form

- The sponsor has updated the summary of safety concerns in line with recommendations by the RMP evaluator as well as to reflect up-to-date safety information for MS-2 Step. At

Round 2, the sponsor has proposed to remove potential risk 'Potential for loss to follow-up' and this is acceptable from an RMP perspective. However, the sponsor has also removed potential risk 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up', which is not supported as there are additional considerations to this risk with regards to access to further advice or treatment if follow-up does not occur.

- The completed post marketing surveillance study has been removed from the pharmacovigilance plan. Routine pharmacovigilance is proposed for all safety concerns. There is one additional pharmacovigilance activity – an ongoing Canadian post-market surveillance study on the effectiveness and safety of combination mifepristone/misoprostol for medical abortion under 63 days gestation. Further changes to the pharmacovigilance plan in the AU-RMP is recommended.

- The sponsor proposes to remove from the risk minimisation plan the requirements for prescriber certification, pharmacist registration and a Sponsor-provided 24 hours aftercare service. Additional risk minimisation activities will consist of a black box warning, inclusion of CMI and instruction insert in pack, and Patient Information and Consent Agreement form. The sponsor will continue to make educational materials available as support to prescribers and dispensers. The proposed risk minimisation plan aligns with that in Canada and the UK. The RMP evaluator has noted the post-market experience with MS-2 Step, its well-established safety profile, and existing safety frameworks in place. The RMP evaluator has also noted the importance of timely access of this medicine in terms of patient-safety and the need to remove requirements that hinder patient access to reproductive services. The proposed changes to the risk minimisation plan are acceptable from an RMP perspective. Further changes to the risk minimisation plan are recommended. The sponsor is also requested to include a copy of the Educational Program materials and Patient Information and Consent Agreement form in the appendix of the AU-RMP.

The MS-2 STEP Australian Risk Management Plan (AU-RMP) (version 4.1, dated 5 April 2023, data lock point 31 May 2022), included with submission PM-2022-05475-1-5, to be revised to the satisfaction of the TGA, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Discussion

The main evidence provided to support the proposed change is from 3 studies, including data for approximately 1800 women receiving MToP up to 63 days gestation [5, 6] and approximately 1100 women receiving MToP up to 8 weeks gestation [7].

The Kopp Kallner *et al*. [5] study is considered most relevant to use in Australia. This study was conducted in a high-resource setting with ultrasound as part of the protocol, whereas the studies by Warriner *et al*. [6] and Jejeebhoy *et al*. [7] were conducted in low-resource settings. Neither of the latter 2 studies included ultrasound assessment per study protocol, nor was hCG testing utilised in the Warriner study. This does not generally align with the Australian MS-2 Step PI [1], which recommends confirmation of pregnancy duration by ultrasound in the indication, and lists 'pregnancy not confirmed by an ultrasound or biological test such as urine or serum HCG' as a contraindication. Furthermore, the study population and dose of misoprostol used in the Jejeebhoy *et al*. [7] study differs from approved use in Australia.

Although the Warriner *et al*. and Jejeebhoy *et al*. studies [6, 7] are less applicable to the Australian setting, overall there were no safety concerns with provision of MToP by MLPs identified in any

of the 3 studies, with effectiveness outcomes comparable for MLPs and doctors. The risk of failure was comparable for MToP performed by MLPs and doctors in all studies and is a known risk described in the MS-2 Step PI [1]. There were no serious adverse events reported. The reasons for complications were provided by Kopp Kallner *et al*. [5] and noted to be consistent with the safety profile of MToP with mifepristone/misoprostol.

There was variability in provider experience across the 3 studies. Nurse-midwives experienced in MToP were recruited in the Kopp Kallner *et al*. [5] study with additional early pregnancy ultrasound training provided. All providers underwent MToP training in the Warriner *et al*. and Jejeebhoy *et al*. studies [6, 7]. The importance of education with regard to the MToP process was endorsed by the Clinical Expert who reiterated *'MS Health proposes to continue providing the same (existing) standardised training for all potential prescribers (as detailed in the current approved Australian RMP) and doing so will ensure a minimum baseline of education regardless of training background',* stating further *'The PI amendments proposed by MS Health simply enable individual jurisdictions to make decisions appropriate for their population'.*

Broadening the prescriber eligibility to include non-physician prescribers (in accordance with individual state and territory requirements) is consistent with established practice in Canada and the USA, noting the USA has REMS program requirements for all prescribers [3].

Overall, the evidence provided supports the proposed changes to the boxed warning of the MS-2 Step PI to amend '*medical practitioner'* to '*healthcare practitioner'* and to amend '*doctors with the appropriate qualifications and certified training'* in Section 4.2 to '*healthcare practitioners with the appropriate qualifications and certified training*' given the Sponsor proposes to maintain the existing standardised training for prescribers.

However, the Sponsor has subsequently submitted proposal to remove the mandatory requirement for prescriber certification from the PI as part of the updated RMP provided to TGA (dated 17th February 2023). The proposed removal of prescriber certification from the PI does potentially bring into question the Sponsor's justification for the proposed changes to the PI as the Clinical Expert's assertion regarding a minimum baseline of education irrespective of training background would not hold if the requirement for prescriber certification is removed. In their S31 response they do however emphasis that the existing standardised training (the Medical Education Program) will still be available for all healthcare practitioners that prescribe MS-2 Step via the existing online website (www.ms2step.com.au). The change proposed in the most recent submitted update to the RMP was to remove the mandatory aspect of the training and the subsequent certification.

But the justification provided by the Clinical Expert in the Clinical Overview Addendum to expand prescriber eligibility to include non-physician prescribers (in accordance with individual state and territory requirements) included assurance the existing standardised training for all potential prescribers as per current approved Australian RMP (i.e. mandatory practitioner training and certification) would be maintained, and was supported by data provided in the dossier. As noted in the clinical evaluation report, all the providers underwent MToP training in the Warriner *et al*. and Jejeebhoy *et al*. studies (including certification in the Warriner *et al*. study) [6, 7], and the Kopp Kallner study [5] recruited nurse-midwives experienced in MToP who received additional ultrasound training. The proposed removal of '*and certified training*' from the proposed PI provided with the Section 31 response does not align with the Clinical Expert's assertion that '*a minimum baseline of education regardless of training background will continue to be provided*' and data included in the submission to support the proposed expansion of prescriber eligibility.

Conclusions

The evidence provided in the submission support the proposed changes to the boxed warning to amend 'medical practitioner' to 'healthcare practitioner' and to amend 'doctors with the appropriate qualifications and certified training' in Section 4.2 to 'healthcare practitioners with

the appropriate qualifications and certified training' (in accordance with individual state and territory requirements) on the basis the existing standardised training for all potential prescribers is maintained.

However, the sponsor's proposal to remove 'certified training' from the PI has created uncertainty regarding the risk of expanding prescriber eligibility and removing the requirement for certified training.

Attachments for ACM

Number	Document name	Location/ID	ACM attachment
1	Clinical Evaluation Report	D23-5339936	☐
2	RMP	D22-6199891	☐
3	Annotated PI	e004967 (0012-) - Product Information - Annotated	☐

References

1. Australian MS-2 Step PI. Available at TGA PI/CMI repository. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent=&id=CP-2014-PI-01965-1&d=20230222172310101

2. Canadian Mifegymiso Product Monograph (date of revision 17th June 2022). Provided in Module 5.4 (e004967 (0007-) - Canada SmPC)

3. US Mifeprex Product Label. Revised 01/2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020687Orig1s025Lbl.pdf

4. WHO Abortion Care Guideline 2022. Geneva: World Health Organization; 2022. Provided in Module 5.4 (e004967 (0007-) - WHO - Abort Care guidelines - 2022)

5. Kopp Kallner H, Gomperts R, Salomonsson E, Johansson M, Marions L, Gemzell-Danielsson K. The efficacy, safety and acceptability of medical termination of pregnancy provided by standard care by doctors or by nurse-midwives: a randomised controlled equivalence trial. *BJOG*. 2015;122:510-517. Provided in Module 5.4 (e004967 (0007-) - Kopp-Kallner 2014).

6. Warriner IK, Wang D, Huong NTM, Thapa K, Tamang A, Shah I *et al*. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomised controlled equivalence trial in Nepal. *Lancet*. 2011;377:1155-1161. Provided in Module 5.4 (e004967 (0007-) - Warriner 2011)

7. Jejeebhoy SJ, Kalyanwala S, Mundle S, Tank J, Zavier AJF, Kumar R *et al*. feasibility of expanding the medication abortion provider baser in India to include ayurvedic physicians and nurses. *Int Perspect Sex Reprod Health*. 2012;38:133-142. Provided in Module 5.4 (e004967 (0007-) - Jejeebhoy 2012)

8. Barnard S, Kim C, Park MH, Ngo TD. Doctors or mid-level providers for abortion. *Cochrane Database of Systematic Reviews* 2015, Issue 7. Art. No.: CD011242. DOI: 10.1002/14651858.CD011242.pub2. Provided in Module 5.4 (e004967 (0007-) - Barnard 2015)

9. Regulatory Decision Summary – Mifegymiso - Health Canada. https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detail.php?linkID=RDS00032

10. Regulatory Decision Summary – Mifegymiso - Health Canada. https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detail.php?linkID=RDS00294

11. Schummers L, Darling EK, Dunn S, McGrail K, Gayowsky A, Law MR *et al*. Abortion safety and use with normally prescribed mifepristone in Canada. *N Engl J Med*. 2022;386:57-67. Provided in Module 5.4 (e004967 (0007-) - Schummers 2022)

12. Schummers L, Darling EK, Dunn S, McGrail K, Gayowsky A, Law MR *et al*. Abortion safety and use with normally prescribed mifepristone in Canada. *N Engl J Med*. 2022;386:57-67. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7489974/

13. Berer M. Provision of abortion by mid-level providers: international policy, practice and perspectives. *Bull World Health Organ*. 2009;87:58-63. Provided in module 5.4 (e004967 (0007-) - Berer 2009)

14. UK SPC Mifepristone Linepharma 200 mg tablet (revised 27/10/22). https://mhraproducts4853.blob.core.windows.net/docs/72e81b0722b04c4d065babba78a7be4e0dbe89fb

Therapeutic Goods Administration

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s47 [redacted]

22 December 2022

The Head
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Therapeutic Goods Administration
PO Box 100
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Category 1 Application – Type J: PI Change Requiring Evaluation of Data

AUST R	Product Details
210574	MS-2 Step composite pack [MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet blister; GyMiso misoprostol 200 microgram tablet blister]

Submission Number: PM-2022-05475-1
eSubmission Identifier: e004967
Sequence: 0007; Related Sequence: 0007

Dear Sir / Madam

This Category 1 Application to make changes to the Product Information (PI) for the above-mentioned product is being submitted on behalf of MS Health Pty Ltd (Client ID 57301). s47 [redacted] are the appointed agents for MS Health Pty Ltd regarding this application.

This application relates to the Pre-submission Planning Form (PPF) submitted on 15th December 2022 with an expected submission due date of 23 December 2022.

The dossier is submitted in eCTD format and further details are provided below under the "Electronic Submission Details" section.

Application Overview:

Currently the MS-2 Step PI defines that the MS-2 Step product can only be prescribed by doctors with the appropriate qualifications and certified training, with the subsequent post administration follow up to be conducted by a medical practitioner, preferably the prescriber. Therefore, access to early medical abortion (as indicated up to 63 days of gestation) is restricted to where a certified medical practitioner is located.

To ensure timely access to patients, and to ensure that the product is prescribed by the persons authorised by state and territory legislation, MS Health, the sponsors of MS-2 Step composite pack are seeking approval to vary the approved PI as proposed below.

s47 [redacted]

Currently the MS-2 Step PI includes the following black box warning relevant to section 4.4 Special Warnings and Precautions for Use:

"It is very important that all patients receiving these medications are followed up by a medical practitioner, preferably the prescriber, to ensure that the medication has been effective. Even if no adverse events have occurred all patients must receive follow-up 14 to 21 days after taking mifepristone. Read the Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE carefully."

Section 4.2 of the MS-2 Step Product Information also states:

MS-2 Step should only be prescribed by doctors with the appropriate qualifications and certified training.

This application is proposing to amend the black box warning from referencing "medical practitioner" to "healthcare practitioner"; and for the reference to "doctors" in section 4.2 to be amended to "healthcare practitioners".

The proposed amendment to the PI will also bring Australia into alignment with global best clinical practice and WHO recommendations for provision of medical termination of pregnancy (MToP). The Departments of Health in individual states and territories will still be the final determinant on who is an appropriate prescriber within their jurisdiction. The PI amendments proposed by MS Health is therefore intended to enable individual jurisdictions to make decisions appropriate for their population.

An addendum to the clinical overview has been submitted in support of the proposed change to the prescriber in module 2.5.

Module 5.2 has not been provided with this submission as it is not applicable to this application.

Risk Management Plan

An updated RMP was submitted to the TGA for review on the 1st December 2022 (version 04). Following the completion of the evaluation of this Category 1 application, the version 04 of the RMP will be updated in accordance with the approved changes and is proposed to be submitted with the next safety update.

Bioequivalence

A justification for not providing biopharmaceutic and/or absolute bioavailability data is not required for this application as there are no changes to the Module 3 data.

The following CTD modules are provided in support of this application:

- 1.0.2 Tracking Table
- 1.2.1 Application form
- 1.2.2 Pre submission details
- 1.3.1 Annotated and Clean PIs
- 1.3.2 Annotated and Clean CMIs
- 1.4.3 Clinical Expert Declaration

- 1.7.3 Declaration of compliance with PPF
- 2.5 Clinical overview
- 5.4 Literature references

Declarations

The following assurances are provided in relation to the application.

- No aspects of the quality information have been changed, including manufacturing procedures, equipment and raw material and finished product specifications, other than the changes nominated in this application.
- The PI provided is the most recent approved version and all of the proposed changes to the PI relate to the changes requested and no other unidentified changes have been proposed or made.

Invoice and contact details

Please issue the invoice for the evaluation fees for this application directly to the Sponsor, MS Health Pty Ltd (i.e. please ensure the invoice is not issued to the agent company).

Please do not hesitate to contact me on s22 [redacted] by facsimile on s22 [redacted] or by email at s47 [redacted] if you require any further regulatory or information technology assistance with this submission.

Yours faithfully,

s22 [redacted]

s22 [redacted]
Senior Consultant, Regulatory, Quality & Compliance
s47 [redacted] **d**
(Agents on behalf of MS Health Pty Ltd)

Electronic Submission Details

eSubmission Identifier	e004967
Format	eCTD
Specification	AU 3.0
eBS Client ID	57301
Approved Name	Mifepristone, Misoprotol
Trade Name	MS-2 STEP COMPOSITE PACK
ARTG Number(s)	210574
Submission Number	PM-2022-05475-1
Sequence Number	0007
Related Sequence Number	0007
Regulatory Activity Lead	Prescription meds-chemical
Sequence Type	Category 1 Type J - PI Change requiring evaluation
Sequence Description	Initial
Submission Mode	Single
Electronic Media	PMMV Portal
Submission Size (Approximate)	~ 7.20 MB
Validation Tool and Version	Lorenz eValidator v.21.2
Validation Findings	Not applicable A copy of the validation report can be provided upon request.
Virus Protection Software and Assurance	Webroot Secure Anywhere Endpoint Protection v9.0.26.61. An assurance is provided that the electronic dossier is virus free.
Contact email	s47 [redacted]

PRE-ACM RESPONSE

24th May 2022

The Director
Prescription Medicines
Authorisation Branch
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606

Sponsor's Name: MS Health Pty Ltd
Return Address:
Attention:
Phone Number:
Fax Number:
Email:

AUST R	Product Details
210574	MS-2 Step composite pack [MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet blister; GyMiso misoprostol 200 microgram tablet blister]

Submission Number: PM-2022-05475-1-5
eSubmission Identifier: e004967
Sequence: 0016; Related Sequence: 0007
Response Due Date: 24 May 2023

Dear Sir / Madam

In response to the Request for ACM's advice (issued by , Delegate of the Secretary, dated 8 May 2023, received 17th May 2023), please find herein copy of the Pre-ACM Response for the aforementioned Category 1 Application. This information is provided on behalf of the Sponsor, MS Health Pty Ltd (Client ID 57301).

It is noted that the Request for ACM's advice was dated the 8th May 2023. Therefore, the request for ACM's advice did not take into consideration the response to the second RMP evaluation report and the response to the second round clinical evaluation report submitted on the 10th May 2023 and the 14th May 2023 respectively. The pre-ACM response therefore makes reference to the responses to the second-round clinical evaluation report as applicable.

The response is submitted as per the required Pre-ACM format with the following information provided:

PreACM component	CTD Location
Sponsor's comment on evaluations	Module 1.0.3 Response to request for information
International regulatory history	Not applicable. A similar application has not been submitted in other territories.

Adverse reactions update	Module 1.0.3 Response to request for information
Sponsor's comments on PI	Module 1.0.3 Response to request for information
Sponsor's comments on foreign PI	Module 1.0.3 Response to request for information
PSUR	Module 1.0.3 Response to request for information
PI (annotated and non-annotated)	Module 1.3.1.1 Product information – clean and Module 1.3.1.2 Product information – annotated
CMI (annotated and non-annotated)	Module 1.3.2.1 Consumer Medicine Information – clean and Module 1.3.2.2 Consumer Medicine Information – annotated
Foreign equivalent to product information	Module 1.11.2 Foreign product information (Canadian Monograph for "Mifegymiso" **mifepr**istone 200 mg tablets and misoprostol 200 mcg tablets) Please note, the same application has not been submitted other countries, therefore the foreign PI has been provided for reference only given the Canadian PSUR has been used as the reference for the RMP.

The dossier is submitted in eCTD format and further details of the electronic submission are provided in Appendix 1 below.

Please do not hesitate to contact me on s22 [redacted] or by email at s47 [redacted] you require any further regulatory or information technology assistance with this submission.

Yours faithfully,

s22 [redacted]

Regulatory Consultant

s47 [redacted]

(Agents on behalf of MS Health Pty Ltd)

Appendix 1: Electronic Submission Details

eSubmission Identifier	e004967
Format	eCTD
Specification	AU 3.0
eBS Client ID	57301
Approved Name	Mifepristone, Misoprotol
Trade Name	MS-2 STEP COMPOSITE PACK
ARTG Number(s)	210574
Submission Number	PM-2022-05475-1-5 PV
Sequence Number	0016
Related Sequence Number	0007
Regulatory Activity Lead	Prescription meds-chemical
Sequence Type	Supplementary Information
Sequence Description	Pre-Advisory Committee Response
Submission Mode	Single
Electronic Media	Email
Submission Size (Approximate)	~ 3.89 MB
Validation Tool and Version	Lorenz eValidator v.21.2
Validation Findings	No validation findings A copy of the validation report can be provided upon request.
Virus Protection Software and Assurance	Webroot Secure Anywhere Endpoint Protection v9.0.26.61. An assurance is provided that the electronic dossier is virus free.
Contact email	s47 [redacted]

PRE-ACM RESPONSE

Overall recommendation – Sponsor Summary Response

The Sponsor acknowledges the Delegate's comments provided in the request for ACM's advice (dated 8th May 2023). Responses to the Delegate's comments are provided in the subsequent sections below.

RESPONSE TO REQUEST FOR ACM ADVICE

Question 1: Please provide your advice on the proposed changes by the sponsor in the PI / RMP

a. Boxed warning of the MS-2 Step PI to amend 'medical practitioner' to 'healthcare practitioner'

***Sponsor Response**:*

The proposed changes to the MS- 2 Step PI will bring the eligible prescribers in line with global guidelines and clinical best practice; enable individual Australian state health authorities to make decisions appropriate for their population; and improve the current access for women by not only increasing the number of eligible prescribers, but also by removing the need for women to travel long distances to access a prescriber and safe abortion services, without increasing risk to patients. MS Health proposes to continue to provide access to the same (existing) standardised training for all potential prescribers and this together with other education and training resources that are available will ensure a minimum baseline of education regardless of training background.

Currently the MS-2 Step Product Information (PI) defines that the MS-2 Step product can only be prescribed by doctors with the appropriate qualifications and certified training, with the subsequent post administration follow up to be conducted by a medical practitioner, preferably the prescriber. Therefore, access to early medical abortion (as indicated up to 63 days of gestation) is restricted to patients and locations where a certified medical practitioner is accessible.

By allowing mid-level healthcare practitioners such as nurses, midwives and Nurse Practitioners to prescribe MS-2 Step (and as defined by the current state and territory legislation), this will improve the current access for women by not only increasing the number of eligible prescribers but also by removing the need for women to travel long distances to access a prescriber and safe abortion services .

Additionally, the use of the term 'healthcare practitioner' will encompass any variability in the state and territory terminology therefore allowing the specific state and territory legislation to define the persons authorised to perform or assist with MToP.

MToP provision by mid-level healthcare practitioners such as nurses, midwives and Nursing Practitioners is already available and part of the standard of care in a number of developed and developing countries such as Canada. Since 2017, there has not been an increase in the incidences of serious adverse events in Canada due to the change in prescriber indicating no

increased risk to patients when MToP is provided by mid-level healthcare professionals. For reference, a copy of the Canadian Product Information has been provided in Module 1.11.2.

The proposed changes to the MS- 2 Step PI will bring it in line with global guidelines and clinical best practice; and will enable individual Australian state health authorities to make decisions appropriate for their population.

The prescriber's obligation to acquire the knowledge and skill to prescribe a drug safely is a fundamental aspect of their practice, regardless of whether the prescriber is a medical professional or healthcare professional and therefore the Sponsor does not believe that the proposed change will result in any additional risk when the prescriber eligibility is changed from a medical professional to a healthcare professional.

b. Removal of the requirement for prescriber certification from the PI as part of the updated RMP.

***Sponsor Response**:*

The Sponsor proposes to remove the requirement for prescriber certification from the PI and the updated RMP, however, the training programs will still be available. The Education Program however will be included as an Annex to the RMP and via the MS Health online website, www.ms2step.com.au.

It is the prescriber's obligation to acquire the knowledge and skill to prescribe a drug safely (which is a fundamental aspect of their practice), regardless of whether the RMP includes mandatory certification of prescribers. Since MS-2 Step was first registered a number of education and training resources have been developed to support prescribers beyond that offered by the MS Health Education Program.

Additionally, it is expected that for other prescribed products, the prescriber would be professionally competent before prescribing any product. The Sponsor is therefore proposing that the requirements for MS-2 Step be aligned with this approach whereby mandatory training programs / certification is not required before the product can be prescribed.

The Sponsor therefore does not believe that the removal of the mandatory certification result in any additional risk as the Medical Education Program will continue to be available online via the existing website (www.ms2step.com.au), along with other education and training resources that are available over and above the Sponsor specific training.

c. Removal of 24-hour phone service for patients.

***Sponsor Response**:*

MS-2 Step has been registered since 2014 and since then the product has been widely used and is well understood by both GPs, hospital clinicians, nurses, midwives and Nurse Practitioners. The current approved PI mandates that patients must have the ability to access 24-hour emergency care if and when required for incomplete abortion and bleeding. Additionally, the patient is fully counselled upon discharge and informed of the importance of having direct access to the treatment centre by telephone or local access.

Due to the history of use, clinicians and healthcare practitioners understand the need to provide post-treatment support to their patients and therefore while a sponsor provided 24-hour phone service may have been required when MS-2 Step was first registered, this is no longer considered needed.

d. Inconsistencies noted in Sections 4.2, 4.4, 4.6 and 4.8 of the MS-2 Step composite pack PI with the proposed expansion of prescriber eligibility.

***Sponsor Response**:*

In accordance with the response to the second-round clinical evaluation report, the inconsistencies noted in Sections 4.2, 4.4, 4.6 and 4.8 of the MS-2 Step PI were addressed. For ease of reference these have been provided below:

Section 4.2

> ***'When MS-2 Step fails to cause termination of intra-uterine pregnancy, the patient should return to the treating doctor for assessment and discussion of treatment options, which may include pregnancy termination by surgery.'***

The above text has been updated to instruct the patient to return to the treating healthcare practitioner, to ensure consistency with the proposed changes to the prescriber listed throughout the Product Information (PI).

Section 4.4

'Patients with medical comorbidities may require additional medical management such as adjustment of inhaled corticosteroid (ICS) therapy for asthma patients for example, that may be outside the scope of practice of non-physician healthcare providers. The Sponsor has not specifically addressed how patients with relevant medical comorbidities as described in the PI will be managed by non-physician healthcare providers.'

The Sponsor has included the following statement in Section 4.4 of the PI to ensure that adequate medical management is provided for conditions that may be outside the scope of practice of non-physician healthcare providers.

'If applicable, medical practitioner's advice should be sought in the event that further management of patients with medical comorbidities or adverse events is required.'

Section 4.4 includes text regarding cases of serious bacterial infection, including very rare cases of fatal septic shock, with statements in the 'Infection' subsection specifically referring to 'doctors' as follows:

> ***- 'Treating doctors evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event.'***

The PI has been updated to refer to the 'treating healthcare practitioner', to ensure consistency with the proposed changes to the prescriber listed throughout the PI.

Section 4.4 and 4.8

> ***'These symptoms, even without a fever, may indicate Clostridium sordellii infection. Strong consideration should be given to obtaining a complete blood count in these patients. Significant leukocytosis with a marked left shift and haemo-concentration may be indicative of sepsis. Doctors should consider immediately initiating treatment with antibiotics that includes coverage of anaerobic bacteria such as Clostridium sordellii.'***

These statements refer to clinical management of a potentially serious infection/possible sepsis including initiation of appropriate antibiotic therapy. As aforementioned, it is not clear whether this is within the scope of practice of non-physician healthcare providers.

The Product Information (PI) has been updated to instruct the healthcare practitioner to immediately seek the advice of a medical practitioner (doctor) which will ensure that the appropriate clinical management of the potentially serious infection occurs.

Section 4.6

> ***'To avoid the potential exposure of a subsequent pregnancy to MS-2 Step it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after administration of MS-2 Step.'***

This is considered important safety information. It is not clear whether prescription of reliable contraceptive methods is within the scope of practice for all healthcare providers for whom expanded prescriber eligibility is proposed (acknowledging different state/territory legislation), and therefore if some patients may need to be referred to a different healthcare provider.

The PI does not state that the healthcare practitioner would be responsible for the prescribing of the contraceptive method. The patient is informed on discharge of the need to follow up within 14-21 days along with the requirements of the medical method. The access to reliable contraceptive methods and whether additional healthcare provider advice is required, is expected to be provided as part of this process.

The information is therefore considered appropriate, and no changes proposed to this section of the PI.

Outstanding issues

RISK MANAGEMENT PLAN

The Delegate has stated that further changes to the risk minimisation plan are recommended. The sponsor has submitted an updated AU-RMP version 4.2 (dated 9 May 2023) which is dated after the Delegate's Overview and was therefore not considered as part of the recommendations.

The Delegate's comments are addressed below and were submitted as part of the response to the RMP Round 2 evaluation report.

Comment 1: At Round 2, the sponsor has proposed to remove potential risk 'Potential for loss to follow-up' and this is acceptable from an RMP perspective. However, the sponsor has also removed potential risk 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up', which is not supported as there are additional considerations to this risk with regards to access to further advice or treatment if follow-up does not occur.

***Sponsor Response**:*
In accordance with the response to the RMP Round 2 evaluation report, the potential risk 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up' has been readded to the AU-RMP. The RMP Round 3 Evaluation report acknowledged this update and stated that no further action was required.

Comment 2: There is one additional pharmacovigilance activity – an ongoing Canadian post-market surveillance study on the effectiveness and safety of combination mifepristone/misoprostol for medical abortion under 63 days gestation. Further changes to the pharmacovigilance plan in the AU-RMP is recommended.

***Sponsor Response**:*
In accordance with the response to the RMP Round 2 evaluation report, the Sponsor provides and assurance that the key findings from the Canadian post-market surveillance study will be submitted together with an updated RMP following completion of the study. The RMP Round 3 Evaluation report acknowledged this update and stated that no further action was required.

Comment 3: Further changes to the risk minimisation plan are recommended. The sponsor is also requested to include a copy of the Educational Program materials and Patient Information and Consent Agreement form in the appendix of the AU-RMP.

***Sponsor Response**:*
In accordance with the evaluator's recommendations, the AU-RMP version 4.2 (dated 9 May 2023) submitted on the 9th May, included the Education Program materials together with the Patient Information and Consent Agreement as Annex 1 to the RMP. The RMP Round 3 Evaluation report acknowledged this update and stated that no further action was required.

PRE-ACM RESPONSE

1.0 Correspondence
1.0.3 Response to request for information
Adverse Reactions Update

An assurance is provided that no new serious unexpected adverse drug reactions have been reported which are not currently mentioned in the proposed Australian Product Information or have not been submitted previously.

PRE-ACM RESPONSE

1.0.3 Response to Request for Information - Sponsor's Comments on PI

The Delegate has noted inconsistencies in Sections 4.2, 4.4, 4.6 and 4.8 of the MS-2 Step PI. These have been addressed with the previously submitted response to the second-round clinical evaluation report. For ease of reference the responses have also been included in Module 1.0.3, Pre ACM Response.

PRE-ACM RESPONSE

1.0 Correspondence
1.0.3 Response to request for information
Sponsor's comments on foreign PI (i.e. PI Comparison Table)

As the Canadian PSUR has been used as the reference for the RMP, a comparison against the Canadian PI has been provided for reference only.

Table 1: Comparison of Australian PI (MS-2 Step) to Canadian Product Monograph (MIFEGYMISO).

Australian PI (dated 20230516), MS5 version	**Canadian Product Monograph**	**Comments on differences**
MS-2 Step	**MIFEGYMISO**	
BOXED WARNING It is very important that all patients receiving these medications are followed up by a healthcare practitioner, preferably the prescriber, to ensure that the medication has been effective. Even if no adverse events have occurred all patients must receive follow-up 14 to 21 days after taking mifepristone. Read the **Section *4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE*** carefully.	**4.1 Dosing considerations** Prior to prescribing Mifegymiso, health professionals must: • Ensure that patients have access to emergency medical care in the 14 days following administration of mifepristone; • Schedule follow-up 7 to 14 days after patients take mifepristone to confirm complete pregnancy termination; • Exclude ectopic pregnancy and confirm gestational age by an appropriate method. • Counsel each patient on the risks and benefits of Mifegymiso, including bleeding, infection and incomplete abortion; • Obtain the patient's informed consent to take the drug.	The AU PI and Canadian PM are aligned.
1 NAME OF THE MEDICINE Mifepristone and Misoprostol	**MIFEGYMISO**	Difference in tradename only.

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences
2 QUALITATIVE AND QUANTATIVE COMPOSITION ***MS-2 Step*** is a composite pack containing: **Mifepristone Linepharma** Each tablet contains 200 mg of mifepristone. For the full list of excipients, see **Section** Error! Reference source not found. **LIST OF EXCIPIENTS**. **GyMiso®** Each tablet contains 200 micrograms of misoprostol as a 1% dispersion of misoprostol-hypromellose. Misoprostol is a clear, colourless or yellowish oily liquid. For the full list of excipients, see **Section** Error! Reference source not found. **LIST OF EXCIPIENTS**.	Mifepristone tablet Tablet, mifepristone 200 mg, oral administration Progesterone receptor modulator and Misoprostol tablets Tablets (4), misoprostol 200 mcg (each), Buccal administration Prostaglandin	The AU PI and Canadian PM are aligned.
3 PHARMACEUTICAL FORM **Mifepristone Linepharma** White to off-white, round biconvex tablets, diameter 11 mm, with "MF" debossed on one side of the tablet. **GyMiso®** White, flat round tablet with "ML" debossed on one side and "200" on the other side.	**6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING** **Description** Mifegymiso (mifepristone tablet/ misoprostol tablets) is a composite pack containing one mifepristone 200 mg tablet and four misoprostol 200 mcg tablets. The two products are provided in two different boxes which are packed together. ***Mifepristone 200 mg tablets*** Mifepristone tablets are white to off white, round, biconvex with "MF" embossed on one side. Mifepristone is packaged in a PVC/PVDC/Aluminum blister of 1 tablet presented in a green box of one	The AU PI and Canadian PM are aligned.

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences
	tablet. ***Misoprostol 200 mcg tablets*** Misoprostol tablets are white, round flat with "ML" debossed on one side and "200" on the other side. Misoprostol tablets are packaged in dual-faced aluminum strips and presented in an orange box of four (4) tablets.	
4.1 THERAPEUTIC INDICATIONS **MS-2 Step** is indicated in females of childbearing age for the medical termination of an intrauterine pregnancy, up to 63 days of gestation. It is recommended that the duration of pregnancy (i.e., up to 63 days gestation) be confirmed by ultrasound. In the event that an ultrasound is not possible, extra caution should be exercised. Ultrasound is also useful to exclude ectopic pregnancy	**1 INDICATIONS** Mifegymiso (mifepristone tablet/misoprostol tablets) is indicated for: • medical termination of a developing intra-uterine pregnancy with a gestational age up to 63 days as measured from the first day of the Last Menstrual Period (LMP) in a presumed 28-day cycle. Mifegymiso is not intended for routine use as a contraceptive.	The AU PI and Canadian PM are aligned.
4.2 DOSE AND METHOD OF ADMINISTRATION **MS-2 Step** is indicated for medical termination of intrauterine pregnancy, up to 63 days of gestation. The method of administration is as follows: Mifepristone: 200 mg of mifepristone (1 tablet containing 200 mg) orally, followed 36 to 48 hours later by the administration of GyMiso®. GyMiso®: 800 micrograms of misoprostol (4 tablets, each tablet containing 200 micrograms) buccally, i.e: kept between the cheek and the gum for 30 minutes before any fragments being swallowed with water. When **MS-2 Step** fails to cause termination of intra-uterine pregnancy, the patient should return to the treating	**4 DOSAGE AND ADMINISTRATION** **4.1 Dosing considerations** […] Mifegymiso should be prescribed by health professionals with adequate knowledge of medical abortion and/or who have completed a Mifegymiso education program. Each patient should be provided with a printed copy of the Mifegymiso Patient Medication Information and a Patient Information Card. The Patient Information Card should be completed by the health professional. These documents as well as a consent form can be obtained and/or ordered from	AU PI states that misoprostol should be taken 36 to 48 hours after mifepristone. Canadian PM states that misoprostol should be taken 24 to 48 hours after mifepristone. The documents are otherwise aligned.

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences
healthcare practitioner for assessment and discussion of treatment options, which may include pregnancy termination by surgery. No dosage adjustment of misoprostol or mifepristone is necessary with renal or hepatic insufficiency when administered at the recommended doses. There are no data available on the effect of food intake on the absorption of mifepristone or misoprostol. MS-2 Step should be taken 2 hours before or 2 hours after a meal. Refer also to **4.3 CONTRAINDICATIONS**, and **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**. **MS-2 Step** should only be prescribed by healthcare practitioners with the appropriate qualifications and training. Ectopic pregnancy should be excluded, an intrauterine device (IUD) (if present) must be removed, consent must be obtained and patients must have the ability to access 24-hour emergency care if and when required for incomplete abortion or bleeding.	www.linepharma.ca or by phone at 1-877-230-4227. The Mifegymiso Patient Medication Information and the Patient Information Card are also included in the box. **Hepatic impairment** Mifepristone and its metabolites showed a decrease in both overall peak and exposure in patients with moderate hepatic impairment compared to healthy-matched participants. However, no dose adjustments are recommended in this population. **4.2 Recommended Dose and Dosage Adjustment** • 200 mg of mifepristone (1 tablet) • 800 mcg of misoprostol (4 tablets, each tablet containing 200 mcg) There are no data available on the effect of food intake on the absorption of mifepristone or misoprostol. **4.3 Administration** **Step 1 Mifepristone:** • 200 mg of mifepristone (1 tablet) should be taken orally, followed 24 to 48 hours (1 to 2 days) later by the administration of misoprostol. • Mifepristone should be administered as directed by the prescribing health professional. **Step 2 Misoprostol:** • 800 mcg of misoprostol (4 tablets, each tablet containing 200 mcg) should be taken in a single intake by buccal route (kept between the cheek	

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences
	4.4 Missed Dose **Step 1 Mifepristone tablet** Patients should be advised to contact their health professional immediately if they delay or do not take the Mifepristone tablet at the time and date directed by the health professional. This information can be found on the completed Patient Information Card. **Step 2 Misoprostol tablets** Patients should be advised to contact their health professional immediately if they forget to take the Misoprostol tablets and it is more than 48 hours after they have taken the Mifepristone tablet. If it is less than 48 hours since the patient took Step 1 but after the time and date on the Patient Information Card, clinical trial data indicates that health professionals can instruct patients to take the Misoprostol tablets (Step 2) right away.	
4.3 CONTRAINDICATIONS ***MS-2 Step*** should not be prescribed in the following situations: • Lack of access to emergency medical care in the 14 days following start of the treatment (i.e. administration of mifepristone); • Suspected or confirmed ectopic pregnancy; • Asthma uncontrolled by therapy; • Intrauterine device (IUD) in place; • Uncertainty about gestational age; • Chronic adrenal failure;	**2 CONTRAINDICATIONS** Mifegymiso should not be prescribed to patients who: • have a confirmed or suspected ectopic pregnancy; • have an intrauterine device (IUD) in place; • have unconfirmed gestational age; • have chronic adrenal failure; • are on concurrent long term systemic corticosteroid therapy; • have haemorrhagic disorders or using concurrent anticoagulation therapy; • have inherited porphyria; • have uncontrolled asthma;	The AU PI lists 'pregnancy not confirmed by an ultrasound or biological test such as urine or serum HCG' – the Canadian PM does not. The Canadian PM lists 'inherited porphyria' – the AU PI does not.

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences
• Concurrent long term corticosteroid therapy; • Suspected or known haemorrhagic disorders or treatment with anti-coagulants; • Hypersensitivity to mifepristone, misoprostol (or any prostaglandin), or any of the excipients used in ***MS-2 Step;*** • Pregnancy not confirmed by an ultrasound or biological test such as urine or serum HCG;	• have known hypersensitivity to mifepristone, misoprostol, other prostaglandins, or any of the excipients used in Mifegymiso. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.	The documents are otherwise aligned.
4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE The prescriber must ensure that consent and treatment of the patient is in accordance with the appropriate state or territory legislation. If applicable, medical practitioner's advice should be sought in the event that further management of patients with medical comorbidities or adverse events is required. Take special care in case of suspected acute adrenal failure. In case of suspected acute adrenal failure, dexamethasone administration is recommended (please refer to the dexamethasone Product Information). Due to the antiglucocorticoid activity of mifepristone, the efficacy of long-term corticosteroid therapy, including inhaled corticosteroids in asthmatic patients, may be decreased during the 3 to 4 days following intake of mifepristone. Therapy should be adjusted. Rare serious cardiovascular accidents have been reported following administration of prostaglandins including misoprostol. For this reason women with risk factors for	**3 SERIOUS WARNINGS AND PRECAUTIONS BOX** • **Risk of skin reactions:** Serious skin reactions including toxic epidermal necrolysis and acute generalized exanthematous pustulosis have been reported in association with Mifegymiso treatment (see WARNINGS AND PRECAUTIONS, Skin) **7 WARNINGS AND PRECAUTIONS** **Immune** Cases of skin rash following misoprostol administration were reported by patients in clinical trials. Angioedema of the face, lips, tongue, and/or larynx, including cases of anaphylaxis have been reported in post-market surveillance with the use of Mifegymiso, including angioedema occurring within an hour of misoprostol intake. Angioedema associated with upper airway swelling may be life threatening. If the tongue, hypopharynx, or larynx has been involved, appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided. **Monitoring and Laboratory Tests**	The AU PI and Canadian PM are aligned.

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences
cardiovascular disease or established cardiovascular disease should be treated with caution. Although no epileptic seizures have been reported with misoprostol, some have been reported with prostaglandins and other prostaglandin analogues, and therefore this possibility should be borne in mind in patients with a history of epilepsy. Bronchospasm may occur with some prostaglandins and prostaglandin analogues. The possibility should be borne in mind in patients with a history of asthma. Severe cutaneous adverse reactions, including toxic epidermal necrolysis and acute generalised exanthematous pustulosis, have been reported in association with mifepristone (see **Section 4.8 ADVERSE EVENTS (UNDESIRABLE EFFECTS)**). In patients who experience severe cutaneous adverse reactions, treatment with mifepristone should be immediately discontinued. Re-treatment with mifepristone is not recommended. Cases of skin rash following misoprostol administration were reported by patients in clinical trials. Angioedema of the face, lips, tongue, and/or larynx, including cases of anaphylaxis have been reported in post-market surveillance with the use of mifepristone and misoprostol, including angioedema occurring within an hour of misoprostol intake. Angioedema associated with upper airway swelling may be life threatening. If the tongue, hypopharynx, or larynx has been involved, appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided. No data is available in patients with inherited porphyria.	Follow-up must take place within a period of 7 to 14 days after administration of Mifegymiso to verify that expulsion has been completed (i.e. clinical examination, ultrasound scan or beta-hCG measurement). Persistent bleeding should be monitored closely for a decrease in hemoglobin concentration, hematocrit and red blood cell count. **Neurologic** Seizures have been reported with prostaglandins and prostaglandin analogues, and therefore this possibility should be considered when treating patients with a history of a seizure disorder. **Renal** The safety and efficacy have not been studied in women suffering from renal failure. Treatment with Mifegymiso is therefore not recommended. **Respiratory** Due to the antiglucocorticoid activity of mifepristone, the efficacy of corticosteroid therapy, including inhaled corticosteroids, may be decreased temporarily following intake of mifepristone. Therapy should be adjusted. Bronchospasm may occur with some prostaglandins and prostaglandin analogues. Caution should be exercised in patients with a history of asthma (see CONTRAINDICATIONS). **Skin** Severe cutaneous adverse reactions, including toxic epidermal necrolysis and acute generalised exanthematous pustulosis, have been reported in association with mifepristone	

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences
In the case of a pregnancy occurring with an intra-uterine device in situ, this device must be removed before administration of Mifepristone Linepharma.	(see ADVERSE REACTIONS). In patients who experience severe cutaneous adverse reactions, retreatment with mifepristone is not recommended.	
• ***Populations not studied:*** In the absence of specific studies, MS-2 Step is not recommended in patients with: o Cardiovascular disease o Hypertensive disease o Hepatic disease o Respiratory disease o Renal disease o Diabetes o Severe anaemia o Malnutrition o Heavy smokers Women who are older than 35 years and who also smoke 15+ cigarettes per day should be treated with caution because such patients were generally excluded from clinical trials of mifepristone.	**7 WARNINGS AND PRECAUTIONS** **Carcinogenesis and Mutagenesis** See Section NON-CLINICAL TOXICOLOGY for the carcinogenesis and mutagenesis on animals. **Cardiovascular** Rare serious cardiovascular accidents have been reported following administration of prostaglandins including misoprostol. Mifegymiso has not been studied, and is therefore not recommended, in women with cardiovascular disease. Women with risk factors for cardiovascular disease (hypertension, diabetes or who are over the age of 35 and are heavy smokers) should be treated with caution. **Endocrine and Metabolism** Patients with suspected acute adrenal failure were excluded from trials and therefore should be treated with caution. If treatment with Mifegymiso is required, therapy should be adjusted. The safety and efficacy have not been studied in women suffering from malnutrition. Treatment with Mifegymiso is therefore not recommended. **Hematologic** Heavy bleeding requiring curettage occurred in some patients in clinical trials. Patients with anemia should be treated with caution. Patients with severe anemia were excluded from clinical trials and administration of Mifegymiso in these patients is not recommended. **Hepatic/Biliary/Pancreatic**	The AU PI and Canadian PM are aligned.

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences
	The safety and efficacy have not been studied in women suffering from hepatic failure. Treatment with Mifegymiso is therefore not recommended.	
• ***Specific precautions relating to medical termination of an intra-uterine pregnancy:*** o Ectopic pregnancy Ectopic pregnancy should be excluded and gestation confirmed prior to medical abortion. o Rhesus alloimmunisation The use of MS-2 Step requires rhesus determination and hence the prevention of rhesus allo-immunisation. o Explanation of requirements for the method	**7 WARNINGS AND PRECAUTIONS** **Rhesus alloimmunisation** The use of Mifegymiso requires measures to prevent rhesus alloimmunisation. **Genitourinary** Gestational age should be confirmed by an appropriate method. Ultrasound imaging is recommended before prescribing Mifegymiso when an ectopic pregnancy is suspected or gestational age is uncertain. Health professionals should remain alert to the possibility that a patient who is undergoing a medical abortion could have an undiagnosed ectopic pregnancy, since some of the symptoms of a medical abortion may be similar to those of a ruptured ectopic pregnancy. The presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed Mifegymiso.	The AU PI and Canadian PM are aligned.
This method requires the involvement of the woman who should be informed of the requirements of the medical method, which involves: ▪ The necessity to take both Mifepristone Linepharma and GyMiso® in sequence according to instructions	**4 DOSAGE AND ADMINISTRATION** **4.1 Dosing considerations** Before starting Mifegymiso, patients must be informed of the following: • Mifepristone and misoprostol must be taken in sequence according to instructions.	The AU PI states the need for a follow-up within 14 to 21 days. The Canadian PM states the need for a follow-up within 7 to 14 days.

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences
▪ The need for follow-up within 14 to 21 days after intake of Mifepristone Linepharma in order to confirm that the abortion is complete ▪ The non-negligible risk of failure (see **Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical Trials**) of the medical method which may require termination by another method ▪ On discharge from the treatment centre all women should be provided with appropriate medications as necessary and be fully counselled regarding the likely signs and symptoms she may experience and have direct access to the treatment centre by telephone or local access The expulsion may take place before GyMiso® administration (in about 3% of cases). This does not preclude the need for follow-up to confirm complete expulsion.	• Follow-up within 7 to 14 days after intake of mifepristone to confirm pregnancy termination and complete abortion is required. • Return to fertility is expected immediately after Mifegymiso administration and reliable contraceptive methods should be started as early as possible. • Failure of Mifegymiso may require surgical termination of pregnancy (see CLINICAL TRIALS). • Signs and symptoms they may experience. • How to access emergency medical care by telephone or local access.	The documents are otherwise aligned.
The following risks related to the medical method must be taken into account and explained to the woman: ○ Failures The non-negligible risk of failure (including continuing pregnancy and incomplete abortion), which occurs in up to 7% of cases prior to 63 days gestation, makes follow up mandatory in order to check that the expulsion is completed. Up to 63 days about 1% women will have continuing pregnancies, the rest needing curettage for other reasons. Exposure of the fetus to misoprostol or mifepristone increases the risk of developing Moebius syndrome and/or an amniotic band syndrome and/or central nervous system	**7 WARNINGS AND PRECAUTIONS** ***Treatment failures*** Failures in clinical studies occurred in 2.7 to 5.1% of cases prior to 63 days of gestation (see CLINICAL TRIALS). The rate of failure increases with advancing gestational age. Reasons for failure requiring a surgical termination of pregnancy included persistent non-viable pregnancies, continuing pregnancies and persistent heavy vaginal bleeding. Follow-up is mandatory to ensure that the expulsion is completed. In the event of an ongoing pregnancy, pregnancy termination should be completed by another method	AU PI states failures in up to 7% of cases prior to 63 days gestation. Canadian PM states failure in 2.7 to 5.1% of cases prior to 63 days of gestation. The documents are otherwise aligned.

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences
anomalies (see **Section 4.6 FERTILITY, PREGNANCY AND LACTATION - Use in Pregnancy**). A second termination of pregnancy procedure shall be considered. In case of continuation of the pregnancy close monitoring by ultrasound scan must be performed in specialised centres. In cases of non-complete expulsion, a surgical intervention may be necessary.	(see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Woman). Animal studies have shown that, if a pregnancy continues after exposure to mifepristone or misoprostol, fetal abnormalities may occur (see NONCLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).	
○ Bleeding The patient must be informed of the occurrence of prolonged vaginal bleeding (an average of 10 to 16 days after Mifepristone Linepharma and GyMiso® intake) which may be heavy. Bleeding occurs in almost all cases and is not in any way proof of complete expulsion. Persistent bleeding can be the consequence of incomplete expulsion. Bleeding can be large enough to necessitate a blood transfusion, in up to 0.2 % of cases up to 63 days gestation and to lead to a significant decrease in haemoglobin levels. The patient should be informed not to travel far away from the prescribing centre as long as complete expulsion has not been recorded. She will receive precise instructions as to whom she should contact and where to go, in the event of any problems emerging, particularly in the case of very heavy vaginal bleeding.	**3 SERIOUS WARNINGS AND PRECAUTIONS BOX** • **Risk of bleeding:** Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. These patients must seek immediate medical attention (see WARNINGS AND PRECAUTIONS, Genitourinary). **7 WARNINGS AND PRECAUTIONS** ***Bleeding*** Bleeding occurs in almost all cases and is not proof of complete expulsion (see CLINICAL TRIALS). Prolonged heavy vaginal bleeding may occur and can be a sign of incomplete expulsion. Bleeding can lead to a significant decrease in hemoglobin levels and may necessitate a blood transfusion. Persistent bleeding should be monitored closely. The patient should have access to emergency medical care until complete termination of pregnancy is confirmed at a follow-up visit.	The AU PI and Canadian PM are aligned.
As per the Royal College of Obstetricians and Gynaecologists guideline, *(The Care of Women Requesting*		AU PI only.

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences
Induced Abortion, November 2011), the following is recommended: "Following abortion, women should be provided with verbal and written information about: • symptoms they may experience, emphasising those which would necessitate an urgent medical consultation • symptoms suggestive of continuing pregnancy. Independent providers of abortion services should have arrangements in place for referring women to a public hospital emergency department for assessment and admission. " "On discharge, all women should be given a letter providing sufficient information about the procedure to allow another practitioner elsewhere to manage any complications".		
Follow-up must take place within a period of 14 to 21 days after administration of Mifepristone Linepharma to verify by the appropriate means (clinical examination, ultrasound scan, or beta-hCG measurement) that expulsion has been completed and that vaginal bleeding has stopped. In case of persistent bleeding (even light) beyond this follow-up, the disappearance of bleeding should be checked within a few days. If an ongoing pregnancy is suspected, a further ultrasound scan may be required to evaluate its viability. Persistence of vaginal bleeding at this point could signify incomplete abortion, or an unnoticed extra-uterine pregnancy, and appropriate treatment should be considered. In the event of an ongoing pregnancy diagnosed after	**3 SERIOUS WARNINGS AND PRECAUTIONS BOX** • It is important that all patients be followed by a health professional 7 to 14 days after taking mifepristone to confirm safety and complete pregnancy termination (see WARNINGS AND PRECAUTIONS, Genitourinary and Monitoring and Laboratory Tests).	The AU PI states the need for a follow-up within 14 to 21 days. The Canadian PM states the need for a follow-up within 7 to 14 days.

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follow-up, termination by another method will be offered to the woman. Since heavy bleeding requiring haemostatic curettage occurs in up to 5 % of cases during the medical method of pregnancy termination, special care should be given to patients with haemostatic disorders with hypocoagulability, or with anaemia. The decision to use the medical or the surgical method should be decided with specialised consultants according to the type of haemostatic disorder and the level of anaemia.		
○ Infection As with other types of abortion, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of mifepristone and misoprostol. No causal relationship between these events and the use of mifepristone and misoprostol has been established. Treating healthcare practitioners evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event and immediately seek a medical practitioner's (doctors) advice. In particular, a sustained fever of 38°C or higher, severe abdominal pain, or pelvic tenderness in the days after a medical abortion may be an indication of infection. A high index of suspicion is needed to rule out sepsis (from e.g. *Clostridium sordellii* or other species e.g. Streptococcus) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhoea) more than 24 hours after taking misoprostol. However, the symptoms of *Clostridium*	**3 SERIOUS WARNINGS AND PRECAUTIONS BOX** • **Risk of infection and sepsis:** Cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of Mifegymiso. Some patients presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. A high index of suspicion is needed to rule out sepsis (from e.g. Clostridium sordellii) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhea) more than 24 hours after taking misoprostol (see WARNINGS AND PRECAUTIONS, Genitourinary). **7 WARNINGS AND PRECAUTIONS** ***Infections*** Cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of mifepristone and misoprostol. A sustained fever of	The AU PI and Canadian PM are aligned.

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences
sordellii infection are sometimes not the usual symptoms of sepsis and very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, haemo-concentration, and general malaise. Therefore, the possibility of sepsis should be considered in all women who are undergoing medical termination and who present with nausea, vomiting, or diarrhoea and weakness with or without abdominal pain. These symptoms, even without a fever, may indicate *Clostridium sordellii* infection. Strong consideration should be given to obtaining a complete blood count in these patients. Significant leukocytosis with a marked left shift and haemo-concentration may be indicative of sepsis. Doctors should consider immediately initiating treatment with antibiotics that includes coverage of anaerobic bacteria such as *Clostridium sordellii*. Most of the reported deaths occurred in women who used vaginally administered misoprostol however deaths following other forms of administration have been reported. No causal relationship between mifepristone and misoprostol use and an increased risk of infection or death has been established. *Clostridium sordellii* and other infections such as *Streptococcus* and other bacteria have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynaecologic and non-gynaecologic conditions. Reviews have estimated overall serious infection rates after medical abortion at less than 1%.	38°C or higher, severe abdominal pain or pelvic tenderness in the days after a medical abortion may be an indication of infection. Sepsis (from e.g. Clostridium sordellii or other species e.g. Streptococcus) should be highly suspected if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhea) more than 24 hours after taking misoprostol. However, the symptoms of Clostridium sordellii infection are sometimes not the usual symptoms of sepsis. Very rarely, deaths have been reported. Therefore, the possibility of sepsis should be considered in all women who present with nausea, vomiting, diarrhea and weakness with or without abdominal pain or fever. Strong consideration should be given to obtaining a complete blood count in these patients. Significant leukocytosis with a marked left shift and hemoconcentration may be indicative of sepsis. Health professionals should consider immediately initiating treatment with antibiotics that include coverage of anaerobic bacteria such as Clostridium sordellii.	
Use in the elderly	**1.2 Geriatrics**	The AU PI and Canadian PM are aligned.

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences
There is no relevant use of ***MS-2 Step*** in the elderly population in the indication.	**Geriatrics (>65 years of age):** Mifegymiso is not indicated in post-menopausal women.	
Paediatric use Limited data are available for use of ***MS-2 Step*** in women under 18 years of age. There is no relevant use of ***MS-2 Step*** in the prepubertal paediatric population in the indication. Administration to adolescents less than 18 years of age should be undertaken with caution.	**7.1.3 Pediatrics** **Pediatrics (<15 years of age):** There are insufficient data in patients less than 15 years old to establish efficacy and safety. Mifegymiso is not indicated in the prepubertal population. **Pediatrics (>15 and <18 years of age):** Patients 15 to 17 years of age had similar efficacy to that seen in the adult population. More pain than expected was reported more frequently in this population, as well as vomiting, compared with adults (see CLINICAL TRIALS). Careful counselling should be provided to adjust patients' expectations from the procedure and identification of safety issues requiring immediate medical attention.	The AU PI and Canadian PM are aligned.
Effects on laboratory tests There are no known effects of mifepristone or misoprostol on laboratory tests.	**9.7 Drug-Laboratory Test Interactions** There are no known effects of mifepristone or misoprostol on laboratory tests.	The AU PI and Canadian PM are aligned.
4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS **Mifepristone Linepharma** No interaction studies have been performed. On the basis of mifepristone's metabolism by CYP3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum levels of mifepristone). Furthermore, rifampicin, dexamethasone, St. John's Wort and certain anticonvulsants (phenytoin, phenobarbital (phenobarbitone),	**9 DRUG INTERACTIONS** **9.2 Drug Interactions Overview** No interaction studies have been performed with mifepristone and misoprostol. *Mifepristone* *In vitro* studies and *in vivo* data showed mifepristone to be metabolized by CYP3A4 and that coadministration of other CYP3A4 substrates inhibited metabolite formation. CYP3A4 inhibitors, such as ketoconazole, itraconazole and erythromycin may inhibit mifepristone metabolism, whereas CYP3A4 inducers, such as rifampicin,	The AU PI and Canadian PM are aligned. The Canadian PI includes additional information regarding a Phase 1 DDI study which was recently approved and not yet submitted in Australia.

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences
carbamazepine) may induce mifepristone metabolism (lowering serum levels of mifepristone). Based on *in vitro* information showing that mifepristone acts as a mechanism-based inhibitor of CYP3A4, co-administration of mifepristone may lead to an increase in serum levels of drugs that are CYP3A4 substrates. Due to the irreversible nature of the CYP binding and the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP3A4 substrates and have narrow therapeutic range, including some agents used during general anaesthesia.	dexamethasone, and certain anticonvulsants (phenytoin, phenobarbital, carbamazepine), may increase its metabolism. In vitro studies also showed mifepristone to be a competitive inhibitor of CYP3A4 and, to a lesser extent, of CYPs 1A, 2B, 2D6, and 2E1. Due to the irreversible nature of the CYP binding and the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP3A4 substrates and have narrow therapeutic range, including some agents used during general anaesthesia. In an open-label, cross-over, phase 1 DDI Study done in healthy female subjects, the co-administration of mifepristone with rifampicin (strong CYP3A4 inducer) was shown to decrease mifepristone AUC by 6.3-fold, and thus a reduced efficacy may be expected. Therefore, in patients treated with strong or moderate CYP3A4 inducers, a different termination of pregnancy procedure might be warranted. In case of concomitant administration with CYP3A4 inducers, a follow-up appointment with the patient is needed to ensure the pregnancy has completely ended. In the event of method failure, a different termination of pregnancy procedure is to be suggested to the patient. Due to the antiglucocorticoid activity of mifepristone, the efficacy of corticosteroid therapy, including inhaled corticosteroids, may be temporarily decreased following intake of mifepristone. Therapy should be adjusted.	

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences
	9.4 Drug-Drug Interactions Table 5: Established or Potential Drug-Drug Interactions *Mifepristone*	

Class/Common name	Source of Evidence	Effect	Clinical comment
CYP3A4 inhibitors (such as ketoconazole, itraconazole and erythromycin)	CT	↑ mifepristone plasma concentration	Mifepristone is metabolized by CYP3A4. Co-administration of mifepristone with itraconazole (strong CYP3A4 inhibitor) was shown to increase mifepristone AUC by 2.6-fold. No dose adjustment is recommended when mifepristone is given concomitantly with a CYP3A4 inhibitor, but caution is warranted.
CYP3A4 inducers (such as rifampicin, dexamethasone and certain anticonvulsants (phenytoin, phenobarbital, carbamazepine)	CT	↓ mifepristone plasma concentration	Mifepristone is metabolized by CYP3A4. Co-administration of mifepristone with rifampicin (strong CYP3A4 inducer) was shown to decrease mifepristone AUC by 6.3-fold. Therefore, a reduced efficacy may be expected when mifepristone is co-administered with a strong or moderate CYP3A4 inducer.
Corticosteroid therapy, including inhaled costicosteroids	T	↓ corticosteroid	Mifepristone has antiglucocorticoid activity. The efficacy of corticosteroid therapy may be temporarily decreased following intake of mifepristone. Therapy should be adjusted.
CYP3A4 substrates that have narrow therapeutic range (including some agents used during general anaesthesia)	T		Due to the irreversible nature of the CYP binding and the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Caution should be exercised when mifepristone is administered with drugs that are CYP3A4 substrates and have narrow therapeutic range.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences
	Grapefruit juice may inhibit mifepristone's metabolism, increasing its serum levels. **9.6 Drug-Herb Interactions** The concomitant use of St. John's Wort may increase mifepristone metabolism, lowering its serum levels.	
GyMiso® Misoprostol has no known drug interactions. No induction of the hepatic cytochrome P-450 enzyme system has been observed. The serum protein binding of misoprostol acid was not affected by indometacin, ranitidine, digoxin, phenylbutazone, warfarin, diazepam, methyldopa, propranolol, triamterene, cimetidine, paracetamol, ibuprofen, chlorpropamide and hydrochlorothiazide. With salicylic acid (300 µg/mL), the protein binding of misoprostol was lowered from 84 to 52% which is not considered clinically significant since the binding of misoprostol acid is not extensive and its elimination half-life is very short. In laboratory studies, misoprostol has no significant effect on the cytochrome P450 linked hepatic mixed function oxidase system, and therefore should not affect the metabolism of theophylline, warfarin, benzodiazepines or other drugs normally metabolised by this system. No drug interactions have been attributed to misoprostol in extensive clinical trials. As such, other drugs would be unlikely to interfere with misoprostol's metabolism in either normal or hepatically-impaired patients.	**9 DRUG INTERACTIONS** **9.2 Drug Interactions Overview** *Misoprostol* Limited studies investigating the metabolism of misoprostol were conducted in the rat. Misoprostol was not found to affect hepatic drug metabolism. No drug interactions have been attributed to misoprostol in extensive clinical trials.	The AU PI and Canadian PM are aligned.
4.6 FERTILITY, PREGNANCY AND LACTATION **Effects on fertility**	**3 SERIOUS WARNINGS AND PRECAUTIONS BOX**	The AU PI and Canadian PM are aligned.

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences
During clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses.	• **Return to fertility**: Patients should be advised of their immediate return to fertility after Mifegymiso administration. To avoid the potential exposure of a subsequent pregnancy to mifepristone and misoprostol, it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive methods should therefore commence as early as possible (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Woman). **7 WARNINGS AND PRECAUTIONS** **Reproductive Health: Female and Male Potential** **• Fertility** During clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses. To avoid the potential exposure of a subsequent pregnancy to mifepristone and misoprostol, conception should be avoided during the next menstrual cycle. Reliable contraceptive precautions should commence as early as possible after Mifegymiso administration (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women).	
Mifepristone Linepharma Mifepristone inhibited oestrus cycling in rats at oral doses of 0.3-1 mg/kg/day (less that the clinical dose adjusted for body surface area) in a 3-week study. This was reversed over the following 2-3 weeks and no subsequent effects on reproductive performance were found.		The AU PI and Canadian PM are aligned. Information included in Non-Clinical Toxicology Section of Canadian PM.

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences
GyMiso® In fertility studies in rats in which treated females were mated with treated males, increased pre-implantation losses were observed with misoprostol at oral doses greater than 1 mg/kg/day (11 times the recommended human dose, on a mg/m^2 basis). Post-implantation loss was also increased at 10 mg/kg/day (114 times the recommended human dose, on a mg/m^2 basis).		The AU PI and Canadian PM are aligned. Information included in Clinical Pharmacology Section of Canadian PM.
Use in pregnancy **Mifepristone Linepharma** In animals, the abortifacient effect of mifepristone precludes the proper assessment of any teratogenic effect of the molecule. Fetal skull/brain malformations, presumed to be related to treatment, have been observed in rabbits and monkeys, but not mice or rats, treated with sub-abortive doses of mifepristone. These most likely occurred secondary to mifepristone's effect on the uterus due to antagonism of progesterone. Delayed development of the righting reflex and slight inhibition of locomotor development were observed in rats when administered mifepristone at the high-dose level (1 mg/kg/day) from day 15 of gestation to the end of the lactation period (postnatal day 21). A review of births from 105 pregnancies exposed during first trimester of pregnancy to mifepristone alone (46 cases) or to both mifepristone and misoprostol (59 cases) has recently been published. There were 94 live births (90.4%) and 10 (9.6%) miscarriages (including one with major malformation). Elective termination of pregnancy was	**7 Warnings and Precautions** **Teratogenic Risk** Reproductive studies conducted in rabbits and monkeys have shown that if a pregnancy continues after exposure to mifepristone, abnormalities in fetal skull, brain and developmental markers may occur. Use of misoprostol has been associated with birth defects. When used alone to induce an abortion, the following effects of misoprostol have been reported: malformations of limbs, abnormalities of fetal movements and of cranial nerves (hypomimia, abnormalities in suckling, deglutition, and eye movements). Misoprostol was shown to be embryotoxic in rabbits, rats and mice, when exposure occurred during embryogenesis. There was also an increase in skeletal abnormalities in rabbits and cleft palate in mice. **7.1.1 Pregnant Women** *Mifepristone* A review of births from 105 pregnancies exposed during first trimester of pregnancy to mifepristone alone (46 cases) or to both mifepristone and misoprostol (59 cases) has been	The AU PI and Canadian PM are aligned.

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences
performed after the subsequent diagnosis of trisomy 21 in one case. The overall rate of major congenital malformations was 4.2% (95% CI: 1.2 – 10.4%), with two cases among 38 patients exposed to mifepristone alone and two cases among 57 patients exposed to both mifepristone and misoprostol. In conclusion, this unique prospective study found that the rate of major malformations after exposure to mifepristone during the first trimester of pregnancy is only slightly higher than the expected 2 – 3% rate in the general population. Nevertheless, data in humans are still too limited to determine whether the molecule is a human teratogen.	published. There were 94 live births (90.4%) and 10 (9.6%) miscarriages (including one with major malformation). Elective termination of pregnancy was performed after the subsequent diagnosis of trisomy 21 in one case. The overall rate of major congenital malformations was 4.2% (95% CI: 1.2 – 10.4%), with two cases among 38 patients exposed to mifepristone alone and two cases among 57 patients exposed to both mifepristone and misoprostol.	
GyMiso® Use of misoprostol has been associated with birth defects. In a few cases where misoprostol was self-administered (orally or vaginally) in order to induce an abortion, the following deleterious effects of misoprostol have been suggested: malformations of limbs, of fetal movements and of cranial nerves (hypomimia, abnormalities in suckling, deglutition, and eye movements). To date, a risk of malformation cannot be excluded. Reproductive toxicity studies in animals showed embryotoxicity (increased resorptions) with oral doses of 1 mg/kg/day in rabbits, 10 mg/kg/day in rats, and 20 mg/kg in mice when treatment occurred during the period of organogenesis. An increased incidence of skeletal abnormalities was observed with an oral dose of 1 mg/kg/day in rabbits (possibly due to maternal toxicity) while an increased incidence of cleft palate was seen at a single oral dose of 30 mg/kg in mice (28 and 170 times the	**7.1.1 Pregnant Women** *Misoprostol* Use of misoprostol has been associated with birth defects. When used alone to induce an abortion, the following effects of misoprostol have been reported: malformations of limbs, abnormalities of fetal movements and of cranial nerves (hypomimia, abnormalities in suckling, deglutition, and eye movements). **3 SERIOUS WARNINGS AND PRECAUTIONS BOX** • **Embryotoxicity:** Patients should be counselled that once the treatment is started, there are risks of embryotoxicity if the pregnancy is not terminated. Both mifepristone and misoprostol are embryotoxic and have been associated with fetal abnormalities (see NONCLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).	The AU PI and Canadian PM are aligned.

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences
recommended human dose, on a mg/m^2 body surface area basis, respectively). Failure of pregnancy termination (continuing pregnancy) Use in pregnancy has been associated with an increased risk of birth defects/malformations for ongoing pregnancies exposed to mifepristone and misoprostol or misoprostol alone, compared to control group. In particular, prenatal exposure to misoprostol has been associated with Moebius syndrome (congenital facial paralysis leading to hypomimia, troubles of sucking and deglutition and eye movements, with or without limb defects) and with amniotic band syndrome (limb deformities/ amputations, especially clubfoot, acheiria, oligodactyly, cleft palate inter alia), and central nervous system anomalies (cerebral and cranial anomalies such as anencephaly, hydrocephaly, cerebellar hypoplasia, neural tube defects). Women considering medical termination of pregnancy should be precisely counselled on the risks to their fetus if an abortion failure occurs and a second termination of pregnancy procedure is not desirable.		
MS-2 Step As a consequence of the above information on mifepristone and misoprostol: • Women should be informed that due to the risk of failure of the medical method of pregnancy termination and to the unknown risk to the fetus, follow-up is very important (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).	*Mifegymiso* Due to the risk of failure of the medical method of pregnancy termination and to the unknown risk to the fetus, follow-up is mandatory (see SERIOUS WARNINGS AND PRECAUTIONS BOX). Should a failure of Mifegymiso be diagnosed at follow-up (viable ongoing pregnancy), it is recommended that pregnancy termination should be completed by another method.	The AU PI and Canadian PM are aligned.

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences
• Should a failure of the medical method be diagnosed at follow-up (viable ongoing pregnancy), and should the patient still agree, pregnancy termination should be completed by another method. Should the patient wish to continue with her pregnancy, she should be appropriately counselled as to the risk of birth defects. In that event of continuation of the pregnancy, careful ultra-sonographic monitoring of the pregnancy should be carried out. To avoid the potential exposure of a subsequent pregnancy to MS-2 Step it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after administration of ***MS-2 Step***.	Should the patient wish to continue with the pregnancy, she should be appropriately counselled as to the risk of birth defects and appropriate ultra-sonographic monitoring of the pregnancy should be carried out.	
Use in lactation Mifepristone is a lipophilic compound and may theoretically be excreted in the mother's breast milk. However, limited data are available. Misoprostol is rapidly metabolised in the mother to misoprostol acid, which is biologically active and is excreted in breast milk. This could cause undesirable effects such as diarrhoea in breast feeding infants. ***MS-2 Step*** use should be avoided during breast-feeding.	**7.1.2 Breast-feeding** Mifegymiso use should be avoided during breast-feeding. Mifepristone is lipophilic and may be excreted in the mother's milk. Misoprostol is rapidly metabolised in the mother to misoprostol acid, which is biologically active and is excreted in breast milk. This could cause undesirable effects such as diarrhea in breastfeeding infants.	The AU PI and Canadian PM are aligned.
4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES The effects of this medicine on a person's ability to drive and use machines were not addressed as part of its registration.	**7 WARNINGS AND PRECAUTIONS** **Driving and Operating Machinery** Caution is warranted when driving or operating a vehicle or potentially dangerous machinery. Dizziness, fatigue, headache, and fainting can occur. The side effects diminish after Day 3 and are gone	The Canadian PM states specific symptoms expected from Days 3 to 14.

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences
	by Day 14. The patient must rest 3 hours after taking the misoprostol tablets.	
4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) The most frequent undesirable effects which are observed during treatment with ***MS-2 Step*** are the following: • Gastrointestinal disorders: nausea (transient and mild), vomiting, diarrhoea, abdominal pain. • Reproductive system disorders: very frequent uterine contractions observed in the hours following the intake of the misoprostol component of the MS-2 Step pack; vaginal bleeding, sometimes heavy and prolonged (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**). • General disorders: headache, dizziness, and chills and fever. (Because castor oil is an excipient of the misoprostol component of the ***MS-2 Step*** pack, digestive symptoms (nausea, vomiting, abdominal pain) can be observed).	**8.1 Adverse Reaction Overview** The most frequent undesirable effects which were observed during treatment with Mifegymiso were: • Reproductive system disorders: vaginal bleeding, sometimes heavy and prolonged uterine cramping (see WARNINGS AND PRECAUTIONS, Genitourinary). • Gastrointestinal disorders: nausea, vomiting, diarrhea and abdominal pain. • General disorders: headache, dizziness, chills and fever. Bleeding was occasionally observed after mifepristone alone. Misoprostol administration resulted in vaginal bleeding, abdominal pain and cramping. In some patients, persistent or heavy vaginal bleeding required treatment with intravenous fluids or blood transfusion. On average, bleeding lasted for 11.4 days and was heavier than a normal period for 2.2 days. Infectious complications, including sometimes fatal sepsis, have been observed. Patients typically presented with abdominal pain or discomfort, fever or general malaise (including weakness, nausea, vomiting or diarrhea) more than 24 hours after taking misoprostol. *Clostridium sordellii* infection was observed in some women without abdominal pain or fever, that progressed rapidly to multi-organ failure and death.	

Australian PI (dated 20230516), MS5 version

The adverse events reported with mifepristone and a prostaglandin analogue such as GyMiso®, classified according to frequency and system organ class, are summarised as shown in Table 1.

Table 1: Adverse Events for the Combined Use of Mifepristone and Misoprostol

MedDRA	Adverse events (frequency)				
System Organ Class	Very common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1000 to < 1/100	Rare ≥ 1/10000 to < 1/1000 and very rare (< 1/10000)*	Unknown frequency
Infections and infestations			Infection	Toxic shock syndrome	
Neoplasms benign, malignant and unspecified				Elevated alpha-foeto protein Elevated carcinoembryonic antigen	
Blood and lymphatic system disorders				Thrombotic thrombocytopenic purpura Thrombocytopenia Induced systemic lupus erythematosus	
Psychiatric disorders				Mania	
Nervous system disorders	Headache Dizziness			Epilepsy Neurogenic tinnitus	
Eye disorders				Ophthalmoplegia	
Cardiac disorders				Myocardial infarction Induced Adam-Stokes syndrome Arrhythmia	
Vascular disorders			Hot flush Hypotension (0.25%)	Superficial thrombophlebitis	
Respiratory, thoracic and mediastinal disorders				Bronchospasm Induced bronchial asthma	

Canadian Product Monograph

The adverse events reported with Mifegymiso, classified according to frequency and system organ class, are summarized as shown in Table 2.

Table 2: Adverse Events for the Use of Mifepristone and Misoprostol

MedDRA	Adverse events (frequency)		
System Organ Class	Very common (≥ 1/10)	Common (> 1/100 to < 1/10)	Uncommon (≥ 1/1000 to < 1/100)
Gastro-intestinal disorders	Nausea; Vomiting; Diarrhea; Gastric discomfort; Abdominal pain	Cramping, light or moderate	
Cardiac disorders			Arrhythmia
Nervous system disorders	Headache		
Reproductive system & breast disorders	Vaginal bleeding; Spotting; Uterine contractions or cramping	Prolonged post-abortion bleeding; Severe hemorrhage; Endometritis; Breast tenderness; Heavy bleeding; Heavy bleeding requiring surgical termination of pregnancy	Hemorrhagic shock; Salpingitis; Heavy bleeding requiring IV fluids or blood transfusion
General disorders and administration site conditions	Fatigue; Chills/fever; Dizziness	Syncope	
Infections and infestations			Infection
Vascular disorders			Hot flush; Hypotension
Respiratory, thoracic and mediastinal disorders			Bronchospasm

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical

Comments on differences

The AU PI lists rare and uncommon adverse events. The adverse events are otherwise aligned.

The Canadian PM also lists the clinical trial adverse reactions.

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences

Table 1: Adverse Events for the Combined Use of Mifepristone and Misoprostol

MedDRA System Organ Class	Adverse events (frequency) Very common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1000 to < 1/100	Rare ≥ 1/10000 to < 1/1000 and very rare (< 1/10000)*	Unknown frequency
Gastrointestinal disorders	Nausea Vomiting Diarrhoea Gastric discomfort Abdominal pain	Cramping, light or moderate		Gastric bleeding Necrotising pancreatitis	
Hepatobiliary disorders				Abnormal liver function tests Hepatic failure Hepatorenal failure	
Skin and subcutaneous tissue disorders			Skin rash / pruritus	Urticarial reaction Toxic epidermal necrolysis Erythema nodosum Angioedema*	Acute generalized exanthematous pustulosis
Musculoskeletal and connective tissue disorders				Limb spasm	
Renal and urinary disorders				Renal failure	
Pregnancy, puerperium and perinatal conditions	Uterine contractions or cramping (10 to 45%) in the hours following prostaglandin intake.	Heavy bleeding occurs in about 5% of the cases and may require haemostatic curettage in up to 1.4% of the cases Fetal malformations		Hydatiform mole Ectopic pregnancy Amniotic band syndrome Gestational trophoblastic tumor Uteroplacental apoplexy	
Reproductive system and breast disorders	Vaginal bleeding Uterine spasm	Prolonged post-abortion bleeding Spotting Severe haemorrhage Endometritis Breast tenderness Heavy bleeding	Haemorrhagic shock Salpingitis	Bilateral adnexal mass Intrauterine adhesion Ovarian cyst rupture Breast abscess Haematosalpynx Uterine rupture	

trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.
Mifegymiso was studied in three open-label multi-center prospective studies. In these studies, a total of 1,596 women were included in the safety analysis. The mean age of women who received mifepristone and misoprostol was 26.0, 26.7 and 25.4 years for Studies 1, 2 and 3, respectively. Treatment-emergent adverse events reported in clinical trials are reported in Table 3. Nausea and vomiting tended to increase slightly with advancing gestational age.

Table 3: Treatment-Emergent Adverse Events Occurring in Clinical Trials, %

Adverse Events	Study 1 N = 212	Study 2 N = 415	Study 3 N = 969
Nausea	70.8	66.0	34.2
Vomiting	37.7	40.2	26.4
Diarrhea	36.8	33.7	59.5
Pain	93.4	-	-
Fever	42.9	18.6	45.3
Chills	-	36.9	
Headache	44.3	34.0	13.9
Dizziness	41.5	32.8	13.1
Weakness	55.7	45.1	21.3

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Study results in women less than 18 years of age

Of the 1,000 women enrolled in Study 3, 67 were less than 18 years of age. The reported frequent adverse events are detailed below. Women less than 18 years old reported vomiting more frequently than women 18 years and older.

<table>
<tr><th>Australian PI (dated 20230516), MS5 version</th><th>Canadian Product Monograph</th><th>Comments on differences</th></tr>
<tr>
<td>
<table>
<tr><td colspan="6">Table 1: Adverse Events for the Combined Use of Mifepristone and Misoprostol</td></tr>
<tr><td>MedDRA</td><td colspan="5">Adverse events (frequency)</td></tr>
<tr><td>System Organ Class</td><td>Very common ≥ 1/10</td><td>Common ≥ 1/100 to < 1/10</td><td>Uncommon ≥ 1/1000 to < 1/100</td><td>Rare ≥ 1/10000 to < 1/1000 and very rare (< 1/10000)*</td><td>Unknown frequency</td></tr>
<tr><td>General disorders and administration site conditions</td><td>Fatigue
Chill / fever</td><td>Fainting</td><td></td><td>Anaphylaxis
Periorbital edema
Vagal symptoms</td><td></td></tr>
</table>
*Including occasional case reports
</td>
<td>
Table 4: Adverse events by women age, % (N=969)
<table>
<tr><th rowspan="2">Adverse Events</th><th>< 18 years</th><th>≥ 18 years</th></tr>
<tr><th>N = 67</th><th>N = 902</th></tr>
<tr><td>Nausea</td><td>29.9</td><td>34.5</td></tr>
<tr><td>Vomiting</td><td>43.3</td><td>25.2</td></tr>
<tr><td>Diarrhea</td><td>62.7</td><td>59.3</td></tr>
<tr><td>Fever/chills</td><td>41.8</td><td>45.6</td></tr>
<tr><td>Headache</td><td>11.9</td><td>14.1</td></tr>
<tr><td>Dizziness</td><td>16.4</td><td>12.9</td></tr>
<tr><td>Weakness</td><td>17.9</td><td>21.6</td></tr>
</table>
</td>
<td></td>
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<td>
• Post-marketing experience indicates that death can occur as a result of medical termination of pregnancy (although this is a very rare outcome, <1 in 100,000). The reported deaths were due to sepsis (fatal toxic shock syndrome) associated with *Clostridium sordellii*, which also occurs in association with childbirth and spontaneous termination. The symptoms of *Clostridium sordellii* infection are sometimes not the usual symptoms of sepsis. Therefore, the possibility of sepsis should be considered in all women who are undergoing medical termination and who present with nausea, vomiting, or diarrhoea and weakness, with or without abdominal pain. These symptoms, even without a fever, may indicate *Clostridium sordellii* infection. Strong consideration should be given to obtaining a complete blood count in these patients. Significant leukocytosis with a marked left shift and
</td>
<td>
8.5 Post-Market Adverse Reactions
The following adverse reaction have been identified during the post-marketing experience in association with Mifegymiso use.
Skin and subcutaneous tissue disorders: Skin rash/pruritus and acute generalized exanthematous pustulosis.
</td>
<td>The AU PI discusses more post-marketing experiences than the Canadian PM.</td>
</tr>
</table>

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences
haemo-concentration may be indicative of sepsis. Doctors should consider immediately initiating treatment with antibiotics that includes coverage of anaerobic bacteria such as *Clostridium sordellii*. Refer to **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**. • Bleeding is an almost constant part of the procedure, whatever the prostaglandin analogue used, and at any pregnancy term, although it is usually more abundant when pregnancy age increases. It can occur after mifepristone alone. When heavy, it usually reflects incomplete abortion and is observed in approximately 3 to 12% of cases, depending on the pregnancy age and the prostaglandin analogue used, and needs specific treatment. It can necessitate a blood transfusion in up to 0.2% of cases. It can be prolonged for several days after prostaglandin analogue administration and sometimes leads to a decrease in haemoglobin levels. This potentially severe complication justifies that after intake (i) follow-up takes place approximately 14 to 21 days after Mifepristone Linepharma administration to ensure that expulsion is complete with no persisting bleeding and (ii) until follow-up has taken place, the woman remains close to a facility where she can be treated at any moment in case of severe or prolonged bleeding. Refer to **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**.		

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences
The issue of the outcome of persisting pregnancy in the case of failure of the medical method remains incompletely solved; a risk of malformation attributable to mifepristone or to prostaglandin analogues such as misoprostol cannot be excluded, and women should be adequately counselled in such a situation. Another fact to take into consideration is the possibility of a pregnancy persisting in the form of an ectopic pregnancy, since evidence suggests that the method does not appear able to terminate an ectopic pregnancy.		
Reporting suspected adverse effects Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems and to MS Health at 1300 515 883.	**Reporting Side Effects** You can report any suspected side effects associated with the use of health products to Health Canada by: • Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/healthcanada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or • Calling toll-free at 1-866-234-2345. *NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*	The AU PI and Canadian PM are aligned.
4.9 OVERDOSE **Mifepristone Linepharma** No case of overdose has been reported. In the event of massive ingestion signs of adrenal failure might occur. Signs of acute intoxication may require specialist treatment including the administration of dexamethasone.	**5 OVERDOSAGE** *Mifepristone* No cases of overdose have been reported. In the event of massive ingestion of mifepristone signs of adrenal failure may occur. Signs of acute intoxication may require specialist treatment including the administration of dexamethasone.	The AU PI and Canadian PM are aligned.

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences
GyMiso® The toxic dose of misoprostol in humans has not been determined. Cumulative total daily doses of 1600 micrograms have been tolerated, with only symptoms of gastrointestinal discomfort reported. Clinical signs that may indicate an overdose are sedation, tremor, convulsions, dyspnoea, abdominal pain, diarrhoea, fever, palpitations, hypotension or bradycardia. Hypertension and tachycardia have also been reported following overdoses. Overdose in pregnancy has resulted in uterine contractions with fetal death. There is no specific antidote. Treatment should be symptomatic and supportive. Consider administration of activated charcoal in the event of a potentially toxic ingestion. Activated charcoal may reduce absorption of misoprostol if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected. For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).	*Misoprostol* Cumulative total daily doses of 1600 mcg have been tolerated, with only symptoms of gastrointestinal discomfort reported. Possible symptoms of an overdose are sedation, tremor, convulsions, dyspnoea, abdominal pain, diarrhea, fever, palpitations, hypotension or bradycardia. Hypertension and tachycardia have also been reported. There is no specific antidote. Treatment should be symptomatic and supportive. Consider administration of activated charcoal in the event of a potentially toxic ingestion. Activated charcoal may reduce absorption of misoprostol if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.	The AU PI and Canadian PM are aligned.
6.1 LIST OF EXCIPIENTS Mifepristone Linepharma 200 mg tablet contains the following excipients: maize starch, povidone, microcrystalline cellulose, colloidal anhydrous silica and magnesium stearate.	**6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING** Table 1-Dosage Forms, Strengths, Composition and Packaging	The AU PI and Canadian PM are aligned.

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences
GyMiso® contains the following excipients: hypromellose, microcrystalline cellulose, sodium starch glycollate type A and hydrogenated castor oil.	<table><tr><th>Route of Administration</th><th>Dosage Form / Strength/Composition</th><th>Non-medicinal Ingredients</th></tr><tr><td>Oral</td><td>Tablet, 200 mg Mifepristone</td><td>Colloidal silica anhydrous, magnesium stearate, maize starch, microcrystalline cellulose, povidone k30.</td></tr><tr><td>Buccal</td><td>Tablet, 200 mcg Misoprostol</td><td>Hydrogenated castor oil, hypromellose, microcrystalline cellulose, sodium starch glycolate</td></tr></table>	
6.2 INCOMPATIBILITIES Incompatibilities were not assessed or not identified as part of the registration of this medicine.		AU PI only.
6.3 SHELF LIFE Do not use after the expiry date printed on the carton labels of the composite pack and the individual components. In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.		AU PI only.
6.4 SPECIAL PRECAUTIONS FOR STORAGE Store below 25°C, keep in the original container to protect from light. Keep out of reach of children. **Mifepristone Linepharma** Keep in the original green carton in order to protect from light. **GyMiso®** Keep in the original purple carton.	**11 STORAGE, STABILITY AND DISPOSAL** Mifegymiso should be stored between 15-25°C in its original outer carton in order to protect from light. Keep out of the sight and reach of children. ***Storage of mifepristone 200 mg tablet*** When separated, mifepristone should be stored between 15-30°C; in the mifepristone (Green) box, in order to protect from light. ***Storage of misoprostol 200 mcg tablets*** When separated, misoprostol should be stored between 15-25°C; in the misoprostol (Orange) box.	The AU PI does not have a lower limit for the storage temperature. The carton colours are different.
6.5 NATURE AND CONTENTS OF CONTAINER Each ***MS-2 Step*** composite pack consists of:		

Australian PI (dated 20230516), MS5 version	Canadian Product Monograph	Comments on differences
• 1 green carton containing Mifepristone Linepharma 200 mg tablet packaged in a PVC/PVDC/Aluminium blister. Pack size of 1 tablet. • 1 purple carton containing GyMiso® misoprostol 200 microgram tablet packaged in a dual-faced Aluminium blister. Pack size of 4 tablets (2 tablets per blister).		

PRE-ACM RESPONSE

1.0.3 Response to request for information – PSUR

The current PSUR (01 June 2021 – 31 May 2022) was provided to the TGA on the 31 October 2022 in response to a request from the RMP Coordinator. A commitment has also been provided to submit the next PSUR (01 June 2022 – 31 May 2023) as soon as this becomes available. A copy of the current PSUR has been provided in Module 5.3.6.

PERIODIC BENEFIT RISK EVALUATION REPORT

PrMIFEGYMISO® (mifepristone and misoprostol)
Mifepristone 200 mg tablets, misoprostol 200 mcg tablets

ATC code: GO3XB01, G02AD06

Canadian Marketing Authorization Holder (MAH)	**Linepharma International Limited** 16, Upper Woburn Place, London, WC1H 0BS United Kingdom

Period covered by this report:	01 June 2021 to 31 May 2022
International Birth Date	28 June 1984 for misoprostol and 29 December 2010 for mifepristone
EUROPEAN UNION REFERENCE DATE (EURD):	31 May 1988 for mifepristone and 29 October 2003 for misoprostol
Report number	7
Date of report:	26 July 2022

Prepared by:	s22 [redacted] Associate director, Pharmacovigilance and Medical Information, Veristat
Signature:	s22 [redacted] Digitally signed by s22 [redacted] Date: 2022.08.18 12:01:25 -04'00'
Date:	
Approved by:	s22 [redacted]
Signature:	
Date:	18 August 2022

Executive Summary

Introduction and reporting interval

This is the 7th Periodic Benefit-Risk Evaluation Report (PBRER) for mifepristone and misoprostol combipack presentations (MIFEGYMISO®). This report covers the period from 01 June 2021 to 31 May 2022 in accordance with the requirements set out in the list of Union reference dates (EURD list). This yearly PBRER for MIFEGYMISO® (*mifepristone 200 mg tablets, misoprostol 200 mcg tablets in one box*) summarises the safety and efficacy/effectiveness data received and evaluated by the Marketing Authorisation Holder or its Partners from 01 June 2021 to 31 May 2022, and places it in the context of the cumulative data and the overall benefit-risk profile.

Medicinal product - mode(s) of action, therapeutic class(es), dose(s), route(s) of administration, formulation(s)

Mifepristone (initially known as RU 486) is a synthetic steroid which binds strongly to the uterine progesterone receptors. In women, at doses of greater than or equal to 1 mg/kg, mifepristone antagonises the endometrial and myometrial effects of progesterone. Administration of mifepristone during pregnancy causes an increase in the production of endogenous prostaglandin by the endometrium and increases the sensitivity of the gravid uterus to the contraction inducing action of prostaglandins (PGs). Detachment of chorionic tissue of the blastocyst from the uterine wall after mifepristone intake produces a decline in human chorionic gonadotropin (hCG). This decline leads in turn to luteolysis and further withdrawal of hormonal support to the endometrium.
In summary, mifepristone is a powerful inhibitor of progesterone inducing disruption of placental function and uterine bleeding. During pregnancy, it increases the sensitivity of the myometrium to the contraction inducing action of PGs. Mifepristone also induces softening and dilatation of the cervix. All these effects are useful to provoke or facilitate termination of pregnancy (ToP).
Misoprostol is a prostaglandin E1 (PGE1) analogue that has been used for more than 20 years for the treatment or prevention of duodenal ulcers, especially in subjects treated with non-steroidal anti-inflammatory drugs (NSAIDs). For more than twenty years, gynaecologists have used misoprostol for its uterine-contracting properties. A large number of publications have substantiated the efficacy and safety of misoprostol used in obstetrician/gynecological indications via various routes (oral, vaginal, buccal), provided that a precise set of recommendations are made for the prescriber and the user.
Misoprostol has been used for artificial pregnancy abortion with mifepristone and is regarded as a representative method of artificial pregnancy abortion worldwide due to its high efficacy and safety.

- **Estimated cumulative exposure of clinical trial subjects:**

During the reporting period, five clinical studies sponsored by Linepharma International Limited were conducted with investigational medicinal products (IMPs) mifepristone (LPI 001), misoprostol (LPI 002) and combination of both. A total of two hundred and five (205) patients were exposed to mifepristone and one hundred and forty-two (142) to misoprostol cumulatively by the data lock point (DLP) of this PBRER.

- **Estimated reporting period and cumulative patient exposure from post-approval (marketing) experience:**

During the reporting period, patient exposure to mifepristone/misoprostol in combipack presentation (including mifepristone and misoprostol use in Mongolia) through commercial distribution was estimated as ninety-six thousand four hundred and eighty-seven (96,487) patients. During the reporting period, the patient exposure to mifepristone in separate boxes through commercial distribution (considering that the UK packaging size is 30 tablets per box) was estimated as one hundred and eighty thousand six hundred and forty-two (180,642) patients. During the reporting period, the patient exposure to misoprostol in separate boxes through commercial distribution was estimated as eight thousand seven hundred and nighty-seven (8797) patients.

Cumulatively, the patient exposure to mifepristone/misoprostol in combipack presentation (including mifepristone and misoprostol use in Mongolia) through commercial distribution was estimated to be three hundred and ninety-eight thousand and seven hundred and fifty-six (398,756) patients. Cumulatively, the patient exposure to mifepristone in separate boxes (considering that the UK packaging size is 30 tablets per box) through commercial distribution was estimated to be three million three hundreds and eleven thousand and one hundred and sixty-one (3,311,161) patients. Cumulatively, the patient exposure to misoprostol in separate boxes through commercial distribution was estimated to be sixty-nine thousand and eighty-seven (69,087) patients.

During the reporting period, no action for safety reasons was initiated concerning MIFEGYMISO® (mifepristone 200 mg tablets, misoprostol 200 mcg tablets in one box) either by the Marketing Authorization Holder or by the Authorities.

Summary of overall benefit-risk evaluation

Based on the review of data received during the reporting period, no amendments to the safety concerns or reference information are considered necessary at this time.
The benefit-risk profile of MIFEGYMISO® (mifepristone 200 mg tablets, misoprostol 200 mcg tablets in one box) for the approved indication continues to be favourable.

Actions taken or proposed for safety reasons

During the reporting period, no action for safety reasons was initiated concerning the MIFEGYMISO® (mifepristone 200 mg tablets, misoprostol 200 mcg tablets in one box) product either by the Marketing Authorization Holder or by the Authorities.

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Table 22. Number and percentage distribution of induced abortions reported by Canadian hospitals (excluding Quebec) in 2020, by gestational age

List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
CIHI	Canadian Institute for Health Information
DLP	Data Lock Point
FU	Follow Up
GVP	Good Pharmacovigilance Practices
hCG	human Chorionic Gonadotropin
HGLT	High-Level Group Terms
IBD	International Birth Date
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
IMP	Investigational medicinal products
LLT	Lowest Level Term
MAH	Canadian Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NSAIDs	non-steroidal anti-inflammatory drugs
PGE1	prostaglandin E1
PT	Preferred Term
SmPC	Summary of product characteristics
RSI	Reference Safety Information
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction

1. Introduction

This is the 7th PBRER for mifepristone and misoprostol combipack presentations (MIFEGYMISO®). This report covers the period from 01 June 2021 to 31 May 2022 in accordance with the requirements set out in the list of Union reference dates (EURD list). This yearly PBRER for MIFEGYMISO® (*mifepristone 200 mg tablets, misoprostol 200 mcg tablets in one box*) summarises the safety and efficacy/effectiveness data received and evaluated by the Marketing Authorisation Holder or its Partners from 01 June 2021 to 31 May 2022, and places it in the context of the cumulative data and the overall benefit-risk profile.
The International Birth Date (IBD) for mifepristone is 29 December 2010 and the IBD for misoprostol is 28 June 1984, however the DLP of the PBRER was established on 31 May 2020, based on PSUR work sharing scheme synchronized DLP.
This PBRER is compiled in accordance with the International Conference on Harmonisation (ICH-E2C (R2)) guideline and the EU Guideline on Good Pharmacovigilance Practices (GVP) Module VII – Periodic Safety Update Report and summarises benefit and risk information regarding MIFEGYMISO® (mifepristone 200 mg tablets, misoprostol 200 mcg tablets in one box) both cumulatively and for the reporting interval.
Unless otherwise specified, the name mifepristone/misoprostol will be used throughout this report to refer to the Mifegymiso products.

1.1. Medicinal product characteristics

1.1.1 Active substance Mifepristone - Progesterone receptor modulator

ATC code: G03XB01
Mifepristone (initially known as RU 486) is a synthetic steroid which binds strongly to the uterine progesterone receptors. In women, at doses of greater than or equal to 1 mg/kg, mifepristone antagonises the endometrial and myometrial effects of progesterone. Administration of mifepristone during pregnancy causes an increase in the production of endogenous prostaglandin by the endometrium and increases the sensitivity of the gravid uterus to the contraction inducing action of PGs. Detachment of chorionic tissue of the blastocyst from the uterine wall after mifepristone intake produces a decline in hCG. This decline leads in turn to luteolysis and further withdrawal of hormonal support to the endometrium.
In summary, mifepristone is a powerful inhibitor of progesterone inducing disruption of placental function and uterine bleeding. During pregnancy it increases the sensitivity of the myometrium to the contraction inducing action of PGs. Mifepristone also induces softening and dilatation of the cervix. All these effects are useful to provoke or facilitate ToP.

1.1.2 Active substance Misoprostol - Prostaglandin

ATC code: G02AD06
Misoprostol is a PGE1 analogue that has been used for more than 20 years for the treatment or prevention of duodenal ulcers, especially in subjects treated with NSAIDs. For more than twenty years, gynaecologists have used misoprostol for its uterine-contracting properties. A large number of publications have substantiated the efficacy and safety of misoprostol used in obstetrician/gynecological indications via various routes (oral, vaginal, buccal), provided that a precise set of recommendations are made for the prescriber and the user.
Misoprostol has been used for artificial pregnancy abortion with mifepristone and is regarded as a representative method of artificial pregnancy abortion worldwide due to its high efficacy and safety.

1.2. Therapeutic indications and doses

MIFEGYMISO® (mifepristone tablet/misoprostol tablets) is indicated for medical termination of a developing intra-uterine pregnancy with a gestational age up to 63 days as measured from the first day of the Last Menstrual Period (LMP) in a presumed 28-day cycle.
MIFEGYMISO® is not indicated in post-menopausal women.
There are insufficient data in patients less than 15 years old to establish efficacy and safety.
MIFEGYMISO® is not indicated in the prepubertal population.
200 mg of mifepristone (1 tablet) should be taken orally.
800 mcg of misoprostol (4 tablets, each tablet containing 200 mcg) should be taken in a single intake by buccal route (kept between the cheek and the gum for 30 minutes before any remaining fragments are swallowed with water).

2. Worldwide Marketing Approval Status

The International Birth Date (IBD) for mifepristone is 29 December 2010 and the IBD for misoprostol is 28 June 1984.
During the reporting period, no new marketing authorization has been received.

The cumulative worldwide marketing authorization status, indications and approved dosages for Mifepristone and Misoprostol are summarized in Table 1.

Table 1. Summary of Marketing Authorization Status of mifepristone and misoprostol

Authorised product	Country	Related product	Active substances	Authorisation procedure	Auth. Status	Auth. Number	Initial authorisation date	Licence holder
Mifepristone								
MIFEPRISTONE 200 MG TABLET	UG	Mifepristone 200 mg tablet UG	MIFEPRISTONE 200 mg/Tablet (TABLET)	National - Non EU	Valid	8514/22/13	03.09.2013	Linepharma International Limited
Mifepristone Linepharma	UY	Mifepristona Linepharma 200 mg UY	MIFEPRISTONE 200 mg/Tablet (TABLET)	National - Non EU	Valid	45523	29.05.2020	Linepharma International Limited
Mifepristone Linepharma 200 mg Tablet	AU	Mifepristone 200 mg tablet AU	MIFEPRISTONE 200 mg/Tablet (TABLET)	National - Non EU	Valid	AUS-R 175671	29.08.2012	MS Health Pty Ltd
MIFEPRISTONE LINEPHARMA 200 MG TABLET	MN	Mifepristone 200 mg tablet MN	MIFEPRISTONE 200 mg/Tablet (TABLET)	National - Non EU	Valid	FT20160831 GH05694	31.08.2016	MS Health Pty Ltd
Mifepristone Linepharma 200 mg tablets	UK	Mifepristone LPI (SE/H/0986/001)	MIFEPRISTONE 200 mg/Tablet (TABLET)	Mutual-recognition	Valid - Transferred Marketing Authorisation	PL 43680/0001	08.10.2012	Linepharma International Limited
MEDIPRIST 200 mg	ZA	Mifepristone 200 mg tablet ZA	MIFEPRISTONE 200 mg/Tablet (TABLET)	National - Non EU	Valid	47/21.12/0034	25.03.2019	Adcock Ingram Limited
MEFAPRIX 200 mg, tableta	MX	Mifepristone 200 mg tablet MX	MIFEPRISTONE 200 mg/Tablet (TABLET)	National - Non EU	Valid	064M2013 SSAIII	06.05.2013	BIOPHARMEX, S.A. de C.V
MIFEAPROFA COMPRIMIDOS 200 MG	CL	Mifepristone 200 mg tablet CL	MIFEPRISTONE 200 mg/Tablet (TABLET)	National - Non EU	Valid	F-25075/19	08.10.2019	ASOCIACIÓN CHILENA DE PROTECCIÓN DE LA FAMILIA (APROFA)
MIFEPRISTONA 200 MG TABLETA	CO	Mifepristone 200 mg tablet CO	MIFEPRISTONE 200 mg/Tablet (TABLET)	National - Non EU	Valid	INVIMA 2016M-0017492	12.12.2016	PROFAMILIA (Asocicion probienestar de la familia colombiana)
MIFEPRISTONA 200 MG TABLETA	BO	Mifepristone 200 mg tablet BO	MIFEPRISTONE 200 mg/Tablet (TABLET)	National - Non EU	Valid	II-73686/2020	21.05.2020	Linepharma International Limited

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Misoprostol								
GyMiso 200 microgram oral tablet blister pack	AU	Misoprostol 200 mcg tablet AU	MISOPROSTOL 200 µg/Tablet (TABLET)	National	Valid	AUS-R 188015	29.08.2012	MS Health Pty Ltd
GyMiso 200 microgram tablet	MN	Misoprostol 200 mcg tablet MN	MISOPROSTOL 200 µg/Tablet (TABLET)	National	Valid	FT20160831 GH5693	31.08.2016	MS Health Pty Ltd
MISOAPROFA COMPRIMIDOS 200 mcg	CL	Misoprostol 200 mcg tablet CL	MISOPROSTOL 200 µg/Tablet (TABLET)	National	Valid	F-25074/19	07.10.2019	ASOCIACIÓN CHILENA DE PROTECCIÓN DE LA FAMILIA (APROFA)
Combipack (mifepristone+misoprostol)								
MS-2 Step	AU	Mifepristone & Misoprostol Combipack AU	MIFEPRISTONE 200 mg/Tablet (TABLET) ||| MISOPROSTOL 200 µg/Tablet (TABLET)	National - Non EU	Valid	AUST R 210574	04.06.2014	MS Health Pty Ltd
MIFEGYMISO	CA	Mifepristone & Misoprostol Combipack CA	MIFEPRISTONE 200 mg/Tablet (TABLET) ||| MISOPROSTOL 200 µg/Tablet (TABLET)	National - Non EU	Valid	DIN 02444038	29.07.2015	Linepharma International Limited

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2. Actions Taken in the Reporting Interval for Safety Reasons

Actions related to investigational use
During the reporting period, there were no actions taken related to the investigational use.

Actions related to marketing experience
During the reporting period there were no actions taken for safety reasons concerning withdrawal, revocation, rejection, suspension or failure to obtain a renewal of a Marketing Authorisation; neither have there been any dosage modifications, changes in target population, formulation changes, restriction on distribution, or clinical trial suspension.

3. Changes to Reference Safety Information

There were changes to the reference safety information (RSI) during the reporting period.
For mifepristone, the CCSI of Mifepristone Linepharma® version 7, dated on 01 November 2021 (included as Appendix 1a) was used to assess the listedness of the ICSRs containing the reactions reported in this PBRER.
The introduced changes were the following:
1) The section "UNDESIRABLE EFFECTS" was updated for align it with the SmPC for the different countries.
2) The section " INTERACTIONS WITH OTHER MEDICAMENTS AND OTHER FORMS OF ADMINISTRATION" was updated with the information regarding the pharmacokinetic study performed with the Cytochrome P450 3A4 (CYP3A4) inhibitor.

For misoprostol, the CCSI of Gymiso® version 7, dated on 01 November 2021 (see Appendix 1b) was used to assess the listedness of the ICSRs containing the reactions reported in this PBRER.

The introduced changes were the following: the section "UNDESIRABLE EFFECTS" was updated for align it with the SmPC for the different countries.

The respective changes to the Canadian product monograph were approved post DLP of the current PBRER. The current version of the Canadian product monograph is dated 17Jun2022.

5. Estimated Exposure and Use Patterns

5.1 Cumulative Subject Exposure in Clinical Trials

Cumulatively, five clinical studies sponsored by Linepharma International Limited were conducted with the investigational medicinal products (IMPs) mifepristone (LPI 001), misoprostol (LPI 002) and combination of both (see Table 3).

Table 2. Summary of clinical trials sponsored by Linepharma International Limited with IMPs mifepristone or/and misoprostol which were approved during the reference period.

Title trial	Study code / EudraCT #	IMPs	Country	Date of first authorization by the CA	Status
A phase 1, non- randomized, open-label, single-dose Study to investigate the pharmacokinetics,safety, and tolerability of LPI001 (Mifepristone Linepharma® 200 mg) in female participants with moderate	LPI001-03/NA (study not conducted in the EU)	LPI 001	United States of America	03 April 2020	Closed

Title trial	Study code / EudraCT #	IMPs	Country	Date of first authorization by the CA	Status
hepatic impairment versus Healthy female participants withnormal hepatic function.					
An open-label, two- period, fixed-sequence, cross-over study in healthy female subjects toevaluate the effect of itraconazole on the pharmacokinetics of LPI001 (Mifepristone Linepharma® 200 mg)	LPI001-04/ 2019-004924-38	LPI 001 Itraconazole	Germany	19 Mar 2020	Closed
An open-label, two- period, fixed-sequence, cross-over study in healthy female subjects toevaluate the effect of rifampicin on the pharmacokinetics of LPI001 (Mifepristone Linepharma 200 mg)	LPI001-05/ 2020-000069-17	LPI 001 Rifampicin	Germany	02 April 2020	Closed
Phase b1 trial Investigating the pharmacokinetics and safety of LPI 002 in Japanese band Caucasian women	LPI002-02 / NA (study notconducted in theEU)	LPI 002	Japan	03 December 2019	Closed
A multicentre, Open- label Phase III trial investigating theefficacy and Safety of LPI 001 and LPI 002 forartificial termination of pregnancy	LP010	LPI 001 And LPI 002	Japan	15 October 2019	Closed

The cumulative subject exposure from these clinical trials by the DLP of this PBRER (31 May 2022) is presented in the Table 3.

Table 3. Cumulative distribution of subject enrollment to mifepristone clinical trials and exposure to mifepristone per clinical trial.

Study ID		Number of subjects signed the consent form	Number of subjects withdrawn	Number of subjects enrolled	Number of patients exposed to investigational product	
LPI001-03	HI	26	10 (*screening failure*)	8	LPI 001	**8**
	HV			8	LPI 001	**8**
LPI001-04		64	34 (*screening failure*) 3 (*consent form withdrawal before exposure*) 8 (*missing PK samples, after exposure*)	30	LPI 001	**27**
LPI001-05		44	24 (*screening failure*) 2 (*consent form withdrawal after IMP administration)*	20	LPI 001	**18**
LPI001-02	Japanese	48	23 (*screening failure*) 1 (*consent form withdrawal, after IMP administration*)	12*	LPI 001	**12***
	Caucasian			12*	LPI 001	**12***

Study ID	Number of subjects signed the consent form	Number of subjects withdrawn	Number of subjects enrolled	Number of patients exposed to investigational product	
LPI002-02	43	2 *(One subject was withdrawn after period 1 because she disliked the hospitalization environment and wished to discontinue. The other subject was withdrawn after period 2 due to the following non-serious adverse events: abdominal pain lower, nausea and floating feeling.*)	24 (12 per group)	LPI 002	**24**
LP010	124	1 *(screening failure)*	123	LPI 001	120
				LPI 002	118
Total	***349***	***108***	***237***	***LPI 001***	***205***
				LPI 002	***142***

HI = hepatic impairment subjects

HV = Healthy volunteers.

**At least one dose.*

Details about exposure by age / group were unknown.

5.2 Cumulative and Interval Patient Exposure from Marketing Experience

5.2.1 Interval patient exposure.

There is no precise information on the number of patients treated with mifepristone/misoprostol during the reporting period.

In order to evaluate the patient exposure regarding combipack presentation in Australia and Canada, it was assumed that one box including one tablet of mifepristone and four tablets of misoprostol, corresponds to the treatment for one patient. Additionally, since mifepristone/misoprostol are used in combination in Mongolia, the calculation of patient exposure should be processed together for these two products; therefore, one box of mifepristone (1 tablet) and one box of misoprostol (4 tablets), corresponds to the treatment for one patient.

Regarding the other countries where only mifepristone or only misoprostol alone are marketed by Linepharma International Limited, it was assumed that one box of mifepristone (1 tablet) or misoprostol (4 tablets) corresponds to one patient (exception is the UK where the packaging size of 30 tablets is marketed thus patient's exposure is calculated is as 1 tablet per patient).

Therefore, the sales volume was used to estimate the number of patients treated with mifepristone/misoprostol during the interval and cumulatively.

The number of subjects treated with mifepristone / misoprostol has been estimated by calculation from the worldwide sales volume as explained above and presented in Table 4.

Table 4: Worldwide distribution of Mifepristone/misoprostol sales and patient exposure calculation (countries where the product is not launched are not included in the table).

Distributor, country	Product	Interval Sales (box)	Interval exposure (nb of patients)	Cumulative Sales (box)	Cumulative exposure (nb of patients)
Celopharma, Canada	Mifegymiso (Mife+Miso Combipack)	51,675	51,675	186,167	186,167
MSI Australia	Mifegymiso (Mife+Miso Combipack)	42,826	42,826	201,124	201,124
MSI Mongolia	Misoprostol (Gymiso)	1,986	1,986*	11,465	11,465*
MSI Mongolia	Mifepristone	1,986	N/A*	11,465	N/A*
Subtotal	***mifepristone / misoprostol***	***98,473***	***96,487***	***410,221***	***398,756***
Profamilia (Colombia)	Mifepristone	17,278	17278	87,266	87,266
MSI Australia	Mifepristone	3,930	3930	40,002	40,002
MSI Mexico	Mifepristone	21,349	21349	196,354	196,354
APROFA (Chile)	Mifepristone	2,846	2,846	3,610	3,610
TES (Bolivia)	Mifepristone	5,176	5,176	7,576	7,576
UK	Mifepristone x1	29,767	29,767	N/A	N/A
UK	Mifepristone x30	3,277	98,310	N/A	N/A
UK Total	Mifepristone x1 and Mifepristone x30	33,044	128,077	1,232,554	1,479,576
Subtotal	***Mifepristone***	***85,609***	***180,642***	***3,062,566***	***3,450,094***
APROFA (Chile)	Misoprostol (Gymiso)	8,797	8,797	8,797	8,797
Australia	Misoprostol (Gymiso)	0	0	60,290	60,290
Subtotal	***Misoprostol (Gymiso)***	***8,797***	***8,797***	***69,087***	***69,087***

*mifepristone/misoprostol are used in combination

During the reporting period, the total sales volume of mifepristone/misoprostol in combipack presentation and sales of mifepristone and misoprostol in Mongolia through commercial distribution accounted for ninety-eight thousand four hundred and seventy-three (98,473) boxes. Thus, patient exposure to mifepristone/misoprostol in combipack presentation (including mifepristone and misoprostol in Mongolia) was estimated as ninety-six thousand four hundred and eighty-seven (96,487) patients (Table 4).
During the reporting period, the total sales volume of mifepristone in separate boxes through commercial distribution accounted for eighty-five thousand six hundred and nine (85,609) boxes, therefore, considering that UK packaging size is 30 tablets per box, patient exposure to mifepristone in separate boxes was estimated as one hundred and eighty thousand six hundred and forty-two (180,642) patients (Table 4).
During the reporting period, the total sales of misoprostol in separate boxes through commercial distribution accounted for eight thousand seven hundred and nighty-seven (8797) boxes. Thus, patient exposure to misoprostol in separate boxes was estimated as eight thousand seven hundred and nighty-seven (8797) patients.

5.2.2 Cumulative patient exposure.

Cumulatively:

- The total sales volume of mifepristone/misoprostol in combipack presentation and sales of mifepristone and misoprostol in Mongolia through commercial distribution accounted for four hundred and ten thousand two hundred and twenty-one (410,221) boxes. Thus, patient exposure to mifepristone/misoprostol in combipack presentation (including mifepristone and misoprostol in Mongolia) was estimated to be three hundred and ninety-eight thousand and seven hundred and fifty-six (398,756) patients (Table 4).
- The total sales volume of mifepristone in separate boxes through commercial distribution accounted for three million sixty-two thousand and five hundred and sixty-six (3,062,566) boxes, therefore the patient exposure was estimated to be three million four hundred and fifty thousand and ninety-four (3,450,094) patients (Table 4).

- The total sales volume of misoprostol in separate boxes through commercial distribution accounted for sixty-nine thousand and eighty-seven (69,087) boxes, therefore the patient exposure was estimated to be sixty-nine thousand and eighty-seven (69,087) patients (Table 4).
- Information about the interval and cumulative post-authorization exposure by age was not available.

5.2.3 Post-approval use in special populations

In accordance with the indication, the targeted population for mifepristone / misoprostol consists of pregnant women only. The exposure during pregnancy / breastfeeding is discussed in the section 16.3.

5.2.4 Other post-approval use

During the reporting period, one (1) prospective non-interventional Phase IV study has been ongoing in Canada and is presented in the table 5 below. Data regarding patient's exposure was included in sections 5.2.1 Interval Patient Exposure from Marketing Experience and 5.2. Cumulative Patient Exposure from Marketing Experience.

Table 5. Summary of clinical trials sponsored by Linepharma International Limited with IMPs mifepristone or/and misoprostol which were approved during the reference period.

Title	Study code	IMPs	Country	Date of first authorization by the CA	Status
A prospective non-interventional Phase IV multi-centre Canadian study on the effectiveness and safety of combination mifepristone/misoprostol for medical abortion under 63 days gestation (The MiMAC Study)	LPI011	LPI 001 And LPI 002	Canada	Not applicable as non-interventional studies are not submitted to Health Canada	First Patient First Visit: 22February 2022 3 sites activated 15 patients recruited

6. Data in Summary Tabulations

6.1 Reference Information

The coding of adverse events (AE) is based on the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.1. MedDRA is periodically updated, and coding conventions can evolve. Thus, over time, the same clinical AE may have been captured by different terms.

6.2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

Serious adverse events/reactions obtained from the clinical trials sponsored by Linepharma International Limited are listed by MedDRA (version 24.1) Preferred Terms (PTs) in the following aggregate summary Table 6.

Table 6. Cumulative Summary of individual Adverse Reactions/Events from the clinical trial LP010 tabulated according to the standard MedDRA System Organ Class (SOC) scheme

Preferred Terms	Number of SAEs
Infections and infestations (3)	
Bacterial infection	1
Cytomegalovirus infection	1

Preferred Terms	Number of SAEs
Endometritis	1
Blood and lymphatic system disorders (1)	
Blood loss anaemia	1
Pregnancy, puerperium and perinatal conditions (1)	
Uterine hypotonus	1
Reproductive system and breast disorders (1)	
Intermenstrual bleeding	1
Injury, poisoning and procedural complications (1)	
Abortion induced incomplete	2
Surgical and medical procedures (1)	
Uterine dilation and curettage	2
Total	10

Cumulatively, a total of 10 SAEs was reported from one clinical trial (LP010) with mifepristone and misoprostol as IMPs. No suspected unexpected serious adverse reactions (SUSARs) were reported. (Refer to Appendix 2a for mifepristone and Appendix 2b for misoprostol).

No serious adverse events (SAEs) were reported for other Linepharma International Limited-sponsored clinical trials with mifepristone as IMP (LPI001-03, LPI001-04 and LPI001-05) or with misoprostol as IMP (LPI002-02).

6.3 Cumulative and Interval Summary Tabulations from Post-Marketing Data Sources

The cumulative and interval summary tabulations of serious and non-serious adverse reactions and special situation terms are organised by SOC and PT. These summary tabulations contain adverse events reported up to the data lock point of this report (31 May 2022) from spontaneous Individual Case Safety Reports (ICSRs), including reports from healthcare professionals, consumer, scientific literature, regulatory authorities, solicited sources and are provided in Appendix 2C1 (mifepristone) and Appendix 2C2 (misoprostol).
Only pharmacovigilance data from MIFEGYMISO® (mifepristone/misoprostol combipack) are included in this report. Since there was one RSI for each active substance, data are presented by active substance separately.
During the reporting period, a total of one thousand and sixty-one (1,061) adverse reactions was reported cumulatively for mifepristone (n=555) and misoprostol (n=506) that was distributed in a total of two hundred and six (206) ICSRs as follows:
- one hundred and sixty-one (161) ICSRs related to the use of both misoprostol/mifepristone in combipack presentation
- thirty -two (32) ICSRs related to the mifepristone use in combipack presentation
- thirteen (13) ICSRs related to the misoprostol use in combipack presentation

Each ICSR includes events that related to either mifepristone or misoprostol or both mifepristone and misoprostol.

Cumulatively, a total of twenty-five thousand one hundred and eighty-eight (25,188) adverse reactions were reported for mifepristone (n=12,742) and misoprostol (n=12,446); these were distributed

throughout the total of three thousand nine hundred and eighty-eight (3,988) ICSRs with combipack presentations as below:
- three thousand six hundred and forty-five (3,645) ICSRs related to the use of both misoprostol/mifepristone in combipack presentation.
- two hundred and twenty-nine (229) ICSRs related to the mifepristone use in combipack presentation.
- one hundred and forty-four (144) ICSRs related to the misoprostol use.

The cumulative and interval summary tabulations of adverse reactions reported to the MAH are presented in Appendix 2C1 (mifepristone) and Appendix 2C2 (misoprostol).

6.3.1. Mifepristone

During the interval period, there were reported thirty -two (32) ICSRs related to the mifepristone use in combipack presentation and one hundred and sixty-one (161) ICSRs related to the use of both misoprostol/mifepristone in combipack presentation. These ICSRs corresponded to five hundred and fifty-five (555) adverse drug reactions (ADRs) and special situations (see Appendix 2.b.1):
- one hundred and one (101) ADRs were serious (among them five (5) ADRs were unlisted);
- four hundred and fifty-four (454) ADRs and special situations were non-serious (among them eighty-seven (87) ADRs were unlisted).

Cumulatively, there were reported two hundred and twenty-nine (229) ICSRs related to the mifepristone use in combipack presentation and three thousand six hundred and forty-five (3,645) ICSRs related to the use of both misoprostol/mifepristone in combipack presentation. These ICSRs corresponded to twelve thousand seven hundred and forty-two (12,742) ADRs and special situations (see Appendix 2.b.1):
- one thousand eight hundred and fifteen (1,815) ADRs were serious (among them ninety (90) ADRs were unlisted);
- ten thousand nine hundred and twenty-seven (10,927) ADRs and special situations were non-serious (among them two thousand one hundred and fifty-four (2,154) ADRs were unlisted).

Information is summarized in the Table 7 below for mifepristone.

Table 7. Distribution of the most frequent PTs and SOCs for mifepristone during the reporting interval (01Jun2021-31May2022) and cumulatively.

SOCs	**Interval period N = 555**	**Cumulatively N=12,742**
Reproductive system and breast disorders	**n=75, 13.51 %**	**n = 2,526, 19.82 %**
Most frequent PTs	'Vaginal haemorrhage' (n=65)	'Vaginal haemorrhage' (n=1874) and 'vaginal discharge (n=318)
General disorders and administration site conditions	**n = 84, 15.13 %**	**n = 2,065, 16.20 %**
Most frequent PTs	'Pain' (n=37)	'Pain' (n=873), 'pyrexia' (n=178), 'chills' (n=152) and 'fatigue' (n=151)
Vascular disorders	**n = 123, 22.16 %**	**n = 2,752; 21.59 %**
Most frequent PTs	Haemorrhage' (n=48), 'Thrombosis' (n=47)	'Thrombosis' (n=1269), 'haemorrhage' (n=755) and 'dizziness' (n=594)

Gastrointestinal disorders	**n = 101, 18.20 %**	**n = 1,695, 13.30 %**
Most frequent PTs	'Vomiting' (n=43), 'Nausea' (n=30)	'Vomiting' (n=485), 'nausea' (n=412) and 'abdominal pain' (n=313).
Injury, poisoning and procedural complications	**N=66; 11.89 %**	**N=730; 5.72 %**
Most frequent PTs	'Abortion induced incomplete' (n=32)	'Abortion induced incomplete' (n=490), 'Induced abortion failed' (n=140)

6.3.2. Misoprostol

During the interval period there were reported thirteen (13) ICSRs related to misoprostol use in combipack presentation and one hundred and sixty-one (161) ICSRs related to the use of both misoprostol/mifepristone in combipack presentation.
These ICSRs corresponded to five hundred and six (506) ADRs and special situations (see Appendix 2.b.2):
- ninety-seven (97) ADRs were serious (among them five (5) ADRs were unlisted);
- four hundred and nine (409) ADRs and special situations were non-serious (one hundred and eleven (111) ADRs were unlisted).

Cumulatively, there were reported one hundred and forty-four (144) ICSRs related to the misoprostol use in combipack presentation and three thousand six hundred and forty-five (3,645) ICSRs related to the use of both misoprostol/mifepristone in combipack presentation. These ICSRs corresponded to twelve thousand four hundred and forty-six (12,446) ADRs and special situations that were reported for misoprostol:
- one thousand seven hundred and ninety-five (1,795) ADRs were serious (one hundred and one (101) ADRs were unlisted);
- ten thousand six hundred and fifty-one (10,651) ADRs and special situations were non-serious (two thousand two hundred and eighty-four (2,284) ADRs were unlisted).

Information is summarized in the Table 8 below for misoprostol.

Table 8. Distribution of the most frequent PTs and SOCs for misoprostol during the reporting interval (01Jun2020-31May2021) and cumulatively.

SOCs	**Interval period N = 506**	**Cumulatively N= 12,446**
Reproductive system and breast disorders	**n = 69, 13.64 %**	**n = 2,480, 19.93 %**
Most frequent PTs	'Vaginal haemorrhage' (n=61)	'Vaginal haemorrhage' (n=1827) and 'vaginal discharge (n=317)
Injury, poisoning and procedural complications	**N= 86; 17 %**	**N= 879; 7.06 %**
Most frequent PTs	'Abortion induced incomplete' (n=32)	'Abortion induced incomplete' (n=492) and 'Induced abortion failed' (n=134)
General disorders and administration site conditions	**n = 71, 14.03 %**	**n = 1,978, 15.89 %**

Most frequent PTs	'Pain' (n=34)	'Pain' (n=858), 'Pyrexia' (n=173), 'Chills' (n=143), and 'Fatigue' (n=146)
Vascular disorders	**n = 97, 19.17 %**	**n=2,635, 21.17 %**
Most frequent PTs	'Thrombosis' (n=39), 'Haemorrhage' (n=33)	'Thrombosis' (n=1230), 'Haemorrhage' (n=715), 'Dizziness' (n=563)
Gastrointestinal disorders	**n = 74, 14.62 %**	**n = 1,510, 12.13 %**
Most frequent PTs	'Vomiting' (n=27), 'Nausea' (n=20)	'Nausea' (n=355), 'Vomiting' (386) and 'Abdominal pain' (n=300)

In addition, a total of four (4) non-valid cluster ICSRs (originated from 3 literature articles) was reported during the interval period:

Case 2022000336: Literature report information was retrieved on 07-Feb-2022 from published literature abstract: Vlad S, Boucoiran I, Imeah B, Roy St-Pierre E, Ferreira E. Mifepristone-Misoprostol Use for Second and Third Trimester Medical Termination of Pregnancy in a Canadian Tertiary Care Centre. J Obstet Gynaecol Can. 2022 Jan 31;S1701-2163(22)00011-1. DOI:10.1016/j.jogc.2021.12.010. Non-valid case (unspecified number of patients). Linepharma reference #NGR-CPK-22-000474.

Follow-up information was received on 09-Feb-2022: complete literature article was obtained. One individual valid case was created involving heavy bleeding. Linepharma reference #NGR-CPK-22-000474. Linked ICSRs included (same article): CA-LINE-2022000335 (cluster case, non-valid), CA-LINE-2022000338.

Case 2022000335: Literature report information was retrieved on 07-Feb-2022 from published literature abstract: Vlad S, Boucoiran I, Imeah B, Roy St-Pierre E, Ferreira E. Mifepristone-Misoprostol Use for Second and Third Trimester Medical Termination of Pregnancy in a Canadian Tertiary Care Centre. J Obstet Gynaecol Can. 2022 Jan 31;S1701-2163(22)00011-1. DOI:10.1016/j.jogc.2021.12.010. Non-valid case (unspecified number of patients). Linepharma reference #NGR-CPK-22-000474.

Follow-up information was received on 09-Feb-2022: complete literature article was obtained. Specific adverse reactions were listed but unable to identify individually. Non valid case. Linked ICSRs included (same article): CA-LINE-2022000336, CA-LINE-2022000338 (this is a valid case).

Case 2022000494: Literature report information was retrieved on 21-Feb-2022 from published literature article: Renner R, Ennis M, Guilbert E, Roy G, Barrett J. Second- and Third-Trimester Medical Abortion Providers and Services in 2019: Results from the Canadian Abortion Provider Survey. J Obstet Gynaecol Can. 2022 Feb 17:S1701-2163(22)00066-4. doi: 10.1016/j.jogc.2022.01.016.

Non-valid cluster case (unspecified number of patients). Linepharma reference #NGR-CPK-22-000584.

Case 2022000923: Literature report information was retrieved on 12-Apr-2022 from published literature article: Ennis M, Renner R, Guilbert E, Norman WV, Pymar H, Kean L et al. Provision of First-trimester Medication Abortion in 2019: Results from the Canadian Abortion Provider Survey. Contraception. 2022 Mar 26:S0010-7824(22)00078-6. doi: 10.1016/j.contraception.2022.03.020. Non-valid cluster case (unspecified number of patients). Linepharma reference #NAP-CPK-22-001099.

7. Summaries of Significant Findings from Clinical Trials during the Reporting Period

7.1. Completed Clinical Trials

No clinically important emerging efficacy and safety findings regarding the IMP mifepristone were identified from the completed studies LPI001-02, LPI001-03, LPI001-04 and LPI001-05, sponsored by Linepharma International Limited during the reporting period. Study LPI001-02 was completed during the current reporting period (01 June 2021-31 May 2022), while studies LPI001-03, LPI001-04 and LPI001-05 were completed during the previous reporting period (01 June 2020-31 May 2021).

There was no other completed study with mifepristone during the reporting period.

7.2. Ongoing Clinical Trials
There was no ongoing study with mifepristone and/or misoprostol during the reporting period.

7.3. Long-Term Follow-up
Not applicable.

7.4. Other Therapeutic Use of Medicinal Product
During the reporting period, one (1) prospective non-interventional Phase IV study LPI011 (The MiMAC Study) has been ongoing in Canada and is presented in the table 5 above.

7.5. New Safety Data Related to Fixed Combination Therapies
There was no new safety data related to the combination therapy of mifepristone and misoprostol arising from the clinical study sponsored by Linepharma International Limited with this combination therapy (phase III study LP010, completed).

8. Findings from Non-Interventional Studies

Not applicable. The sponsor was not aware of other non-interventional studies conducted with mifepristone during the reporting period.

9. Information from Other Clinical Trials and Sources

9.1. Other clinical trials
No relevant safety information for mifepristone was obtained from other clinical trials or studies during the reporting period.

9.2. Medication errors

MIFEPRISTONE
Interval period data
For the reporting purposes, the following PTs under the hierarchy of High-Level Group Terms (HGLT) Medication errors and other product use errors and issues were reviewed: *Circumstance or information capable of leading to medication error, Inappropriate schedule of product administration, Intercepted product prescribing error, Product storage error, Product use in unapproved indication, Recalled product administered.*
During the reporting interval, there were nineteen (19) events of medication errors related to the use of mifepristone, which represents 3.42 % of the total number of events (n=555).

Cumulative period data
Cumulatively, the following PTs under the hierarchy of High-Level Group Terms (HGLT) Medication errors and other product use errors and issues were reviewed: *Circumstance or information capable of leading to medication error, Inappropriate schedule of product administration, Incorrect dose administered, Incorrect route of product administration, Intercepted product prescribing error, Labelled drug-food interaction medication error, Medication error, Product administration error, Product dose omission issue, Product storage error, Product use in unapproved indication, Recalled product administered.*

Cumulatively there were seventy-three (73) events of medication errors related to the use of mifepristone, which represents 0.57 % of the total cumulative number of events (n=12,742).

MISOPROSTOL

Interval period data:

For the reporting purposes, the following PTs under the hierarchy of High-Level Group Terms (HGLT) Medication errors and other product use errors and issues were reviewed: *Circumstance or information capable of leading to medication error, Inappropriate schedule of product administration, Incorrect dose administered, Incorrect product administration duration, Incorrect route of product administration, Intercepted product prescribing error, Medication error, Product prescribing error, Product storage error, Product use in unapproved indication, Product use issue, Recalled product administered.*

During the reporting interval there were thirty-seven (42) events of medication errors related to the use of misoprostol, which represents 8.30 % of the total number of events (n=506).

Cumulative period data

Cumulatively, the following PTs under the hierarchy of High-Level Group Terms (HGLT) Medication errors and other product use errors and issues were reviewed: *Circumstance or information capable of leading to medication error, Duplicate therapy error, Inappropriate schedule of product administration, Incorrect dose administered, Incorrect product administration duration, Incorrect route of product administration, Intercepted product prescribing error, Medication error, Product administration error, Product dispensing error, Product prescribing error, Product storage error, Product use in unapproved indication, Product use issue, Recalled product administered, Wrong dose, Wrong product administered, Wrong schedule.*

Cumulatively, there were two hundred and eighteen (225) events of medication errors related to the use of misoprostol, which represents 1.81 % of the total cumulative number of events (n= 12,446).

Medication errors reported during the reporting interval were not reported in combination with the PT of Off label. Medication errors distribution during the reporting interval is present in table 9 below.

Table 9. Medication errors distribution for misoprostol and mifepristone during the reporting interval

Reaction/event in MedDRA terminology Lowest Level Term (LLT)	**Reaction/event (PT)**	Misoprostol*	Mifepristone*
Circumstance or information capable of leading to medication error	Circumstance or information capable of leading to medication error	2	2
Inappropriate schedule of product administration	Inappropriate schedule of product administration	5	5
Drug dose administration interval too short	Inappropriate schedule of product administration	4	4
Drug dose administration interval too long	Inappropriate schedule of product administration	3	2
Incorrect dose administered	Incorrect dose administered	5	0
Drug administration duration too long	Incorrect product administration duration	1	0
Drug administration duration too short	Incorrect product administration duration	1	0
Incorrect route of product administration	Incorrect route of product administration	2	0
Intercepted product prescribing error	Intercepted product prescribing error	4	1
Product prescribing error	Product prescribing error	1	0

Product storage error temperature too low	Product storage error	1	1
Drug use for unapproved indication	Product use in unapproved indication	8	8
Drug use in unapproved population	Product use issue	1	0
Recalled product administered	Recalled product administered	4	4

* Events reported in the non-valid case were not included

10. Non-Clinical Data

There were no major safety findings from non-clinical in vivo and in vitro studies, ongoing and/or completed during the period covered by this report.

11. Literature

A worldwide literature search for safety information was performed in the international journal Reactions Weekly and in PubMed database from 01 June 2021 to 31 May 2022.
The search terms included: 'mifepristone' or 'MS-2 STEP' or 'MIFEGYMISO' without restrictions to human data.
The article exclusion criteria included well established safety information outlined in the product's reference safety documentation, overview/ letters to editor etc., which mentioned results of earlier published studies, clinical trials or studies with other principal IMP, with no new information regarding mifepristone use.

11.1. New safety information

During the reporting period of this PBRER, there were no literature articles identified related to the new safety information of MIFEGYMISO® in the approved and unapproved indications.

11.2. Efficacy

During the reporting period of this PBRER, there were one (1) literature article was identified related to the efficacy of MIFEGYMISO® in the approved and unapproved indications.
Renner R, Ennis M, Guilbert E, Roy G, Barrett J, Second- and Third-Trimester Medical Abortion Providers and Services in 2019: Results from the Canadian Abortion Provider Survey, Journal of Obstetrics and Gynaecology Canada (2022), doi: https://doi.org/10.1016/j.jogc.2022.01.016.
This study evaluated the impact of the implementation a mifepristone/misoprostol protocol (MIFE/MISO) on the induction-to-expulsion interval in the context of second- and third-trimester pregnancy termination or intrauterine fetal death (IUFD) compared with misoprostol alone (MISO), and the authors shared the experience of a Canadian tertiary hospital concerning the feasibility and safety of such a protocol. Ninety-four patients were included in the MIFE/MISO group and 103 patients, in the MISO group. Median time to expulsion was significantly lower in the MIFE/MISO group than the MISO group (13.5 and 19.5 h respectively; $P < 0.001$). The total dose of misoprostol administered was significantly lower in the MIFE/MISO group than the MISO group, and adverse effects were reported in 60% and 82% of patient records, respectively ($P < 0.001$). Complication rates were similar between the two groups. The authors concluded that the MIFE/MISO protocol was highly effective for second- and third-trimester induction for pregnancy termination or IUFD, without increasing complication rates and with fewer reported adverse effects, its implementation was safe and feasible in a tertiary medical centre.

Consolidated conclusion:
The review of the published literature during the reporting period of this report did not reveal any new significant safety information. Based on the review of the published data, no further updates to the reference safety information are considered necessary at the current time.

12. Other Periodic Reports

This report covers the reporting period 01 June 2021 to 31 May 2022 and there were no other periodic reports prepared during the reporting interval.

13. Lack of Efficacy in Controlled Clinical Trials

Not applicable since no serious adverse events of lack of efficacy were reported during the reporting period.

14. Late-Breaking Information

Since the DLP of this PBRER, no new information of potentially important safety and efficacy/effectiveness findings was received by Linepharma International Limited.

15. Overview of Signals: New, Ongoing, or Closed

There was 1 (one) closed signal of acute generalized exanthematous pustulosis (AGEP) in the reporting period. There were no new or ongoing signals in the reporting period. A summary tabulation of new, ongoing or closed signals for mifepristone and/or misoprostol is provided in the following Table 10.

Table 10. Tabular summary of safety signals new, ongoing or closed during the reporting interval for mifepristone and misoprostol.

Product	Signal term	Date detected	Status	Date closed	Source of the signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action taken or planned
Mifepristone	AGEP	Nov-2017	Closed	17Jun2022	Literature case report (found in PSUSA)	Literature case report identified in the previous PBRER. Isolated case based on the literature article in 2015, one new literature article was found in 2020, no were found in safety database, but to be followed to identify other occurrences in next years.	Global safety database and literature search	Routine pharmacovigilance

15.1. Method and sources screened for signal detection

Linepharma International Limited has included in its safety database ICSRs associated with the use of mifepristone in the labelled and unlabelled indications, directly transmitted to LinepharmaInternational Limited and/or transmitted by Health Authorities as well as all case reports identified in the worldwide literature in which the mifepristone/misoprostol marketed by Linepharma International Limited could be involved.

The detection and evaluation of signals for mifepristone/misoprostol is based on the analysis of seriousand non-serious adverse reactions taking into account the nature, severity and frequency of ADRs received from the post-marketing experience (including reports from healthcare professionals, consumers, health

authorities, scientific literature), as well as all adverse reactions received from non-interventional studies, other non-interventional solicited sources and from interventional clinical trials, for which causality with drug administration was not ruled out either by the investigator/reporter or the company. Reactions assessed as 'unrelated' by both the reporter and the company were excluded. Information obtained from the worldwide published sources for mifepristone/misoprostol during the reporting period was also reviewed for the purposes of signal detection.

15.2. Overview of signals detected during the reporting period, under evaluation or with evaluation completed within the reporting period

No new signals for mifepristone or misoprostol arose during the period of this PBRER.

15.3. Ongoing signal

There were no ongoing signals for neither mifepristone nor misoprostol during the reporting period of this PBRER.

16. Signal and Risk Evaluation

16.1 Summary of Safety Concerns

The Risk Management Plan (RMP) remained unchanged during the reporting period. The current version of the RMP is dated 27Aug2020 and contains the safety concerns listed in Table 11 below.

Table 11. Summary of safety concerns regarding mifepristone and misoprostol

Identified risk:	Method failure Infection Toxic shock syndrome Cardiac disorders
Potential risk:	Inadvertent risk of pregnancy Induced bronchial asthma Incorrect determination of gestational age Complication arising from the use in undiagnosed ectopic pregnancy
Missing information:	Pregnant and lactating subjects Paediatric patients Geriatric patients Patients with Renal, Hepatic or Cardiac Impairment Off Label use

16.2 Signal Evaluation

One (1) signal of acute generalized exanthematous pustulosis (AGEP) was closed during the reporting period of 01 June 2021 to 31 May 2022.

16.2.1 Closed and rejected/refuted signals

For mifepristone, the signal acute generalized exanthematous pustulosis (AGEP) was closed during the reporting period of 01 June 2021 to 31 May 2022 with the approval of the new version of the European SmPC. Consequentially, the new version of the Canadian product monograph was proposed. On 17Jun2022, this new Canadian product monograph has been approved..

The variation IAin– C.I.3.a), implementing the outcome of the PRAC Assessment Report on the PSUR(s) for mifepristone (addition of a new adverse event "Acute generalised exanthematous pustulosis" in sections

4.8 on the European SmPC with frequency "Unknown", and a warning on severe cutaneous adverse reactions in section 4.4.), ended on 17Jun2021 (change to the SmPC was implemented on 12May2021).
Variation to update the local Australian labelling of PrMIFEGYMISO® combipack and Mifepristone Linepharma 200 mg in alignment with the RSI and SmPC changes was approved on 12Aug2021.
Variation to update the local Canadian labelling of PrMIFEGYMISO® combipack in alignment with the RSI and European SmPC changes was approved on 17Jun2022.
No cases involving events of acute generalised exanthematous pustulosis were reported in the Linepharma pharmacovigilance database since the product commercialization and during the reporting period.

16.2.2 Closed signals categorised as important potential risks

There were no (0) signals categorized as an important potential risk for MIFEGYMISO® during the reporting period of 01 June 2021 to 31 May 2022.

16.2.3 Closed signals categorised as important identified risks

There were no (0) signals categorized as an important identified risk for MIFEGYMISO® during the reporting period of 01 June 2021 to 31 May 2022.

16.2.4 Closed signals that are potential risks not categorised as important

There were no (0) signals evaluated as a potential risk and was not categorized as important for MIFEGYMISO® during the reporting period of 01 June 2021 to 31 May 2022.

16.2.5 Closed signals that are identified risks not categorised as important

There were no (0) signals evaluated as an identified risk and was not categorized as important for MIFEGYMISO® during the reporting period of 01 June 2021 to 31 May 2022.

16.2.6. Ongoing signals

There were no (0) ongoing signals for MIFEGYMISO® (mifepristone or misoprostol) during the reporting period of 01 June 2021 to 31 May 2022.

16.3 Evaluation of Risks and New Information

16.3.1 New information on important identified risks

a) Method failure

During the reporting period, there were reported forty-eight (48) ICSRs (forty-seven (47) of them included both mifepristone and misoprostol) corresponding to the ninety-six (96) adverse events (AEs). The distribution of the type of method failure from these ICSRs is presented in Table 12.

Table 12. Interval data on medical termination of pregnancy (MTOP) failures for mifepristone and misoprostol

MedDRA PT (v 24.1)	Abortion failures LLTs	# of AEs mifepristone	# of AEs misoprostol
Induced abortion failed	Induced abortion failed	11	10*
Abortion induced incomplete	Abortion induced incomplete (reported retained products of conception)	32	32*
Abortion incomplete	Not applicable	0	0
Retained products of conception	Not applicable	0	0
Evacuation of retained	Not applicable	0	0

products of conception			
Drug ineffective	The patients did not have any bleeding	4	4*
Treatment failure	The patient had retained products of conception post MTOP that passed spontaneously	1	1*

*Events were reported in the same ICSR for **Mifepristone and Misoprostol**

In addition, during the reporting period, four (4) non-valid cases with the PTs related to the method failure were identified (PTs reported included: Drug ineffective for unapproved indication (1), Abortion induced incomplete (2), Induced abortion failed (1)):

Case 2022000335: Literature report information was retrieved on 07-Feb-2022 from published literature abstract: Vlad S, Boucoiran I, Imeah B, Roy St-Pierre E, Ferreira E. Mifepristone-Misoprostol Use for Second and Third Trimester Medical Termination of Pregnancy in a Canadian Tertiary Care Centre. J Obstet Gynaecol Can. 2022 Jan 31;S1701-2163(22)00011-1. DOI:10.1016/j.jogc.2021.12.010. Non-valid case (unspecified number of patients). Linepharma reference #NGR-CPK-22-000474
Follow-up information was received on 09-Feb-2022 : complete literature article was obtained. Specific adverse reactions were listed but unable to identify individually. Non valid case. Linked cases included (same article): CA-LINE-2022000336, CA-LINE-2022000338.

Case 2022000581: This spontaneous serious report was received on 03-Mar-2022 from a physician via the partner in Australia (MS Health reference 2022COML000120). LPI reference #NAP-CPK-22-000684. Non-valid case.

Case 2022000923: Literature report information was retrieved on 12-Apr-2022 from published literature article: Ennis M, Renner R, Guilbert E, Norman WV, Pymar H, Kean L et al. Provision of First-trimester Medication Abortion in 2019: Results from the Canadian Abortion Provider Survey. Contraception. 2022 Mar 26:S0010-7824(22)00078-6. doi: 10.1016/j.contraception.2022.03.020. Non-valid cluster case (unspecified number of patients). Linepharma reference #NAP-CPK-22-001099. This cluster case involves unspecified number of female patients (unspecified age), included in the MIFE/MISO group of this retrospective study.

Case 2022000283: This spontaneous serious non-valid report was received on 04-Feb-2022 from a physician via the partner in Australia (MS Health reference 2022COML000071). Linepharma reference #NAP-CPK-22-000443.
Amendment was received on 18-Feb-2022: quality department confirmed that several packaging issues have occurred with Batch number LFK2020M and it was recalled from the market.

<u>Off label use encountered in ICSRs of failed MTOP</u>
There were 0 (no) off label use events reported during the reporting period.

b) Infection and Toxic shock syndrome
During the interval period, there were 0 (no) adverse events of toxic shock syndrome.
During the interval period, there were reported 2 (two) events of 'infection' (reported in the same ICSR for both mifepristone and misoprostol), one (1) event of 'Amniotic cavity infection' (reported in the same ICSR for both mifepristone and misoprostol), and five (5) event of 'Endometritis' (four (4) were related to the use of mifepristone and misoprostol and related in four (4) ICSRs and one (1) was related to the use of

mifepristone only and reported in the separate ICSR).

One (1) case 2022000335 that contained PT 'Amniotic cavity infection' was reported as non-valid and was identified in the published literature.

c) Cardiac disorders

- There were no events related to the SOC "Cardiac disorders' reported for neither mifepristone nor misoprostol during the interval period.

16.3.2 Potential risks

a) Inadvertent risk of pregnancy

During the reporting period, no new information was received regarding the potential risk of 'inadvertent risk of pregnancy'.

b) Induced bronchial asthma

No new information regarding the potential risk of Induced bronchial asthma arose during the reporting period.

c) Incorrect determination of gestational age

During the reporting period, no new information was received regarding the potential risk of incorrect determination of gestational age.

d) Complication arising from the use in undiagnosed ectopic pregnancy

During the reporting period, no new information was received regarding the potential risk of complication arising from the use in undiagnosed ectopic pregnancy.

16.3.3 Missing information

a) Pregnant and lactating subjects

Regarding breastfeeding, no new information was received during the reporting period regarding the exposure to mifepristone alone or misoprostol alone.

For mifepristone and misoprostol, two (2) ICSRs were reported with the event 'Exposure during pregnancy' and two (2) ICSRs were reported with the event 'Pregnancy test urine positive'. Additional two (2) ICSRs were reported with the event 'Exposure during pregnancy' related to the mifepristone use. Events 'Exposure during pregnancy' were associated with either 'Refusal of treatment' event or 'Induced abortion failed' event.

b) Pediatric and Geriatric patients

During the reporting interval, seven (7) ICSRs were reported where the product was administered to an adolescent patient (< 18 years old). Three (3) of them were related to both mifepristone and misoprostol (2021002075, 2022000390, 2022001408) and four (4) of them were related to the mifepristone only (2021001701, 2021001716, 2021002127, 2021002545).

All the seven (7) ICSRs were spontaneously received from Australia as non-serious reports. The most common events were 'vomiting' (3) and 'haemorrhage' (3).

During the reporting interval, there was one (1) report for patients in the post-menopausal age group (> 49 years old). Case 2021001301 describes the use of misoprostol (unspecified trade name) tablets (unspecified time frame, dosage, route and indication) in a 70-year-old female patient. This serious case

was identified in Canada Vigilance Adverse Reactions Online database and was initially reported by an unspecified MAH (from literature, article reference not provided) to Health Canada.
Cumulatively, among the three thousand nine hundred and eighty-eight (3,988) ICSRs with mifepristone and/or misoprostol, two hundred and twenty-nine (229) were reported for mifepristone in combipack presentation, one hundred and forty-four (144) ICSRs were reported for misoprostol in combipack presentation, and three thousand six hundred and forty-five (3,645) ICSRs were reported for mifepristone and misoprostol in combipack presentation. The age/ age group split per ingredient is presented in Table 13 below.

Table 13. Cumulative distribution of mifepristone and misoprostol use (together) in adolescent patients and in post-menopausal ages

	ICSRs for adolescent patients (< 18 years old)	ICSRs for patients in post-menopausal ages (> 49 years old)
Mifepristone alone (total number of ICSRs is 229)	9 (3.93%)	0
Misoprostol alone (total number of ICSRs is 144)	2 (1.39%)	4 (2.77%)
Mifepristone and misoprostol together (total number of ICSRs is 3,988)	67 (1.84%)	2 (0.05%)

c) Patients with Renal, Hepatic or Cardiac Impairment
No new information regarding the missing information on Patients with Renal, Hepatic or Cardiac Impairment arose during the report period.

d) Off Label use
No events were coded for the PT of "Off label use". No new information regarding the missing information of Off label use arose during the report period.

16.4 Characterization of risks
16.4.1. Identified Risk
Table 14. Identified risk: Method failure

Method Failure Medical abortion is aimed to terminate a pregnancy with no need for additional surgical procedure. We will define method failure as recourse to a surgical procedure, as result of a continuing pregnancy, incomplete expulsion, and the physician's judgment or upon request from the woman.
Severity and nature of risk ***Heavy prolonged bleeding*** Pivotal studies describe bleeding occurrence and specify that it is a cause of emergency visit (along with pain) of patient. Post-marketing experience described in literature reports that bleeding is an almost constant part of the procedure, whatever the prostaglandin analogue use and at any pregnancy term, although it is usually more abundant when pregnancy age increases. It can occur after mifepristone alone. When heavy, it usually reflects incomplete abortion that is observed in approximately 3 to 12 % of the cases, depending on the pregnancy age and the prostaglandin analogue used, and needs specific treatment. It can necessitate a blood transfusion in 0.1-0.2% of cases up to 49 days last menstrual period (LMP) and around 0.5% in the second trimester. It can be prolonged for several days after prostaglandin analogue administration and sometimes leads to a decrease in haemoglobin levels. The average drop in haemoglobin is 0.7% (601) and most studies of medical abortion excluded women with a haemoglobin under 10g/dl. In the Australian phase IV safety study, heavy vaginal bleedingwas reported by 3.2% of patients. ***Surgical intervention***

Pivotal studies (Middleton T et al., 2005, Winikoff B et al., 2008, Pena N et al., 2014) report occurrence of surgical intervention in 2.7 to 5.1% of patient, however there was no complication following these interventions.
In the Australian phase IV safety study, the occurrence of incomplete abortion requiring surgical intervention was 4.2%.
Post-marketing experience described in literature reports that failure of the medical abortion could lead to a surgical procedure with its associated risks of anaesthesia and of the technic used. Surgical termination complications are rare and include uterine perforation, cervical laceration, haemorrhage, incomplete removal and infection (Kulier, Cheng, Fekih, Hofmeyr, & Campana, 2001).

Continuing pregnancy

In case of failure of the method, persisting pregnancy may occur. During pivotal studies continuing pregnancies were followed by surgical termination of pregnancy.
In the Australian phase IV safety study, continuing pregnancy occurred with a frequency of 0.76% (Goldstone P et al., 2017).
Post-marketing experience described in literature reports that up to date there does not seem to be clear-cut foetal malformations attributable to mifepristone or to prostaglandin analogues (Sitruk-Ware R et al., 2006), suchpossibility cannot be definitively ruled out and women should be adequately counselled in such a situation.
In addition, misoprostol, through its smooth muscle contracting activity, could have effects on the developing foetus and there are several reports in the literature on the occurrence of congenital defects in children born to mothers who had taken misoprostol to terminate pregnancy; this off-label use of misoprostol appears to have been a particular problem in Brazil, from where considerable evidence has accumulated on its possible teratogenic activity in humans (cited by Orioli et al, 2000; Paumgarten et al, 1995). Data would suggest a link between misoprostol and congenital malformations, based on a retrospective analysis of cases, and a prospective study based on Brazilian data suggested that misoprostol may increase the incidence of congenital anomalies, but that the magnitude of the increased risk is low (Schuler et al, 1999).

Frequency

During pivotal studies, method failure was reported between 2.7 and 5.1%. In the Australian phase IV safety study, method failure was reported between 1.12% (gestational age < 35 days) and 5.69% (gestational age 57-63 days). From cumulative data to 31st March 2016, incidence (%) of method failure by gestational ages is provided below:

≤ 35 days	36-42 days	43-49 days	50-56 days	57-63 days	Total
1.1	2.6	4.8	5.6	5.7	4.2

In literature, studies and post-marketing experience occurrence of treatment failure is reported between 1.3 to 7.5 % in medical abortion.

Background incidence/prevalence

Surgical pregnancy termination has a lower rate of failure than medical termination. Early vacuum aspirationfailure rate is estimated at up to 5% (Ashok PW et al.,2002).

Risk group or risk factors

None identified.

Potential mechanism

Incomplete detachment of conceptus from uterine wall, insufficient uterine contractility.

Preventability

Information about the potential occurrence of method failure, severe bleeding and continuing pregnancy are in the Product Monograph and the Patient Medication Information.
Follow-up visit must take place within a period of 07 to 14 days after administration of mifepristone and misoprostol to verify by the appropriate means that expulsion has been completed and that vaginal bleeding has stopped.
Persistent bleeding should be monitored closely for a decrease in haemoglobin concentration, hematocrit and red blood cell count.
If continuing pregnancy is suspected, a further ultrasound scan may be required to evaluate its viability.
The Product Monograph states that prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed and that the patient should be informed not to travel far away from the prescribing centre as long as complete expulsion has not been recorded. Patient will receive precise instructions as to whom she should contact and where to go, in the event of any problems emerging,

particularly in the case of very heavy vaginal bleeding.
Potential public health impact Practitioners should be properly trained to inform their patients on this risk and on the need for a follow up visit to be done.
Evidence source Data to evaluate the risk of method failure after the administration of mifepristone and misoprostol are derived from Australian phase IV safety study and analyses conducted of extensive review of literature published in English and in Chinese as well as non-Linepharma sponsored trials and reports from post-marketing setting.
Regulatory action taken Information relating to the method failure and its consequences has been included in the Product Monograph.

Table 15. Identified risk: Infection, toxic shock syndrome

Infection, Toxic shock syndrome

Adverse event reports of infection, toxic shock syndrome are identified using a prespecified list of terms inMedDRA: SOC Infections and infestations.

Seriousness and outcomes for risk

No infection was reported during pivotal studies, however in literature studies and post-marketing experience infection in medical termination regardless of seriousness criteria occurs in 0.3-0.9% of cases (Shannon C et al., 2004). Serious infection after medical termination by mifepristone and buccal misoprostol occurs 0.06 per 1 000 (Fjerstad M et al., 2009). Fatal toxic shock syndrome is described rarely in medical termination.

Severity and nature of risk

Altogether, worldwide, 13 deaths from infection following medical abortion (8 in the United States, 7 from C. sordellii and 1 from C. perfringens; 1 in Canada from C. sordellii; 2 in England & Wales, both from C. septicum; 1 in Portugal from C. sordellii; 1 in Australia from Grp A Strep pyogenes) have been reported: 9 with vaginal misoprostol and no antibiotics, 1 with misoprostol route unknown and no antibiotics, 2 with buccal misoprostol and no antibiotics, and 1 with vaginal misoprostol and doxycycline. For the Australian case the relationship between her pregnancy termination and her death was uncertain and the events may have been coincidental.
Clinicians should be aware of this potentially fatal complication.

Frequency

Infection in medical termination regardless of seriousness criteria occurs in 0.3-0.9% of cases (Shannon C etal., 2004).
In the Australian phase IV safety study, infection occurred in 0.2% of cases. From cumulative data to 31stMarch 2016, incidence (%) of infection by gestational ages is provided below:

≤ 35 days	36-42 days	43-49 days	50-56 days	57-63 days	Total
0	0.1	0.3	0.2	0.3	0.2

Serious infection after medical termination by mifepristone and buccal misoprostol occurs 0.06 per 1 000(Fjerstad M et al., 2009).

Background incidence/prevalence

Infection following termination occurs in less than 5% of cases regardless of the method.

Risk group or risk factors

A risk factor that has been discussed is the use of misoprostol via the vaginal route.
All reported infection-related mortalities during first trimester medical abortion in the United States andworldwide have used regimens that employed misoprostol vaginal route or did not use antibiotics at thetime of mifepristone ingestion (Trussell, Nucatola, Fjerstad, & Lichtenberg, 2014)

Potential mechanism

Unknown

Preventability

Information about the potential occurrence of the event in presented in the Product Monograph (Warnings and Precautions) and information about the possibility of infection occurring is included in the Patient Medication

Information.

Potential public health impact
Practitioners should be properly trained to inform their patients on this risk.

Evidence source
Data to evaluate the risk of method failure after the administration of mifepristone and misoprostol are derived from Australian phase IV safety study and analyses conducted of extensive review of literature published in English and in Chinese as well as non Linepharma sponsored trials and reports from post- marketing setting.

Regulatory action taken
Information relating to the method failure has been included in the ProductMonograph.

Table 16. Identified risk: Cardiovascular events

Cardiovascular events
Adverse event reports of cardiovascular events are identified using a prespecified list of Standard MedDRA query: SOC Cardiac disorders

Seriousness and outcomes for risk
No cardiovascular event was reported during pivotal studies.
Cardiovascular events reported with misoprostol use in a gynaecological indication, in literature studies and post-marketing experience, include myocardial infraction, myocardial ischemia, sudden death, stroke and transient ischemic accident. Most of these events have a favourable outcome, but event with sequel or fatal outcome has also been reported. If some occurred after a treatment including mifepristone and misoprostol, for most of them mifepristone administration was unknown

Severity and nature of risk
In a prospective study on 9 women evaluating cardio-vascular safety of 600 µg misoprostol administration via vaginal route, none of evaluated parameters (cardiac frequency, arterial pressure, cardiac index…) for 4 days after the take were significantly modified (Ramsey 2000).
An investigation on cardiovascular effect of misoprostol was performed by the French National Agency in 2013. This evaluation based on international literature search, French and international post-marketing reports (from commercialisation to December 2012) concludes in the existence of coronary and cerebral adverse reaction with the use of misoprostol in medical termination of a pregnancy.
Regarding mifepristone potential effect on cardiovascular system, non-clinical data, clinical data, post- marketing surveillance of adverse events and the drug's action mechanism on the adrenocortical pathway do not associate the product with typical proarrhythmic events that could indicate a QT/QTc interval prolongation.

Frequency
French National Agency estimated the incidence of cardiovascular events with the use of misoprostol at 2.7cases [0.3 to 9.8] for 106 exposed women.
In the Australian phase IV safety study, from cumulative data to 31st March 2016, incidence (%) of cardiovascular event by gestational ages is provided below:

≤ 35 days	36-42 days	43-49 days	50-56 days	57-63 days	Total
0	0.1	0.1	0.3	0.2	0.1

Background incidence/prevalence
There are no specific studies that evaluate prevalence of cardiovascular risks of first trimester pregnant women. Some case reports describe occurrence of myocardial infraction in the first trimester of pregnancy (Hutchison, Holden, & Lorimer, 1985 and Matana, Pavlin, Karlovic, & Sepic, 1983) but no meta-analysis or large scale study has been done.
In addition, first trimester miscarriage has been linked to subsequent maternal ischemic heart disease(Oliver-Williams, Heydon, Smith, & Wood, 2013) and first trimester bleeding without miscarriage is associated with maternal cardiovascular morbidity (Lykke & Langhoff-Roos, 2012).

Risk group or risk factors
Vascular risks factors such as tobacco use, hypertension and heredity as well as a sur-exposure tomisoprostol.

Potential mechanism

Coronary manifestations observed during medical termination of pregnancy could be explained by the existence of vascular risks factors (tobacco use, hypertension, heredity…) and a sur-exposition to misoprostol related to the high dose (double posology) and the vaginal administration, this way leading to a doubling of AUC. PGE1 is not known to have coronary vasoconstrictive effects by coronary adverse events have been reported with gemeprost (CervagemR) another synthetic analogue of the PGE1 used in medical termination of pregnancy. Warning and cardiovascular contraindications also exist for sulprostone (NaladorR) synthetic analogue of PGE2 for which coronary spasms and myocardic ischemia were reported. However, for PGE1 and PGE2 there is no physiopathological explanation of this adverse reaction. Nevertheless, we can note that sulprostone coronary accident have so far only be reported in women over 30years and/or with a tobacco use above 10 cigarettes per day, spasms being favoured by chronic or recent tobacco use.
Preventability Product Monograph and Patient Medication Information (Warnings and Precautions) specifies that women with risk factors for cardiovascular disease (hypertension, diabetes or who are over the age of 35 and are heavy smokers) should be treated with caution. Product Monograph and Patient Medication Information (Warnings and Precautions) also specifies that treatment is not recommended, in women with cardiovascular disease.
Potential public health impact Practitioners should be properly trained to inform their patients on this risk.
Evidence source Data to evaluate the risk of cardiovascular risks after the administration of mifepristone in sequential combination with misoprostol are derived from extensive literature search as well as worldwide post- marketing reports evaluated by the French National Agency.
Regulatory action taken Information regarding cardiovascular risks has been included in the Product Monograph. Cardiac events assessed to misoprostol are monitored for the following 3 years on PRAC request in December 2020

16.4.2. Potential risks

The following are specified as potential risks for mifepristone use in sequential combination with misoprostol therapy in medical termination of a pregnancy:

- Inadvertent risk of pregnancy
- Induced bronchial asthma
- Incorrect determination of gestational age
- Complications arising from use in undiagnosed ectopic pregnancy

Table 17. Potential risk: Inadvertent risk of pregnancy

Seriousness and outcomes for risk There is a possibility for a pregnancy to occur between embryo expulsion and the resumption of menses. Thiscould potentially expose the foetus to mifepristone and misoprostol and potentially lead to congenital malformation. If no such case has been reported during pivotal studies, this could potentially occur.
Severity and nature of risk In literature studies and post-marketing experience, up to date there does not seem to be clear-cut foetal malformations attributable to mifepristone or to prostaglandin analogues (Sitruk-Ware R et al., 2006), such possibility cannot be definitively ruled out and women should be adequately counselled in such a situation. In addition, misoprostol, through its smooth muscle contracting activity, could have effects on the developingfoetus and there are several reports in the literature on the occurrence of congenital defects in children born to mothers who had taken misoprostol to terminate pregnancy; this off-label use of misoprostol appears to have been a particular problem in Brazil, from where considerable evidence has accumulated on its possible teratogenic activity in humans (cited by Orioli et al, 2000; Paumgarten et al, 1995). Data would suggest a link between misoprostol and congenital malformations, based on a retrospective analysis of cases, and a prospective study based on Brazilian data suggested that misoprostol may increase the incidence of congenital anomalies, but that the magnitude of the increased risk is

low (Schuler et al, 1999).
Frequency Frequency of such event is unknown.
Background incidence/prevalence After expulsion of embryo and before resumption of menses there is a possibility for women to be pregnant.
Risk group or risk factors There is no specific risk factor, women who don't take contraceptive precautions after medical termination of pregnancy could be affected.
Potential mechanism Medical termination of a pregnancy with mifepristone in sequential combination with misoprostol doesn't have a contraceptive effect, as a consequence, women could be pregnant before the resumption of menses.
Preventability Product Monograph and Patient Medication Information (Warnings and Precautions) recommend that conception is avoided during the next menstrual cycle and that reliable contraceptive precautions should therefore commence as early as possible after mifepristone administration.
Potential public health impact Practitioners should be properly trained to inform their patients on this risk.
Evidence source Data to evaluate the inadvertent risk of pregnancy after the administration of mifepristone and misoprostol are derived from analyses conducted of extensive review of literature published in English and in Chinese as well as non Linepharma International Limited sponsored trials and reports from post-marketing setting.
Regulatory action taken Information regarding inadvertent risk of pregnancy has been included in the Product Monograph.

Table 18. Potential risk: Induced bronchial asthma

Induced bronchial asthma Reports of induced bronchial asthma are identified using a prespecified list of preferred terms in MedDRA version 24.1 'Asthma'.
Seriousness and outcomes for risk Mifepristone binds to the glucocorticoid receptor. It may therefore interfere with the action of glucocorticoid treatments. This might be relevant in case of severe asthma inadequately controlled by oral or inhaled glucocorticoid. If no such cases occur during pivotal studies, in light of action mechanism bronchospasm may occur with some prostaglandins and prostaglandin analogues. The possibility should be borne in mind in patients with a historyof asthma.
Severity and nature of risk Risk would be for asthma patient uncontrolled by their corticosteroid treatment to present a severe asthma reaction.
Frequency Frequency of such event is not known.
Background incidence/prevalence An estimated 300 million people are affected by asthma worldwide and the burden is likely to rise substantially in the next few decades. Estimates of the prevalence of asthma range from 7% in France and Germany to 11% in the USA and 15-18% in the United Kingdom. Approximately 20% of these patients have severe asthma, of which 20% is inadequately controlled. Patients with inadequately controlled severe persistent asthma are at a particularly high risk of exacerbations, hospitalization and death, and often have severely impaired quality of life (Peters, Ferguson, Deniz, & Reisner, 2006).
Risk group or risk factors Severe asthma uncontrolled by oral or inhaled glucocorticoïd.

Potential mechanism Due to antiglucocorticoïd activity of mifepristone, the efficacy of long-term corticosteroid therapy, including inhaled corticosteroids in asthma patients, may be decreased during the 3 to 4 days following intake of mifepristone.
Preventability Product Monograph and Patient Medication Information (Warnings and Precautions) specify that efficacy of long-term corticosteroid therapy including inhaled corticosteroid may be decrease and that therapy should be adjusted. It also specifies that bronchospasm may occur with some prostaglandins and prostaglandin analogues and that caution should be exercised in patients with a history of asthma
Potential public health impact Practitioners should be properly trained to inform their asthmatic patients on this risk.
Evidence source Data to evaluate the inadvertent risk of induced bronchial asthma after the administration of mifepristone and misoprostol are derived from analyses conducted of extensive review of literature published in English and in Chinese as well as non Linepharma International Limited sponsored trials and reports from post-marketing setting.
Regulatory action taken Information regarding induced bronchial asthma has been included in the Product Monograph.

Table 19. Potential risk: Incorrect determination of gestational age

Incorrect determination of gestational age Reports of incorrect determination of the gestational are identified using a prespecified list of preferred terms in MedDRA version 24.1 'Inappropriate schedule of drug administration'.
Seriousness and outcomes for risk The efficacy of the combination of mifepristone and misoprostol has been demonstrated to slightly decrease with the gestational age. The 3 pivotal studies presented in the Product Monograph showed a mean efficacy rate of 97.4% at ≤ 49 days of gestation, 96.2% between 50 and 56 days of gestation, and 95.6% between 56 and 63 days of gestation. An underestimation of the gestational age could lead to decreased efficacy of the treatment and an increase in incidence or seriousness of adverse reactions.
Severity and nature of risk Ultrasonography is the most reliable way to evaluate the gestational age, but is not always available to physicians, who then have to rely on other methods of determining the gestational age. An underestimation of the gestational age could lead to decreased efficacy of the treatment and an increase in incidence or seriousness of adverse reactions. The risks of ongoing pregnancy, incomplete expulsion or need for surgical procedures increase as the efficacy of the treatment decreases. Overestimation of the gestational age does not represent a risk.
Frequency Frequency of such event is not known.
Risk group or risk factors Women with irregular menstrual cycles; Women living in remote areas or not having access to hospitals are more at risk of not having access to ultrasonography; Large- or small-for-gestational-age fetus; Women with large uterus, fibroids or thickened endometrium.
Potential mechanism The efficacy of the combination of mifepristone and misoprostol has been demonstrated to slightly decrease with the gestational age.

Preventability Gestational age should be evaluated using an effective method, preferably by ultrasound (vaginal or pelvic). In the event where ultrasonography facilities are not available, gestational age should be determined using another method as per clinical practice and pregnancy termination guidelines, such as reliable menstrual dating combined with clinical examination and/or HCG levels. Overestimation of the gestational age does not represent a risk.
Potential public health impact Practitioners should be properly trained to inform their patients on this risk.
Evidence source Data to evaluate the risks associated with an incorrect determination of gestational age are derived from analyses conducted of extensive review of literature published in English and in Chinese, as well as non Linepharma International Limited sponsored trials, reports from post-marketing setting, clinical expert reports and clinical practice guidelines.
Regulatory action taken Information regarding gestational age determination with different methods has been included in the Product Monograph, in line with current clinical practice guidelines.

Table 20. Potential risk: Complications arising from use during an undiagnosed ectopic pregnancy

Complications arising from use during an undiagnosed ectopic pregnancy Reports of use during an ectopic pregnancy are identified using a prespecified list of preferred terms in MedDRA version 24.1 'Ectopic pregnancy', 'Ruptured ectopic pregnancy'.
Seriousness and outcomes for risk Mifepristone does not appear effective for terminating an ectopic pregnancy; therefore, its use during an ectopic pregnancy can result in an ongoing non-viable pregnancy, and an increased risk of ruptured ectopic pregnancy and internal bleeding, which may lead to hypovolemic shock and death.
Severity and nature of risk Mifepristone does not appear effective for terminating an ectopic pregnancy; therefore, its use during an ectopic pregnancy can result in an ongoing ectopic pregnancy, and an increased risk of ruptured ectopic pregnancy.
Frequency Frequency of use of Mifegymiso during an ectopic pregnancy is not known. Ectopic pregnancy is an uncommon event, occurring in 1.5–2% of pregnancies, with an even lower incidence in unplanned pregnancies.
Risk group or risk factors The risk of ectopic pregnancy increases with age and number of sexual partners, history of ectopic pregnancy,pelvic infection, infertility, cigarette smoking, prior caesarean section, pelvic or tubal surgery, prior tubal damage, *Chlamydia trachomatis* infection.
Potential mechanism Mifepristone does not appear to have an effect on tubular motility. If an ectopic pregnancy is not detected, it can result in a method failure.
Preventability Clinical examination including physical exam, and if ectopic pregnancy is suspected, ultrasonography, measurement of serum β-hCG levels, and/or serum progesterone levels. Mifegymiso if not effective interminating an ectopic pregnancy; complete pregnancy termination should be confirmed during the follow-up visit.
Potential public health impact Practitioners should be properly trained to inform their patients on this risk. Women should be told to seek medical advice promptly if they experience symptoms that may indicate ectopic pregnancy, such as severe and intensifying abdominal pain, particularly if it is one-sided. Complete pregnancy termination should be confirmed during the follow-up visit.

Evidence source Data to evaluate the risks associated with the use during an ectopic pregnancy are derived from analyses conducted of extensive review of literature published in English and in Chinese, as well as non Linepharma International Limited sponsored trials, reports from post-marketing setting, clinical expert reports and clinicalpractice guidelines
Regulatory action taken Information regarding the need to exclude an ectopic pregnancy has been included in the Product Monograph in line with the current clinical practice guidelines, as well as the need for a follow-up visit to confirm the termination of pregnancy.

16.5 Effectiveness of risk minimization

Risk minimization activities consisted of routine risk minimization measures.
There was no additional risk minimization activity for mifepristone and misoprostol. The measure of effectiveness is based on the number of cases.

17. Benefit Evaluation

17.1 Important Baseline Efficacy/Effectiveness Information

Mifepristone /misoprostol is indicated for medical termination of a developing intra-uterine pregnancy with a gestational age up to 63 days as measured from the first day of the Last Menstrual Period (LMP) in a presumed 28-day cycle.

Mifepristone

Mifepristone is an orally active antiprogestogen which acts by competing with progesterone for receptor binding. It also possesses anti-glucocorticoid and antiandrogenic activity. It is devoid of estrogenic, antiestrogenic, mineralocorticoid and anti-mineralocorticoid properties. Its ability to block the action of progesterone on the pregnant uterus provides a medical approach to termination of early pregnancy. In normally menstruating women, the effect of mifepristone depends on the timing of administration. When administered in the first half of the luteal phase, menstrual induction occurs independently of luteolysis; mifepristone administration during the mid-luteal phase produced bleeding within a few days in most women but there was a second bleed at the time of expected menses in about two-thirds. The first episode of bleeding occurred in the presence of elevated progesterone and estrogen concentrations. Administration during the late luteal phase resulted in bleeding within 1 to 3 days, shortening the luteal phase of the treatment cycle and lengthening of the subsequent follicular phase. Administration on the first 3 days of the menstrual cycle had no effect on cycle length but when given in the late follicular phase, mifepristone prolonged the follicular phase by preventing the development of a normal luteinizing hormone (LH) surge and delaying the new surge for about 15 days.
In the first trimester of pregnancy, mifepristone induced uterine activity in virtually all women 36 and 48 hours after administration and increased the sensitivity of myometrium to exogenous prostaglandins (PG). The accompanying increase in decidual PGF2α production was attenuated by indomethacin, but the increase in uterine activity was not: thus, mechanisms other than an increase in decidual PG production contribute to the abortifacient effect of mifepristone. Mifepristone administration also resulted in cervical ripening in pregnant women.

Misoprostol

Misoprostol is a synthetic analogue of prostaglandin E1 (PGE1). At the recommended dosages, misoprostol induces contractions of the smooth muscle fibers in the myometrium and relaxation of the uterine cervix. The uterotonic properties of misoprostol should facilitate cervical opening and evacuation of intrauterine content.

In the event of an early termination of pregnancy, the combination of misoprostol used in a sequential regimen after mifepristone leads to an increase in the success rate and accelerates the expulsion of the conceptus. Among other effects, misoprostol inhibits the acid gastric secretion and increases the digestive peristalsis.
Uterine contractility following administration of misoprostol via the buccal route was investigated with an intrauterine pressure transducer in women seeking termination of pregnancy. Results indicated that the average time to onset of increased tone and first uterine contraction were 41.2 and 67.1 minutes, respectively. Sustained uterine activity was observed on average after 90.0 minutes and peak uterine activity after 264.0 minutes.

17.2 Newly Identified Information on Efficacy and Effectiveness

No new information on efficacy and effectiveness in authorized indication was identified during the reporting interval.

17.3 Characterisation of Benefits

As there is no new relevant benefit data and no change in the risk profile, the benefits are identical to those reported in section 17.1.

18. Integrated Benefit-Risk Analysis for Approved Indications

18.1 Benefit-Risk Context - Medical Need and Important Alternatives

Mifepristone/misoprostol is indicated for medical termination of a developing intra-uterine pregnancy with a gestational age up to 63 days as measured from the first day of the LMP in a presumed 28-day cycle.
Medical termination of developing intrauterine pregnancy, up to 63 days of gestation constitutes the main indication of mifepristone. Available data from the Canadian Institute for Health Information on induced abortion (CIHI, 2020- published on 17 March 2022) indicates that 74,155 (seventy-four thousand one hundred and fifty-five) were reported by Canadian hospitals and clinic in 2020 and details are provided in the tables 20 and 21 below (note: some abortions not included, for example, most medical abortions in primary care settings*).
For information it was around 94,030 abortions per year for the previously available data issued from CIHI in 2019.

Table 21. Number of induced abortions reported in Canada in 2020, by province/territory of hospital or clinic and age group

Age group (years)	Number of induced abortions reported by hospitals	Number of induced abortions reported by clinics	Total
≤17	545	384	**1,514**
18–24	4,713	5,161	**16,171**
25–29	3,718	8,147	**17,308**
30–34	3,089	7,233	**14,962**
35+	2,750	7,807	**15,407**
Unknown	6,994	23,614	**8,793**
Total	**21,809**	**52,346**	**74,155**

NOTES: * In recent years, medical abortions have become more accessible in primary care settings (e.g., nurse practitioner and physician offices, community and public health clinics), and most of these are not included in the data tables. Therefore, volumes reported underestimate the true number of induced abortions in Canada.

- † Detailed age breakdowns are not available from Ontario clinics for patients younger than age 25. Data for the affected age categories is presented in the age group "unknown (≤24)" for the Ontario row. For the pan-

Canadian Total reported row, Ontario clinic cases for patients younger than 25 are included in the "unknown" category.

- Table includes induced abortions performed in a hospital or in a clinic providing abortion services in Canada (numbers are presented by the province/territory in which the abortion was performed). Quebec induced abortions with an unknown location (0.12% of Quebec cases) are grouped under "clinic."
- As of 2020, the total abortion volumes for Ontario are derived using a more accurate methodology. The impact of the revised methodology on previously reported historical volumes for Ontario is a reduction of approximately 1%.

Table 22. Number and percentage distribution of induced abortions reported by Canadian hospitals (excluding Quebec) in 2020, by gestational age

Gestational age (weeks)	Number of induced abortions reported by hospitals	Percentage of induced abortions reported by hospitals
≤8	4,725	31.9%
9–12	4,002	27.0%
13–16	1,278	8.6%
17–20	749	5.1%
21+	652	4.4%
Unknown	3,409	23.0%
Total	**14,815**	**100.0%**

18.2 Benefit-Risk Analysis Evaluation

During the period covered by this report, no modification of the efficacy of mifepristone / misoprostol has been shown. During the period covered by this report, no new safety concerns were identified.
Safety data collected for mifepristone/misoprostol from spontaneous reporting and identified from the literature did not highlight any new safety issues. At the end of the period, all the risks were included in the product information.
The risk-benefit profile of mifepristone / misoprostol remains favourable.

19. Conclusions and Actions

Data relating to the benefit-risk profile of MIFEGYMISO® received in the reporting period 01 June 2021 to 31 May 2022 have been reviewed and placed in a cumulative context.

Based on the review of data received during the reporting period, no amendments of the reference information due to safety concerns are considered necessary at this time. A close monitoring will be continued in the framework of routine pharmacovigilance activities.

There were no new potential risks identified in association with MIFEGYMISO® during the reporting period. As such, the benefit/risk profile of MIFEGYMISO® for approved indication continues to be favourable.

20. Appendices

Company Core Safety Information

Mifepristone Linepharma, 200 mg tablet

Laboratoire Linepharma International Limited
16 Upper Woburn Place, London WC1H OBS,
United Kingdom

Version: 07
Effective Date: 01 November 2021

	Name	Signature
Approval:	s22 [redacted] EUQPPV	s22 [redacted]
Author:	s22 [redacted] Drug Safety and Medical Information Officer	s22 [redacted]

INDICATION

In Europe:

Medical termination of a developing intra-uterine pregnancy in sequential combination with a prostaglandin analogue up to 63 days of amenorrhea.

In Australia:

Mifepristone Linepharma 200 mg tablet is indicated in females of childbearing age for:

Preparation for the action of registered prostaglandin analogues that are indicated for the termination of pregnancy for medical reasons beyond the first trimester.

In Mexico:

During the first trimester of pregnancy for:

- unavoidable abortion in case of fetal death in utero.
- when the mother has serious health problems with live embryo.
- obstetric management of nonviable pregnancies.

During the second trimester of pregnancy for:

- late abortion in case of fetal death.
- late abortion unavoidable.
- premature rupture of membranes.
- infection with corioamniotis.
- partial dilatation with exposure of membranes.

In Canada:

Mifegymiso (mifepristone tablet/misoprostol tablets) is indicated for medical termination of a developing intra-uterine pregnancy with a gestational age up to 63 days as measured from the first day of the Last Menstrual Period (LMP) in a presumed 28-day cycle.

In Colombia:

Medical termination of intrauterine pregnancy up to 63 days of amenorrhea, followed by misoprostol after 36 or 48 hours, for the following specific circumstances declared by the Constitutional Court:

- When continuing pregnancy constitutes a danger for the mother's life or health, certified by a physician,
- When a severe malformation of the fetus lead to unviable life, certified by a physician,

- When the pregnancy is the consequence of a behavior, duly denounced, such as a carnal relation or a non-consented sexual act, abusive, or an artificial insemination or a transfer of fertilized ovum, or an incest.

In Bolivia:

Medical termination of intrauterine pregnancy up to 63 days of amenorrhea, followed by misoprostol after 36 or 48 hours, for the following specific circumstances declared by the Constitutional Court:

- When continuing pregnancy constitutes a danger for the mother's life or health, certified by a physician,
- When a severe malformation of the fetus lead to unviable life, certified by a physician,
- When the pregnancy is the consequence of a behavior, duly denounced, such as a carnal relation or a non-consented sexual act, abusive, or an artificial insemination or a transfer of fertilized ovum, or an incest.

In Chile:

MifeAprofa is indicated, in a regimen with misoprostol, for the medical interruption of intrauterine pregnancy up to 70 days of gestation.

In Mongolia:

Mifepristone Linepharma 200 mg tablet is indicated in females of childbearing age for: Preparation for the action of registered prostaglandin analogues that are indicated for the termination of pregnancy for medical reasons beyond the first trimester.

POSOLOGY (DOSING) AND METHOD OF ADMINISTRATION

For termination of pregnancy, Mifepristone Linepharma 200 mg tablet and prostaglandins can only be prescribed and administered in accordance with countries national laws and regulations.

In Europe:

The method of administration is 200 mg of mifepristone in a single oral dose, followed 36 to 48 hours later by the administration of the prostaglandin analogue gemeprost 1 mg per vaginam.

The dose of 200 mg should not be exceeded.

In Australia:

The method of administration is as follows:

200 mg of mifepristone (1 tablet containing 200 mg) orally, followed 36 to 48 hours later by the scheduled prostaglandin analogue administration, which will be repeated as often as indicated.

In Mexico:

The method of administration is 200 mg of mifepristone in a single oral dose, followed 36 to 48 hours later by the administration of the prostaglandin analogue (800 mcg misoprostol, buccal route).

In Canada:

200 mg of mifepristone (1 tablet) should be taken orally, followed 24 to 48 hours (1 to 2 days) later by the administration of misoprostol.

In Colombia:

The method of administration is 200 mg of mifepristone in a single oral dose, followed 36 to 48 hours later by the administration of the prostaglandin analogue gemeprost 1 mg per vaginam.

The dose of 200 mg should not be exceeded.

In Bolivia:

The method of administration is 200 mg of mifepristone in a single oral dose followed by an administration of misoprostol 24 hours later.

In Chile:

- The dosage regimen for MifeAprofa and misoprostol is: MifeAprofa 200 mg orally + misoprostol 800 mcg buccally Day one: administration of 200 mg tablet of MifeAprofa is taken in a single oral dose.
- Day two or three: misoprostol administration (minimum interval of 24 hours between MifeAprofa and misoprostol). Four 200 mcg tablets (total dose 800 mcg) of misoprostol are taken by mouth.

Instruct the patient to place two 200 mcg misoprostol tablets in each cheek bag (the area between the cheek and gums) for 30 minutes and then swallow the remains with water or other liquid.

In Mongolia:

The method of administration is as follows:
200 mg of mifepristone (1 tablet containing 200 mg) orally, followed 36 to 48 hours later by the scheduled prostaglandin analogue administration, which will be repeated as often as indicated.

No studies have been conducted on the effect of food intake on the absorption of mifepristone. It is recommended that Mifepristone Linepharma should not be taken within 2 hours of a meal.

CONTRAINDICATIONS

This product should never be prescribed in the following situations:

- known hypersensitivity to the active substance or to any of the excipients;
- chronic adrenal failure;
- asthma uncontrolled by therapy;
- inherited porphyria;
- suspected ectopic pregnancy;
- contraindication to the prostaglandin analogue selected;
- intrauterine device (IUD) in place;
- concurrent long term systemic corticosteroid therapy
- haemorrhagic disorders or using concurrent anticoagulation therapy
- pregnancy not confirmed by an ultrasound or biological test;
- have an unconfirmed gestational age.

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS OF USE

A study has investigated the pharmacokinetics, the safety and the tolerability of Mifepristone 200 mg in women participants with moderate hepatic impairment versus healthy women participants with normal hepatic function. The results on the total plasma concentrations data concluded that no lack of efficacy or changes in the safety profile were likely. However, the possible consequences of moderate hepatic impairment on the unbound fraction could not be determined.

In the absence of specific studies, Mifepristone Linepharma is not recommended in patients with:

- Renal failure,
- Malnutrition
- Severe hepatic impairment

This method requires the involvement of the woman who should be informed of the requirements of the method:

- The necessity to combine treatment with prostaglandin to be administered at a second visit.

- The need for a follow up visit (3rd visit) within 14 to 21 days after intake of Mifepristone Linepharma in order to check for complete expulsion.
- The non-negligible risk of failure of the method which may require termination by another method.

In the case of a pregnancy occurring with an intra-uterine device in situ, this device must be removed before administration of Mifepristone Linepharma.

The expulsion may take place before prostaglandin administration (in about 3% of cases). This does not preclude the control visit in order to check for the complete expulsion and the uterine vacuity.

The risks related to the method must be taken into account and explained to the woman:

Failures:

The non-negligible risk of failure, which occurs in up to 7.6% of the cases, makes the control visit mandatory in order to check that the expulsion is completed.

In rare case of non-complete expulsion, a surgical revision may be necessary.

The efficacy of the method decreases with parity, and consequently increasing age of the woman.

Bleeding:

The patient must be informed of the occurrence of prolonged vaginal bleeding (an average of 10 to 16 days after Mifepristone Linepharma intake) which may be heavy. Bleeding occurs in almost all cases and is not in any way proof of complete expulsion.

The patient should be informed not to travel far away from the prescribing center as long as complete expulsion has not been recorded. She will receive precise instructions as to whom she should contact and where to go, in the event of any problems emerging, particularly in the case of very heavy vaginal bleeding.

A follow-up visit must take place within a period of 14 to 21 days after administration of mifepristone to verify by the appropriate means (clinical examination, ultrasound scan, and beta-hCG measurement) that expulsion has been completed and that vaginal bleeding has stopped. In case of persistent bleeding (even light) beyond the control visit, its disappearance should be checked within a few days.

If an ongoing pregnancy is suspected, a further ultrasound scan may be required to evaluate its viability.

Persistence of vaginal bleeding at this point could signify incomplete abortion, or an unnoticed extra-uterine pregnancy, and appropriate treatment should be considered.

In the event of an ongoing pregnancy diagnosed after the control visit, termination by another method will be proposed to the woman.

Since heavy bleeding requiring haemostatic curettage occurs in up to 5 % of the cases during the medical method of pregnancy termination, special care should be given to patients with haemostatic disorders with hypocoagulability, or with anaemia. The decision to use the medical or the surgical method should be decided with specialised consultants according to

the type of haemostatic disorder and the level of anaemia. Patients with severe anemia were excluded from clinical trials and administration of mifepristone in these patients is not recommended.

Infection:

Very rare cases of fatal toxic shock caused by Clostridium sordellii endometritis presenting without fever or other obvious symptoms of infection, have been reported after medical abortion with the use of 200mg mifepristone followed by non authorised vaginal administration of misoprostol tablets for oral use. Clinicians should be aware of this potentially fatal complication.

In all instances:

The use of Mifepristone Linepharma requires rhesus determination and hence the prevention of rhesus allo-immunisation as well as other general measures taken usually during any termination of pregnancy.

During clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses.

To avoid potential exposure of a subsequent pregnancy to mifepristone, it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after mifepristone administration.

In case of suspected acute adrenal failure, dexamethasone administration is recommended. 1 mg of dexamethasone antagonises a dose of 400 mg of mifepristone.

Due to the antiglucocorticoid activity of mifepristone, the efficacy of long-term corticosteroid therapy, including inhaled corticosteroids in asthmatic patients, may be decreased during the 3 to 4 days following intake of Mifepristone Linepharma. Therapy should be adjusted.

A decrease of the efficacy of the method can theoretically occur due to the antiprostaglandin properties of non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin (acetyl salicylic acid). Limited evidence suggests that co-administration of NSAIDs on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medical termination of pregnancy.

INTERACTIONS WITH OTHER MEDICAMENTS AND OTHER FORMS OF ADMINISTRATION

The pharmacokinetic study performed with the Cytochrome P450 3A4 (CYP3A4) inhibitor itraconazole reported a moderate drug-drug interaction with an increase in plasma concentrations of mifepristone and its metabolites.
The pharmacokinetic study performed with the Cytochrome P450 3A4 (CYP3A4) inducer rifampicin reported a strong drug-drug interaction leading to a significant reduction in plasma concentrations of mifepristone and its metabolites.

On the basis of these data, similar drug-drug interactions are possible with other CYP3A4 inhibitors (such as ketoconazole, erythromycin and grapefruit juice) or CYP3A4 inducers

(such as dexamethasone, St. John's Wort and certain anticonvulsants as phenytoin, phenobarbital, carbamazepine).

Due to the slow elimination of mifepristone from the body, and as observed in the two pharmacokinetic studies mentioned above, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP3A4 substrates and have narrow therapeutic range, including some agents used during general anaesthesia.

A decrease of the efficacy of the method can theoretically occur due to the antiprostaglandin properties of non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin (acetyl salicylic acid). Some evidence suggests that co-administration of NSAIDs on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medical termination of pregnancy.

USE IN PREGNANCY

In animals, the abortifacient effect of mifepristone precludes the proper assessment of any teratogenic effect of the molecule.

With sub abortive doses, isolated cases of malformations observed in rabbits, but not in rats or mice were too few to be considered significant, or attributable to mifepristone.

In humans, the few reported cases of malformations do not allow a causality assessment for mifepristone alone or associated to prostaglandin. Therefore, data is too limited to determine whether the molecule is a human teratogen.

Consequently:

- Patient should be informed that due to the risk of failure of the medical method of pregnancy termination and to the unknown risk to the fetus, the control visit is mandatory.
- Should a failure of the method be diagnosed at the control visit (viable ongoing pregnancy), and should the patient still agree, pregnancy termination should be completed by another method.
- Should the patient wish to continue with her pregnancy, the available data is too limited to justify a systematic termination of an exposed pregnancy. In that event, careful ultra-sonographic monitoring of the pregnancy should be carried out.

USE DURING LACTATION

Mifepristone is a lipophilic compound and may theoretically be excreted in the mother's breast milk. However, limited data is available. Consequently, Mifepristone Linepharma use should be avoided during breast-feeding.

FERTILITY

Mifepristone inhibited oestrus cycling in rats at doses below the clinical dose in a 3-week study. This was reversed over the following 2-3 weeks and no subsequent effects on reproductive performance were found.

No human data on the effect of active substance mifepristone on fertility are available.

PAEDIATRIC POPULATION

No data are available for women under 18 years.

EFFECTS ON ABILITY TO DRIVE VEHICLES AND OPERATE MACHINERY

No studies on the effect on the ability to drive and use machines have been performed.

UNDESIRABLE EFFECTS

The adverse events reported with mifepristone, classified according to frequency and system organ class, are summarized in the following table:

MedDRA	**Adverse events (frequency)**				
System Organ Class	**Very common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1000 to < 1/100**	**Rare ≥ 1/10000 to < 1/1000 and very rare (< 1/10000)***	**Not Known**
Infections and infestations			Infection	Toxic shock syndrome	
Neoplasms benign, malignant and unspecified				Elevated alpha-feto protein Elevated carcinoembryogenic antigen	
Blood and lymphatic system disorders				Thrombotic thrombocytopenic purpura Thrombocytopenia Induced systemic lupus erythematous	

MedDRA	Adverse events (frequency)				
System Organ Class	**Very common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1000 to < 1/100**	**Rare ≥ 1/10000 to < 1/1000 and very rare (< 1/10000)***	**Not Known**
Psychiatric disorders				Mania	
Nervous system disorders	Headache Dizziness			Epilepsy Neurogenic tinnitus	
Eye disorders				Ophtalmoplegia	
Cardiac disorders				Myocardial infarction Induced Adam-Stokes syndrome Arrhythmia	
Vascular disorders			Hot flush Hypotension (0.25%)	Superficial thrombophlebitis	
Respiratory, thoracic and mediastinal disorders				Bronchospasm Induced bronchial asthma	
Gastrointestinal disorders	Nausea Vomiting Diarrhea Gastric discomfort Abdominal pain	Cramping light or moderate		Gastric bleeding	
Hepatobiliary disorders				Abnormal liver function tests Hepatic failure Hepatorenal failure	
Skin and subcutaneous tissue disorders			Skin rash / pruritus	Urticarial reaction Toxic epidermal necrolysis Erythema nodosum Angioedema	Acute generealised exanthemaous pustulosis
Musculoskeletal and connective tissue disorders				Limb spasm	
Renal and urinary disorders				Renal failure	
Pregnancy, puerperium and perinatal conditions	Very common uterine contractions or cramping (10 to 45%) in the hours following prostaglandin intake.	Heavy bleeding occurs in about 5% of the cases and may require haemostatic curettage in up to 1.4% of the cases		Hydatiform mole Ectopic pregnancy Amniotic band syndrome Gestational trophoblastic tumor Uteroplacental apoplexy	

MedDRA	Adverse events (frequency)				
System Organ Class	**Very common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1000 to < 1/100**	**Rare ≥ 1/10000 to < 1/1000 and very rare (< 1/10000)***	**Not Known**
Reproductive system and breast disorders	Vaginal bleeding Uterine spasm	Prolonged post-abortion bleeding Spotting Severe hemorrhage Endometritis Breast tenderness Heavy bleeding	Hemorragic shock Salpingitis	Bilateral adnexal mass Intrauterine adhesion Ovarian cyst rupture Breast abscess Hematosalpynx Uterine rupture	
General disorders and administration site conditions	Fatigue Chill / fever	Fainting		Anaphylaxis Periorbital edema Malaise Vagal symptoms	

* Including occasional case reports

-Post-marketing experience for first trimester termination of pregnancy indicates that death can occur as a result of medical termination of pregnancy (although this is a very rare outcome, <1 in 100,000). The reported deaths were due to sepsis (fatal toxic shock syndrome) associated with Clostridium sordellii, which also occurs in association with childbirth and spontaneous termination. The symptoms of Clostridium sordellii infection are sometimes not the usual symptoms of sepsis. Therefore, the possibility of sepsis should be considered in all women who present with nausea, vomiting, or diarrhoea and weakness, with or without abdominal pain following mifepristone/prostaglandin use. These symptoms, even without a fever, may indicate Clostridium sordellii infection. Strong consideration should be given to obtaining a complete blood count in these patients. Significant leukocytosis with a marked left shift and haemo-concentration may be indicative of sepsis. Practitioners should consider immediately initiating treatment with antibiotics that includes coverage of anaerobic bacteria such as Clostridium sordellii. No causal relationship between mifepristone and prostaglandin use and an increased risk of infection or death has been established. Clostridium sordellii and other infections such as Streptococcus and other bacteria have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynaecologic and non-gynaecolgic conditions. Reviews have estimated overall serious infection rates after medical abortion at less than 1%.

-Bleeding is an almost constant part of the procedure, whatever the prostaglandin used, and at any pregnancy term although it is usually more abundant when pregnancy age increases. It can occur after mifepristone alone. When heavy, it often reflects incomplete abortion leading to a surgical procedure in approximately 5 percent of the cases. It can necessitate a blood transfusion in 0.5 to 1 percent of the cases.

OVERDOSE

No case of overdose has been reported.
In the event of massive ingestion signs of adrenal failure might occur. Signs of acute intoxication may require specialist treatment including the administration of dexamethasone.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Other Sex Hormone and Modulator of the Reproductive function/ Antiprogestogen. ATC code: GO3XB01

Mifepristone is a synthetic steroid with an antiprogestational action as a result of competition with progesterone at the progesterone receptors.

At doses ranging from 3 to 10 mg/kg orally, it inhibits the action of endogenous or exogenous progesterone in different animal species (rat, mouse, rabbit and monkey). This action is manifested in the form of pregnancy termination in rodents.

In patient at doses of greater than or equal to 1 mg/kg, mifepristone antagonises the endometrial and myometrial effects of progesterone. During pregnancy it sensitises the myometrium to the contraction inducing action of prostaglandins. During the first trimester, pre-treatment with mifepristone allows the dilatation and opening of the cervix uteri. While clinical data have demonstrated that mifepristone facilitates dilatation of the cervix, no data is available to indicate that this results in a lowering of the rate of early or late complications to the dilatation procedure.

In the event of an early termination of pregnancy, the combination of a prostaglandin analogue used in a sequential regimen after mifepristone leads to an increase in the success rate and accelerates the expulsion of the conceptus.

In clinical trials, according to the prostaglandin used and the time of application, the results vary slightly.

When 1 mg vaginal gemeprost following 200 mg mifepristone is used, the efficacy rate in pregnancies 57 to 63 DA is 92.4% (95% confidence interval: 89.6 – 94.7%)

Failures are due to either incomplete abortion or to persisting pregnancy: in practical terms, whatever their nature, failure necessitate a surgical procedure (vacuum aspiration or dilatation and curettage).

Mifepristone binds to the glucocorticoid receptor. In animals at doses of 10 to 25 mg/kg it inhibits the action of dexamethasone. In man the antiglucocorticoid action is manifested at a dose equal to or greater than 4.5 mg/kg by a compensatory elevation of ACTH and cortisol. Glucocorticoid bioactivity (GBA) may be depressed for several days following a single administration of 200 mg mifepristone for termination of pregnancy. The clinical implications of this are unclear, however vomiting and nausea may be increased in susceptible women.

Mifepristone also has some anti-androgenic activity. In toxicological studies in rats and monkeys up to a duration of 6 months, mifepristone produced effects related to its antihormonal (antiprogesterone, antiglucocorticoid and antiandrogenic) activity.

Pharmacokinetics

Absorption

After oral administration of a single dose of 200 mg, mifepristone is rapidly absorbed. The peak concentration of 2.3 to 2.7 mg/L is reached after 0.75 hours (mean of 49 subjects). The half-life of mifepristone is 36.5 to 38.3 hours.

Mifepristone shows non-linear pharmacokinetics. Following the distribution phase, the elimination is at first slow, with a half-life of approximately 12 to 72 hours, and then the concentration is more rapidly reduced with a half-life of 18 hours. With radio-receptor analysis, the final half-life is shown to be up to 90 hours, including all mifepristone metabolites that can bind to progesterone receptors.

After administration of low doses of mifepristone (20 mg orally or intravenously), the absolute bioavailability is 69%.

Distribution

In plasma, mifepristone is 99% bound to plasma proteins: albumin and principally alpha-1-acid glycoprotein (AAG), to which binding is saturable. Due to this specific binding, the volume of distribution and plasma clearance of mifepristone are inversely proportional to the plasma concentration of AAG.

Metabolism/elimination

N mono- and di-demethylation and terminal hydroxylation of the 17-propynyl chain are primary metabolic pathways of hepatic oxidative metabolism. Metabolites are detectable in plasma 1 hour after ingestion of mifepristone. Plasma AUC for the dominant metabolite, monodemethylated mifepristone, is approximately double that of the unchanged mifepristone at the clinical dose, and this metabolite retains significant affinity for the progesterone receptor. The other metabolites also display some progesterone receptor affinity (approximately 10 to 15% that of mifepristone). The metabolites may contribute to the pharmacological effects of mifepristone.

In vitro CYP3A4 appears as the isoenzyme primarily responsible for mifepristone demethylation and hydroxylation in human liver microsomes. CYP3A4 substrates progesterone and midazolam inhibited metabolite formation by up to 77%. Other isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1) had apparently no action on mifepristone metabolism.

After administration of 600 mg radiolabeled mifepristone, 10% of the total radioactivity was recovered in urine and 90% in faeces.

Clinical trials

In clinical trials the results vary slightly according to the prostaglandin analogue used and the time of application. Failures are due to either incomplete abortion or to persisting pregnancy: in practical terms, whatever their nature, failure necessitates a surgical procedure (vacuum aspiration or dilatation and curettage).

Preclinical safety data

In toxicological studies in rats and monkeys up to a duration of 6 months, mifepristone produced effects related to its antihormonal (antiprogesterone, antiglucocorticoid and antiandrogenic) activity.

In reproduction toxicology studies, mifepristone acts as a potent abortifacient. No teratogenic effect of mifepristone was observed in rats and mice surviving foetal exposure. In rabbits surviving foetal exposure, however, isolated cases of severe abnormalities occurred (cranial vault, brain and spinal cord). The number of foetal anomalies was not statistically significant and no dose-effect was observed. In monkeys, the number of foetuses surviving the abortifacient action of mifepristone was insufficient for a conclusive assessment.

Genotoxicity
Mifepristone has been evaluated in tests for mutagenicity in bacterial, yeast and mammalian cells; gene conversion in yeast; unscheduled DNA synthesis in HeLa cells; and for clastogenicity in vitro (Chinese hamster ovary cells) and in vivo (mouse bone marrow micronucleus test). No evidence of genotoxicity was observed.

Carcinogenicity
No long-term animal carcinogenicity studies have been conducted with mifepristone. Based on the negative genotoxicity results, findings in general repeat-dose toxicity studies and considering the pattern of clinical use, mifepristone is not predicted to pose a particular carcinogenic risk.

Company Core Safety Information

Gymiso (misoprostol)

**Laboratoire Linepharma International16 Upper Woburn Place, London WC1H OBS,
United Kingdom**

Version: 07
Effective Date: 01 November 2021

	Name	Signature
Approval:	s22 [redacted] EUQPPV	s22 [redacted]
Author:	s22 [redacted] Drug Safety and Medical Information Officer	s22 [redacted]

INDICATION

In France:

- Medical termination of early pregnancy of less than 49 days of amenorrhea, in combination with mifepristone.
- Preparation of the cervix for surgical termination of pregnancy in the first trimester.

In Australia:

MS-2 Step (mifepristone tablet/misoprostol tablets) is indicated in females of childbearing age for the medical termination of a developing intrauterine pregnancy, up to 63 days of gestation. It is recommended that the duration of pregnancy (i.e., up to 63 days gestation) be confirmed by ultrasound. In the event that an ultrasound is not possible, extra caution should be exercised.

In Canada:

Mifegymiso (mifepristone tablet/misoprostol tablets) is indicated for medical termination of a developing intra-uterine pregnancy with a gestational age up to 63 days as measured from the first day of the Last Menstrual Period (LMP) in a presumed 28-day cycle.

In Chile:

MisoAprofa ® is indicated in women of childbearing age for the medical termination of a developing intrauterine pregnancy in sequential combination with a 200 mg tablet of mifepristone, up to 49 days gestation.

In Mongolia:

GyMiso® is indicated in females of childbearing age for the medical termination of a developing intrauterine pregnancy in sequential combination with a mifepristone 200 mg tablet, up to 49 days of gestation.

POSOLOGY (DOSING) AND METHOD OF ADMINISTRATION

In France:

GyMiso Tablet 200µg is dedicated to oral route only and should not be administered through any other route.

Medical termination of early pregnancy of less than 49 days of amenorrhea, in combination with mifepristone.
Gymiso must be administered 36 to 48 hours after the oral intake of mifepristone.
Gymiso dosage is of 400 micrograms, i.e. 2 tablets in a single intake, orally.
Preparation of the cervix for surgical termination of pregnancy in the first trimester.
Gymiso should be administered 3 to 4 hours before surgical termination.
Gymiso dosage is of 400 micrograms, i.e. 2 tablets in a single intake, orally.

In Australia:

800 micrograms of misoprostol (4 tablets, each tablet containing 200 micrograms) buccally, i.e: kept between the cheek and the gum for 30 minutes before any fragments being swallowed with water.

In Canada:

800 mcg of misoprostol (4 tablets, each tablet containing 200 mcg) should be taken in a single intake by buccal route (kept between the cheek and the gum for 30 minutes before any remaining fragments are swallowed with water).

In Chile:

MisoAprofa ® should be administered between 36 and 48 hours after oral intake of mifepristone.
The dose of MisoAprofa ® is 800 micrograms, i.e. 4 tablets in a single intake, orally or, if preferred, two doses of 400 micrograms, i.e. two tablets administered orally followed two hours later by two other tablets. MisoAprofa® tablets can be taken by mouth, that is, they are kept between the cheek and gum for 30 minutes before any fragment is ingested with water. A repeated dose of misoprostol may be offered after 1-7 days if the abortion has not occurred.

In Mongolia:

GyMiso® must be administered 36 to 48 hours after the oral intake of mifepristone.
GyMiso® dosage is 800 micrograms, i.e. 4 tablets in a single intake, orally, or if preferred taken as two doses of 400 micrograms, i.e. two tablets taken orally followed two hours later by another two tablets. GyMiso® tablets may be taken buccally i.e: kept between the cheek and the gum for 30 minutes before any fragments being swallowed with water.
A repeat dose of misoprostol may be offered after 1-7 days if abortion has not occurred.

There are no data available on the effect of food intake on the absorption of misoprostol. Misoprostol should be taken 2 hours before or 2 hours after a meal.

No dosage adjustment of misoprostol is necessary with renal or hepatic insufficiency when administered at the recommended doses.

CONTRAINDICATIONS

This product should never be prescribed in the following situations:

- Known hypersensitivity to misoprostol (or any prostaglandin) or to any of the excipients
- Suspected ectopic pregnancy
- Pregnancy not confirmed biologically or by ultrasonography
- Intrauterine device (IUD) in place
- Have an unconfirmed gestational age
- Contraindication to the use of mifepristone (not applicable in France for one indication).

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS OF USE

Medical termination of early pregnancy of less than 49 days (France, Chile and Mongolia) or 63 days (Australia and Canada) of amenorrhea, in combination with mifepristone.

Misoprostol should not be administered if an intrauterine contraceptive device is present: it should be removed first.

Because of its abortive properties, Gymiso should not be used by a woman with a viable pregnancy and who intends to carry that pregnancy to term.

This method requires the involvement of the woman who should be informed of the necessity to take both mifepristone and GyMiso® in sequence according to instructions and the need for follow up visit. On discharge from the treatment centre all women should be provided with appropriate medications as necessary and be fully counselled regarding the likely signs and symptoms she may experience (e.g. heavy vaginal bleeding) and have direct access to the treatment centre by telephone or local access

The expulsion may take place before GyMiso® administration (in about 3% of cases). This does not preclude the need for follow-up to confirm complete expulsion.

The use of Gymiso requires rhesus determination and hence the prevention of rhesus allo-immunisation.

The following risks related to the medical method must be taken into account and explained to the woman:

<u>Failures:</u>

The non-negligible risk of failure, which occurs in up to 7% of cases prior to 63 days gestation, and in up to 1 % of cases after oral administration prior to 49 days of amenorrhea, makes follow up mandatory (within 14 to 21 days after intake of mifepristone) in order to check that the expulsion is completed. Up to 63 days about 1% women will have continuing pregnancies, the rest needing curettage for other reasons.
Exposure of the fetus to misoprostol or mifepristone increases the risk of developing Moebius syndrome and/or an amniotic band syndrome and/or central nervous system anomalies (see section 4.6). A second termination of pregnancy procedure shall be considered. In case of continuation of the pregnancy close monitoring by ultrasound scan must be performed in specialized centres.

<u>Bleeding:</u>

The patient must be informed of the occurrence of prolonged vaginal bleeding (an average of 10 to 16 days after mifepristone) which may be heavy. Bleeding occurs in almost all cases and is not in any way proof of complete expulsion. Persistent bleeding can be the consequence of incomplete expulsion. Bleeding can be large enough to necessitate a blood transfusion, in up to 0.2 % of cases up to 63 days gestation and to lead to a significant decrease in haemoglobin levels.

Since heavy bleeding requiring haemostatic curettage occurs in up to 5 % of cases during the medical method of pregnancy termination, special care should be given to patients with haemostatic disorders with hypocoagulability, or with anaemia. The decision to use the medical or the surgical method should be decided with specialised consultants according to the type of haemostatic disorder and the level of anaemia.

Follow-up must take place within a period of 14 to 21 days after administration of mifepristone to verify by the appropriate means (clinical examination, ultrasound scan, or beta-hCG measurement) that expulsion has been completed and that vaginal bleeding has stopped. In case of persistent bleeding (even light) beyond this follow-up, the disappearance of bleeding should be checked within a few days.

Persistence of vaginal bleeding at this point could signify incomplete abortion, or an unnoticed extra-uterine pregnancy, and appropriate treatment should be considered. In the event of an ongoing pregnancy diagnosed after follow-up, a further ultrasound scan may be required to evaluate its viability. A termination by another method will be offered to the woman.

Cardiovascular risk:

Serious cardiovascular accidents potentially fatal (myocardial infarction and/or spasm of the coronary arteries and / or cerebrovascular accident) have been reported following administration of prostaglandins, including misoprostol, in particular at high doses. Risk factors for cardiovascular disease (in particular chronic and / or recent smoking,…) should be taken in consideration.

Infection :

Serious cases (including fatal cases) of toxic choc syndrome and septic choc following infection by atypical bacteria (Clostridium sordellii and perfringens, Klebsiella pneumoniae, group A Streptococcus) have been reported with the medical abortion, performed with unauthorised vaginal administration of misoprostol tablets dedicated to oral use and can be potentially life threatening. If you have symptoms occurring more than 24 hours after taking misoprostol of ongoing abdominal pain, or feeling unwell, or feeling weak, with or without a fever you should contact your doctor without delay.

Patients should be advised of their immediate return to fertility after mifepristone and misoprostol administration. To avoid the potential exposure of a subsequent pregnancy to mifepristone and misoprostol, it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive methods should therefore commence as early as possible.

Patients with suspected acute adrenal failure were excluded from trials and therefore should be treated with caution. If treatment with mifepristone and misoprostol is required, therapy should be adjusted. The safety and efficacy have not been studied in women suffering from malnutrition.

The safety and efficacy have not been studied in women suffering from hepatic failure.
The safety and efficacy have not been studied in women suffering from renal failure.

Cases of skin rash following misoprostol administration were reported by patients in clinical trials. Angioedema of the face, lips, tongue, and/or larynx, including cases of anaphylaxis have been reported in post-market surveillance with the use of mifepristone and misoprostol, including angioedema occurring within an hour of misoprostol intake. Angioedema associated with upper airway swelling may be life threatening. If the tongue, hypopharynx, or larynx has been involved, appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided**.**

Although no epileptic seizures have been reported with misoprostol, some have been reported with prostaglandins and other prostaglandin analogues, and therefore this possibility should be borne in mind in patients with a history of epilepsy.

Bronchospasm may occur with some prostaglandins and prostaglandin analogues. The possibility should be borne in mind in patients with a history of asthma.

Preparation of the cervix for surgical termination of pregnancy in the first trimester.

In France:

Woman should be informed of the possibility of heavy vaginal bleeding following the intake of Gymiso.

Woman should also be informed of the possibility that the abortion will begin prior to surgery, although this risk is slight.

Given the possible risk of uterine rupture (although very rare during the first trimester of pregnancy), GyMiso should be used with caution in case of uterine fragility, especially in case of large multiparity or scar uterus.

As soon as misoprostol has been administered, the surgical procedure must be completed.

INTERACTIONS WITH OTHER MEDICAMENTS AND OTHER FORMS OF ADMINISTRATION

No drug interactions have been attributed to misoprostol in extensive clinical trials.

As a prostaglandin, Gymiso efficacy could be reduced when used in combination with non-steroidal anti-inflammatory drugs: it is then preferable if necessary to prescribe paracetamol-type analgesics.

The serum protein binding of misoprostol acid was not affected by indomethacin, ranitidine, digoxin, phenylbutazone, warfarin, diazepam, methyldopa, propranolol, triamterene, cimetidine, paracetamol, ibuprofen, chlorpropamide and hydrochlorothiazide. With salicylic acid (300 microgram/mL), the protein binding of misoprostol was lowered from 84 to 52% which is not considered clinically significant since the binding of misoprostol acid is not extensive and its elimination half-life is very short.

In laboratory studies, misoprostol has no significant effect on the cytochrome P450 linked hepatic mixed function oxidase system, and therefore should not affect the metabolism

oftheophylline, warfarin, benzodiazepines or other drugs normally metabolized by this system.
No drug interactions have been attributed to misoprostol in extensive clinical trials. As such, other drugs would be unlikely to interfere with misoprostol's metabolism in either normal or hepatically-impaired patients.

USE IN PREGNANCY

Failure of pregnancy termination (continuing pregnancy) Use in pregnancy has been associated with a 3-fold increased risk of birth defects/malformations for ongoing pregnancies exposed to mifepristone and misoprostol or misoprostol alone, compared to control group (about 2%). In particular, prenatal exposure to misoprostol has been associated with Moebius syndrome (congenital facial paralysis leading to hypomimia, troubles of sucking and deglutition and eye movements, with or without limb defects) and with amniotic band syndrome (limb deformities/ amputations, especially clubfoot, acheiria, olygodactyly, cleft palate inter alia), and central nervous system anomalies (cerebral and cranial anomalies such as anencephaly, hydrocephaly, cerebellar hypoplasia, neural tube defects).

Women considering medical termination of pregnancy should be precisely counselled on the risks to their foetus if an abortion failure occurs and a second termination of pregnancy procedure is not desirable.

As a consequence:

- Women should be informed that because of the risk of failure to terminate pregnancy and the risk to the fetus, a follow-up visit is mandatory
- If a failure of the method is diagnosed at the control visit (ongoing pregnancy) and if the patient still agrees, a second procedure of termination of pregnancy will be performed.
- Should the patient wish to continue with her pregnancy, a careful ultrasound scan monitoring of the pregnancy, with a special attention to the limbs and head, must be established in a specialised centre.

USE DURING LACTATION

In absence of data on misoprostol concentration in the milk of breastfeeding mothers, this medicinal product should not be used in breastfeeding mothers.

Misoprostol is rapidly metabolized in the mother to misoprostol acid, which is biologically active and is excreted in breast milk. GyMiso® should not be administered to breastfeeding mothers because the excretion of misoprostol acid could cause undesirable effects such as diarrhoea in breast feeding infants.

FERTILITY

During clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses. To avoid the potential exposure of a subsequent pregnancy to GyMiso®, it is recommended that conception be avoided during the next menstrual cycle. Reliable

contraceptive precautions should therefore commence as early as possible after administration of GyMiso®.
In fertility studies in rats in which treated females were mated with treated males, increased pre-implantation losses were observed with misoprostol at oral doses greater than 1 mg/kg/day (11 times the recommended human dose, on a mg/m2 basis). Post-implantation loss was also increased at 10 mg/kg/day (114 times the recommended human dose, on a mg/m2 basis).

PAEDIATRIC POPULATION

Limited data are available for use of misoprostol in women under 18 years of age. There is no relevant use of misoprostol in the prepubertal paediatric population in the indication.

EFFECTS ON ABILITY TO DRIVE VEHICLES AND OPERATE MACHINERY

No studies on the effect on the ability to drive and use machines have been performed.

UNDESIRABLE EFFECTS

The adverse events reported with misoprostol, classified according to frequency and system organ class, are summarized in the following table:

MedDRA	**Adverse events (frequency)**			
System Organ Class	**Very common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1000 to < 1/100**	**Rare ≥ 1/10000 to < 1/1000 and very rare (< 1/10000)***
Infections and infestations			Infection	Toxic shock syndrome
Neoplasms benign, malignant and unspecified				Elevatedalpha-feto protein Elevated carcinoembryogenic antigen
Blood and lymphatic system disorders				Thrombotic thrombocytopenic purpura Thrombocytopenia Induced systemic lupus erythematous
Psychiatric disorders				Mania
Nervous system disorders	Headache Dizziness			Epilepsy Neurogenic tinnitus
Eye disorders				Ophtalmoplegia

MedDRA	Adverse events (frequency)			
System Organ Class	**Very common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1000 to < 1/100**	**Rare ≥ 1/10000 to < 1/1000 and very rare (< 1/10000)***
Cardiac disorders				Myocardial infarction Induced Adam-Stokes syndrome Arrhythmia
Vascular disorders			Hot flush	Superficial thrombophlebitis Hypotension
Respiratory, thoracic and mediastinal disorders				Bronchospasm Induced bronchial asthma
Gastrointestinal disorders	Nausea Vomiting Diarrhea Gastric discomfort Abdominal pain			Gastric bleeding
Hepatobiliary disorders				Abnormal liver function tests Hepatic failure Hepatorenal failure
Skin and subcutaneous tissue disorders			Skin rash Pruritus	Urticarial reaction Toxic epidermal reacion
Musculoskeletal and connective tissue disorders				Limb spasm
Renal and urinary disorders				Renal failure
Pregnancy, puerperium and perinatal conditions		foetal malformations		Hydatiform mole Ectopic pregnancy Amniotic band syndrome Gestational trophoblastic tumor Uteroplacental apoplexy
Reproductive system and breast disorders	Vaginal bleeding Uterine spasm	Prolonged post-abortion bleeding Spotting Severe hemorrhage Endometritis Breast tenderness Heavy bleeding	Hemorragic shock Salpingitis	Bilateral adnexal mass Intrauterine adhesion Ovarian cyst rupture Breast abscess Hematosalpynx Uterine rupture
General disorders and administration site conditions	Fatigue Chill / fever	Fainting		Anaphylaxis Periorbital edema

OVERDOSE

The toxic dose of misoprostol in humans has not been determined. Cumulative total daily doses of 1600 micrograms have been tolerated, with only symptoms of gastrointestinal discomfort reported.
Clinical signs that may indicate an overdose are sedation, tremor, convulsions, dyspnoea, abdominal pain, diarrhea, fever, palpitations, hypotension or bradycardia. Hypertension and tachycardia have also been reported following overdoses. Overdose in pregnancy has resulted in uterine contractions with fetal death.
There is no specific antidote. Treatment should be symptomatic and supportive. Consider administration of activated charcoal in the event of a potentially toxic ingestion. Activated charcoal may reduce absorption of misoprostol if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Other gynecological medicines - prostaglandins ATC code: G02AD Misoprostol is a synthetic analogue of prostaglandin E1.
At the recommended dosages, misoprostol induces contractions of the smooth muscle fibers in the myometrium and relaxation of the uterine cervix. The uterotonic properties of misoprostol should facilitate cervical opening and evacuation of intrauterine debris.

Pharmacodynamic studies in early pregnancy have found an increase in uterine tone around 8 minutes after oral and 40 minutes after buccal misoprostol, with sustained contractions achieved by a mean of around 90 minutes and uterine activity peaking prior to 5 hours. Following oral administration uterine activity rises earlier than other routes but is lower overall. Pretreatment with mifepristone has previously been shown to increase uterine contractility in response to misoprostol

Pharmacokinetics

Absorption

When administered orally, misoprostol is rapidly absorbed and metabolized.

Peak concentrations around 1.1 ng/mL were reached about 15 minutes after a 400-microgram dose in the fasting state. Plasma concentrations of its main degradation metabolite, misoprostol acid, reach their peak of 2 - 2.5 ng/mL after a 2 microgram/kg oral dose within approximately 30 minutes and rapidly decline thereafter. As a result, uterine contractility increases and then plateaus after about one hour. Absorption is almost complete, measured at levels between 64 - 73% from urinary data. While not compared directly with oral administration, buccal administration has been found to result in peak concentrations

comparable to those following vaginal administration, which have been found in turn to be lower and later than those for oral administration.

Distribution

Serum protein binding of labeled misoprostol acid was studied in man and was similar in young (81-88%) and elderly (81-89%) subjects. Accumulation in erythrocytes was not seen.

Metabolism/elimination

Metabolism of misoprostol to misoprostol acid is rapid with no intact misoprostol found in plasma consistent with an in vitro half-life of 6.4 minutes for de-esterification of misoprostol in human plasma at 37ºC. Elimination of misoprostol and its metabolites is also rapid with a plasma elimination half-life of 35 minutes.
The liver is the primary site of metabolism and between 1-4% of misoprostol acid is excreted in the urine.
Misoprostol has no known drug interactions. No induction of the hepatic cytochrome P-450 enzyme system has been observed.

Clinical trials

Clinical efficacy of early medical abortion is defined as complete abortion without surgical intervention, regardless of the reason for the intervention, which may include continuing pregnancy, missed or incomplete abortion, prolonged or heavy vaginal bleeding or a woman's request.
A study of 966 patients with pregnancies up to 63 DA, randomized to 200 mg mifepristone followed 24-36 hours later by 800 micrograms of misoprostol orally or buccally, reported efficacy rates of 91.3% for the oral and 96.2% for the buccal group (RR 0.95, 95%CI 0.92-0.98, p=0.003). When patients at 43-49 days gestation were considered, efficacy rates were not significantly different according to route of administration, 94.7% for the oral and 96.4% for the buccal group. This study allowed a repeat dose of misoprostol if abortion had not occurred by 7 to 14 days.
Clinical trials have reported efficacy rates varying from 89-98% with oral misoprostol in doses of 400 to 800 micrograms 24-48 hours after mifepristone. Varying results are likely due in part to varying follow up and intervention practices. Some studies reported higher efficacies when a repeat dose of misoprostol was offered at a varying time interval (1-14 days) after the first dose.
For patients up to 49 days gestation clinical trials have consistently reported efficacy rates of at least 93% using 800 micrograms misoprostol orally in single or divided doses or 800 micrograms buccally 24-48 hours after 200 mg mifepristone, when a follow up dose could be used.
Most studies that have reported mifepristone and oral misoprostol regimens in women after 49 days gestation have found significantly lower efficacy rates at later gestations, often less than 90%; for this reason, oral misoprostol should not be used in medical abortion regimens after 49 days gestation. Such a decline has not been observed using buccal misoprostol to 63 days.

Preclinical safety data

Genotoxicity
Misoprostol has been evaluated in tests for mutagenicity in bacterial, yeast and mammalian cells; and for clastogenicity *in vitro* (Chinese hamster ovary cells) and *in vivo* (mouse bone marrow micronucleus test). No evidence of genotoxicity was observed.

Carcinogenicity
The potential carcinogenicity of misoprostol has been evaluated in both mice and rats. There was no evidence of an effect of misoprostol on tumor occurrence or incidence in rats, receiving oral doses up to 2.4 mg/kg/day for 24 months. Similarly, there was no effect of misoprostol on tumour occurrence or incidence in mice receiving oral doses up to 16 mg/kg/day for 21 months. These doses are at least 27 times the recommended human dose, on a mg/m2 body surface area basis.

Soc Meddra / Pt	Study Drug		Blinded		Active Comparator		Placebo	
Infections and infestations (3)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	3	0	0	0	0	0	0
Bacterial infection	0	1	0	0	0	0	0	0
Cytomegalovirus infection	0	1	0	0	0	0	0	0
Endometritis	0	1	0	0	0	0	0	0
Blood and lymphatic system disorders (1)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	1	0	0	0	0	0	0
Blood loss anaemia	0	1	0	0	0	0	0	0
Pregnancy, puerperium and perinatal conditions (1)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	1	0	0	0	0	0	0
Uterine hypotonus	0	1	0	0	0	0	0	0
Reproductive system and breast disorders (1)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	1	0	0	0	0	0	0
Intermenstrual bleeding	0	1	0	0	0	0	0	0
Injury, poisoning and procedural complications (1)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	2	0	0	0	0	0	0
Abortion induced incomplete	0	2	0	0	0	0	0	0
Surgical and medical procedures (1)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	2	0	0	0	0	0	0
Uterine dilation and curettage	0	2	0	0	0	0	0	0
Total	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	10	0	0	0	0	0	0

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Soc Meddra / Pt	Study Drug		Blinded		Active Comparator		Placebo	
Infections and infestations (3)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	3	0	0	0	0	0	0
Bacterial infection	0	1	0	0	0	0	0	0
Cytomegalovirus infection	0	1	0	0	0	0	0	0
Endometritis	0	1	0	0	0	0	0	0
Blood and lymphatic system disorders (1)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	1	0	0	0	0	0	0
Blood loss anaemia	0	1	0	0	0	0	0	0
Pregnancy, puerperium and perinatal conditions (1)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	1	0	0	0	0	0	0
Uterine hypotonus	0	1	0	0	0	0	0	0
Reproductive system and breast disorders (1)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	1	0	0	0	0	0	0
Intermenstrual bleeding	0	1	0	0	0	0	0	0
Injury, poisoning and procedural complications (1)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	2	0	0	0	0	0	0
Abortion induced incomplete	0	2	0	0	0	0	0	0
Surgical and medical procedures (1)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	2	0	0	0	0	0	0
Uterine dilation and curettage	0	2	0	0	0	0	0	0
Total	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	10	0	0	0	0	0	0

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Soc Meddra / Pt	Spontaneous Serious Unlisted		Spontaneous Serious Listed		Spontaneous Non Serious Unlisted		Spontaneous Non Serious Listed		Solicited Serious Unlisted		Solicited Serious Listed		Solicited Non Serious Unlisted		Solicited Non Serious Listed		Total	
Infections and infestations (25)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	2	5	31	0	13	2	65	2	2	0	8	0	6	0	14	9	141
Abortion infected	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Amniotic cavity infection	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	1	1
Bacterial infection	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Bacterial vaginosis	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	2
Bronchitis	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Candida infection	0	0	0	0	0	0	0	6	0	0	0	0	0	0	0	0	0	6
Chlamydial infection	0	1	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	3
Cystitis	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Endometritis	0	0	5	11	0	0	0	1	0	0	0	3	0	0	0	2	5	17
Genital herpes	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Infection	0	0	0	9	0	0	2	40	0	0	0	4	0	0	0	9	2	62
Influenza	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	3
Laryngitis	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Lower respiratory tract infection	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Nasopharyngitis	0	0	0	0	0	5	0	0	0	0	0	0	0	3	0	0	0	8
Ovarian abscess	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Pelvic inflammatory disease	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
Sepsis	0	0	0	6	0	0	0	0	0	0	0	0	0	0	0	0	0	6
Septic shock	0	0	0	1	0	0	0	0	1	1	0	1	0	0	0	0	1	3
Tonsillitis	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Toxic shock syndrome	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	2
Urinary tract infection	0	0	0	2	0	0	0	9	0	0	0	0	0	0	0	1	0	12
Uterine infection	0	0	0	0	0	0	0	4	0	0	0	0	0	0	0	0	0	4
Vaginal infection	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Viral infection	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Blood and lymphatic system disorders (3)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	0	0	1	0	0	0	5	0	0	0	1	0	1	0	1	0	9
Anaemia	0	0	0	1	0	0	0	5	0	0	0	0	0	0	0	1	0	7
Blood loss anaemia	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1
Lymphadenopathy	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Immune system disorders (2)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	0	0	8	0	0	0	2	0	0	0	0	0	0	0	1	0	11
Drug hypersensitivity	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Hypersensitivity	0	0	0	7	0	0	0	2	0	0	0	0	0	0	0	1	0	10
Metabolism and nutrition disorders (7)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	3	0	0	1	20	0	0	0	0	0	0	0	0	0	0	1	23
Decreased appetite	0	0	0	0	0	11	0	0	0	0	0	0	0	0	0	0	0	11
Dehydration	0	2	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	5
Food craving	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Hypophagia	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Hypovolaemia	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Iron deficiency	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	2
Polydipsia	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1
Psychiatric disorders (16)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	8	0	0	0	12	0	15	0	0	0	0	0	1	0	0	0	36
Anxiety	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Autoscopy	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Confusional state	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Depressed mood	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Depression	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	3
Depression suicidal	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Hallucination	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Insomnia	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Irritability	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Libido increased	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Mood altered	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Nervousness	0	0	0	0	0	0	0	15	0	0	0	0	0	0	0	0	0	15
Nightmare	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Panic reaction	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Paranoia	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1

Suicidal ideation	0	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4
Nervous system disorders (23)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	1	15	1	11	12	124	2	138	0	0	0	2	0	20	0	14	16	324
Burning sensation	0	0	0	0	1	3	0	0	0	0	0	0	0	0	0	0	1	3
Consciousness fluctuating	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Disturbance in attention	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Dysarthria	0	0	0	0	3	3	0	0	0	0	0	0	0	0	0	0	3	3
Dysgeusia	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Dysstasia	0	0	0	0	1	2	0	0	0	0	0	0	0	0	0	0	1	2
Dystonia	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Headache	0	0	1	1	0	0	2	95	0	0	0	1	0	0	0	11	3	108
Hypoaesthesia	0	2	0	0	0	18	0	0	0	0	0	0	0	0	0	0	0	20
Lethargy	0	0	0	0	0	54	0	0	0	0	0	0	0	7	0	0	0	61
Loss of consciousness	0	5	0	10	0	0	0	3	0	0	0	0	0	2	0	3	0	23
Migraine	0	0	0	0	0	7	0	0	0	0	0	0	0	2	0	0	0	9
Paraesthesia	0	2	0	0	1	19	0	0	0	0	0	0	0	3	0	0	1	24
Parosmia	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Seizure	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
Sensory disturbance	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Sensory loss	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	2
Slow speech	0	0	0	0	2	2	0	0	0	0	0	0	0	0	0	0	2	2
Somnolence	0	0	0	0	3	9	0	0	0	0	0	0	0	4	0	0	3	13
Speech disorder	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Tonic convulsion	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Tremor	0	0	0	0	1	2	0	40	0	0	0	1	0	0	0	0	1	43
Unresponsive to stimuli	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Eye disorders (8)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	0	0	4	1	18	0	6	0	0	0	0	0	4	0	1	1	33
Blindness unilateral	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Eye pain	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Eye pruritus	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Eye swelling	0	0	0	1	0	0	0	5	0	0	0	0	0	0	0	1	0	7
Ocular hyperaemia	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Swelling of eyelid	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	3
Vision blurred	0	0	0	0	1	7	0	0	0	0	0	0	0	1	0	0	1	8
Visual impairment	0	0	0	0	0	9	0	0	0	0	0	0	0	2	0	0	0	11
Ear and labyrinth disorders (6)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	1	0	0	1	7	0	1	0	0	0	0	0	0	0	0	1	9
Deafness	0	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	2
Ear pain	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	3
Ear pruritus	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Hyperacusis	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Hypoacusis	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Tinnitus	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Cardiac disorders (3)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	2	0	0	0	45	0	0	0	0	0	0	0	5	0	0	0	52
Cardiomyopathy	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Palpitations	0	0	0	0	0	43	0	0	0	0	0	0	0	4	0	0	0	47
Tachycardia	0	1	0	0	0	2	0	0	0	0	0	0	0	1	0	0	0	4
Vascular disorders (14)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	1	2	10	76	1	4	110	2119	0	0	0	44	0	0	1	507	123	2752
Dizziness	0	0	0	4	0	0	18	522	0	0	0	2	0	0	0	66	18	594
Dizziness exertional	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Dizziness postural	0	0	0	0	0	0	0	23	0	0	0	0	0	0	0	2	0	25
Flushing	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	1	0	3
Haematoma	0	0	0	0	1	2	0	0	0	0	0	0	0	0	0	0	1	2
Haemorrhage	0	0	2	19	0	0	45	453	0	0	0	13	0	0	1	270	48	755
Hot flush	0	0	0	0	0	0	0	22	0	0	0	0	0	0	0	2	0	24
Hypertension	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Hypotension	0	0	0	3	0	0	1	7	0	0	0	0	0	0	0	0	1	10
Neurogenic shock	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2
Peripheral coldness	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Presyncope	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	3
Syncope	0	0	6	20	0	0	1	34	0	0	0	2	0	0	0	6	7	62
Thrombosis	0	0	2	30	0	0	45	1052	0	0	0	27	0	0	0	160	47	1269
Respiratory, thoracic and mediastinal	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	8	0	6	9	179	0	3	0	0	0	0	0	12	0	1	9	209
Asthma	0	0	0	2	0	0	0	1	0	0	0	0	0	0	0	0	0	3
Cough	0	0	0	0	1	12	0	0	0	0	0	0	0	0	0	0	1	12

Dry throat	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	2
Dysphonia	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	2
Dyspnoea	0	4	0	0	6	126	0	0	0	0	0	0	0	3	0	0	6	133
Hyperventilation	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Nasal congestion	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Oropharyngeal discomfort	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Oropharyngeal pain	0	0	0	0	2	17	0	0	0	0	0	0	0	6	0	0	2	23
Painful respiration	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Paranasal sinus hypersecretion	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Pharyngeal swelling	0	0	0	4	0	0	0	2	0	0	0	0	0	0	0	1	0	7
Productive cough	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Respiration abnormal	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	3
Rhinorrhoea	0	0	0	0	0	5	0	0	0	0	0	0	0	0	0	0	0	5
Sneezing	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Tachypnoea	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Throat irritation	0	1	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	3
Throat tightness	0	1	0	0	0	1	0	0	0	0	0	0	0	2	0	0	0	4
Gastrointestinal disorders (43)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	1	9	3	45	3	130	94	1283	0	0	0	18	0	18	0	192	101	1695
Abdominal discomfort	0	0	0	0	0	0	0	8	0	0	0	0	0	0	0	5	0	13
Abdominal distension	0	0	0	0	0	55	0	0	0	0	0	0	0	13	0	0	0	68
Abdominal pain	0	0	1	12	0	0	14	249	0	0	0	2	0	0	0	50	15	313
Abdominal pain lower	0	0	0	2	0	0	3	97	0	0	0	1	0	0	0	15	3	115
Abdominal pain upper	0	0	0	0	0	0	4	34	0	0	0	0	0	0	0	2	4	36
Abdominal tenderness	0	0	0	0	0	0	0	12	0	0	0	0	0	0	0	3	0	15
Anal haemorrhage	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Anorectal discomfort	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Constipation	0	0	0	0	0	21	0	0	0	0	0	0	0	0	0	0	0	21
Diarrhoea	0	0	0	3	0	0	1	104	0	0	0	1	0	0	0	13	1	121
Diarrhoea haemorrhagic	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Dry mouth	0	0	0	0	0	14	0	0	0	0	0	0	0	1	0	0	0	15
Dyspepsia	0	0	0	0	0	0	1	6	0	0	0	0	0	0	0	0	1	6
Dysphagia	0	0	0	0	1	7	0	0	0	0	0	0	0	0	0	0	1	7
Eructation	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Gastric dilatation	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Gastritis	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Gastrointestinal motility disorder	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Gastrointestinal pain	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Gingival blister	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Gingival pain	0	0	0	0	1	2	0	0	0	0	0	0	0	1	0	0	1	3
Gingival swelling	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Glossodynia	0	0	0	0	0	1	0	0	0	0	0	0	0	2	0	0	0	3
Haematemesis	1	8	0	0	0	7	0	0	0	0	0	0	0	0	0	0	1	15
Haemoperitoneum	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Haemorrhoids	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	2
Intestinal obstruction	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Lip pruritus	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Lip swelling	0	0	0	2	0	0	0	2	0	0	0	0	0	0	0	0	0	4
Mouth swelling	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	2
Nausea	0	0	1	6	0	0	29	354	0	0	0	7	0	0	0	45	30	412
Odynophagia	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Oral mucosal erythema	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Oral pain	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	3
Proctalgia	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Rectal discharge	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Retching	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	2
Salivary hypersecretion	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1
Swollen tongue	0	0	0	4	0	0	0	6	0	0	0	0	0	0	0	1	0	11
Tongue discomfort	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Tongue pruritus	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Toothache	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Vomiting	0	0	1	16	0	1	42	403	0	0	0	7	0	0	0	58	43	485
Skin and subcutaneous tissue	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative

disorders (21)	0	2	0	9	1	136	4	71	0	1	0	0	0	12	0	1	5	232
Acne	0	0	0	0	0	4	0	0	0	0	0	0	0	2	0	0	0	6
Blister	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Cold sweat	0	2	0	0	0	34	0	0	0	0	0	0	0	0	0	0	0	36
Drug eruption	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Erythema	0	0	0	1	0	0	0	4	0	0	0	0	0	0	0	0	0	5
Hyperhidrosis	0	0	0	0	0	91	0	0	0	1	0	0	0	9	0	0	0	101
Lip swelling	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Night sweats	0	0	0	0	0	4	0	0	0	0	0	0	0	0	0	0	0	4
Petechiae	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Pruritus	0	0	0	0	0	0	1	29	0	0	0	0	0	0	0	0	1	29
Rash	0	0	0	2	0	0	1	17	0	0	0	0	0	0	0	1	1	20
Rash erythematous	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	2
Rash macular	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Rash papular	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Rash pruritic	0	0	0	2	0	0	0	3	0	0	0	0	0	0	0	0	0	5
Skin discolouration	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Skin irritation	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Skin tightness	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Sweating increased	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1
Swelling face	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	3
Urticaria	0	0	0	1	0	0	2	10	0	0	0	0	0	0	0	0	2	11
Musculoskeletal and connective tissue disorders (19)	Interval 0	Cumulative 6	Interval 0	Cumulative 2	Interval 4	Cumulative 170	Interval 22	Cumulative 525	Interval 0	Cumulative 1	Interval 0	Cumulative 8	Interval 0	Cumulative 21	Interval 0	Cumulative 62	Interval 26	Cumulative 795
Arthralgia	0	0	0	0	0	16	0	0	0	0	0	0	0	2	0	0	0	18
Back pain	0	2	0	0	3	92	0	0	0	0	0	0	0	14	0	0	3	108
Coccydynia	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Flank pain	0	0	0	0	0	8	0	0	0	0	0	0	0	1	0	0	0	9
Groin pain	0	0	0	0	0	2	0	0	0	0	0	0	0	1	0	0	0	3
Intervertebral disc protrusion	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
Joint stiffness	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Joint swelling	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Limb discomfort	0	0	0	0	0	2	0	0	0	0	0	0	0	1	0	0	0	3
Muscle spasms	0	0	0	2	0	3	22	524	0	0	0	8	0	0	0	62	22	599
Muscle tightness	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Muscular weakness	0	0	0	0	0	2	0	0	0	0	0	0	0	1	0	0	0	3
Musculoskeletal chest pain	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	2
Musculoskeletal stiffness	0	0	0	0	1	2	0	0	0	0	0	0	0	0	0	0	1	2
Myalgia	0	0	0	0	0	19	0	0	0	0	0	0	0	0	0	0	0	19
Neck pain	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	3
Pain in extremity	0	1	0	0	0	15	0	0	0	0	0	0	0	1	0	0	0	17
Pain in jaw	0	1	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	3
Pubic pain	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Renal and urinary disorders (13)	Interval 0	Cumulative 1	Interval 0	Cumulative 0	Interval 0	Cumulative 46	Interval 0	Cumulative 0	Interval 0	Cumulative 0	Interval 0	Cumulative 0	Interval 0	Cumulative 5	Interval 0	Cumulative 0	Interval 0	Cumulative 52
Bladder discomfort	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	3
Chromaturia	0	0	0	0	0	4	0	0	0	0	0	0	0	1	0	0	0	5
Dysuria	0	1	0	0	0	18	0	0	0	0	0	0	0	2	0	0	0	21
Hypertonic bladder	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Micturition disorder	0	0	0	0	0	2	0	0	0	0	0	0	0	1	0	0	0	3
Micturition frequency decreased	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Micturition urgency	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	3
Oliguria	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Pollakiuria	0	0	0	0	0	3	0	0	0	0	0	0	0	1	0	0	0	4
Renal pain	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Urinary retention	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Urine abnormality	0	0	0	0	0	4	0	0	0	0	0	0	0	0	0	0	0	4
Urine odour abnormal	0	0	0	0	0	4	0	0	0	0	0	0	0	0	0	0	0	4
Pregnancy, puerperium and perinatal conditions	Interval 0	Cumulative 3	Interval 0	Cumulative 1	Interval 0	Cumulative 1	Interval 1	Cumulative 224	Interval 0	Cumulative 0	Interval 0	Cumulative 2	Interval 0	Cumulative 0	Interval 0	Cumulative 40	Interval 1	Cumulative 271
Abortion incomplete	0	0	0	0	0	0	0	5	0	0	0	0	0	0	0	0	0	5
Cervical dilatation	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	1	1
Morning sickness	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	3
Neonatal disorder	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1

Pregnancy with injectable contraceptive	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Retained products of conception	0	0	0	1	0	0	0	214	0	0	0	2	0	0	0	40	0	257
Ruptured ectopic pregnancy	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
Uterine hypertonus	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1

Reproductive system and breast disorders (39)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	1	4	95	7	407	63	1654	0	4	1	149	0	76	0	140	75	2526
Adnexa uteri pain	0	0	0	0	0	0	1	3	0	0	0	0	0	0	0	0	1	3
Amenorrhoea	0	0	0	0	0	21	0	0	0	0	0	0	0	2	0	0	0	23
Breast discharge	0	0	0	0	0	4	0	0	0	0	0	0	0	0	0	0	0	4
Breast discomfort	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
Breast pain	0	0	0	0	0	0	0	12	0	0	0	0	0	0	0	5	0	17
Breast swelling	0	0	0	0	0	5	0	0	0	0	0	0	0	1	0	0	0	6
Breast tenderness	0	0	0	0	0	0	0	26	0	0	0	0	0	0	0	10	0	36
Cervix disorder	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Dysmenorrhoea	0	0	0	0	0	5	0	0	0	0	0	0	0	3	0	0	0	8
Dyspareunia	0	0	0	0	1	2	0	0	0	0	0	0	0	0	0	0	1	2
Endometrial thickening	0	0	0	0	0	6	0	0	0	0	0	0	0	0	0	0	0	6
Endometriosis	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Enlarged clitoris	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Genital blister	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Genital discomfort	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Genital rash	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Heavy menstrual bleeding	0	0	0	0	1	18	0	0	0	0	0	0	0	6	0	0	1	24
Labia enlarged	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Menstruation delayed	0	0	0	0	1	3	0	0	0	0	0	0	0	5	0	0	1	8
Menstruation irregular	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Nipple pain	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Ovarian cyst	0	0	0	0	0	2	0	0	0	0	0	0	0	2	0	0	0	4
Ovarian cyst ruptured	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Pelvic discomfort	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	2
Pelvic pain	0	0	0	1	0	0	1	50	0	0	0	0	0	0	0	20	1	71
Pruritus genital	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Uterine cervical pain	0	0	0	0	0	0	1	3	0	0	0	0	0	0	0	0	1	3
Uterine pain	0	0	0	0	0	0	0	13	0	0	0	0	0	0	0	0	0	13
Uterine spasm	0	0	0	0	0	0	0	4	0	0	0	0	0	0	0	0	0	4
Uterine tenderness	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Vaginal discharge	0	0	0	0	2	259	0	0	0	4	0	0	0	55	0	0	2	318
Vaginal haemorrhage	0	0	4	92	0	0	60	1530	0	0	1	149	0	0	0	103	65	1874
Vaginal odour	0	1	0	0	0	60	0	0	0	0	0	0	0	2	0	0	0	63
Vulval disorder	0	0	0	0	0	6	0	0	0	0	0	0	0	0	0	0	0	6
Vulvovaginal discomfort	0	0	0	0	1	2	0	0	0	0	0	0	0	0	0	0	1	2
Vulvovaginal inflammation	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Vulvovaginal pain	0	0	0	0	1	5	0	0	0	0	0	0	0	0	0	0	1	5
Vulvovaginal pruritus	0	0	0	0	0	0	0	7	0	0	0	0	0	0	0	0	0	7
Vulvovaginal swelling	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1

General disorders and administration site conditions (34)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	7	4	37	19	429	61	1312	0	3	0	21	0	68	0	188	84	2065
Administration site pain	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Adverse event	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Asthenia	0	0	0	0	2	113	0	0	0	2	0	0	0	23	0	0	2	138
Chest discomfort	0	0	0	0	0	8	0	0	0	0	0	0	0	0	0	0	0	8
Chest pain	0	4	0	0	0	9	0	0	0	0	0	0	0	2	0	0	0	15
Chills	0	0	1	2	0	0	3	128	0	0	0	1	0	0	0	21	4	152
Cyst	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Discomfort	0	0	0	0	1	11	0	0	0	0	0	0	0	2	0	0	1	13
Drug ineffective	0	0	0	1	0	0	4	13	0	0	0	0	0	0	0	0	4	14
Drug interaction	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Facial pain	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1
Fatigue	0	0	0	1	0	7	2	116	0	0	0	2	0	0	0	25	2	151
Feeling cold	0	0	0	1	0	0	1	94	0	0	0	0	0	0	0	6	1	101
Feeling hot	0	0	0	1	0	0	2	106	0	0	0	0	0	0	0	8	2	115
Hunger	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Hyperhidrosis	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1

Ill-defined disorder	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Influenza like illness	0	0	0	0	0	15	0	0	0	0	0	0	0	4	0	0	0	19
Lethargy	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1
Malaise	0	1	0	0	14	97	0	0	0	1	0	0	0	30	0	2	14	131
Mass	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Pain	0	0	1	22	0	137	36	601	0	0	0	14	0	4	0	95	37	873
Pallor	0	1	0	1	0	3	1	56	0	0	0	2	0	0	0	4	1	67
Peripheral swelling	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Pyrexia	0	0	1	4	0	0	12	148	0	0	0	2	0	0	0	24	13	178
Sensation of foreign body	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Sluggishness	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Suprapubic pain	0	0	0	0	0	0	0	4	0	0	0	0	0	0	0	0	0	4
Swelling	0	0	0	0	0	3	0	0	0	0	0	0	0	1	0	0	0	4
Swelling face	0	0	0	2	0	0	0	7	0	0	0	0	0	0	0	0	0	9
Tenderness	0	0	0	0	0	0	0	5	0	0	0	0	0	0	0	0	0	5
Therapeutic response decreased	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Thirst	0	0	0	0	0	11	0	0	0	0	0	0	0	2	0	0	0	13
Treatment failure	0	0	1	2	0	0	0	33	0	0	0	0	0	0	0	3	1	38
Investigations (21)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	4	0	3	3	59	3	66	0	0	0	0	0	5	0	5	6	142
Blood glucose increased	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Blood iron decreased	0	1	0	0	0	4	0	0	0	0	0	0	0	0	0	0	0	5
Blood pressure decreased	0	0	0	0	0	0	1	2	0	0	0	0	0	0	0	0	1	2
Blood urine present	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Body temperature increased	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	2
Haemoglobin decreased	0	0	0	1	0	0	0	7	0	0	0	0	0	0	0	2	0	10
Heart rate abnormal	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Heart rate decreased	0	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	2
Heart rate increased	0	1	0	0	1	17	0	0	0	0	0	0	0	0	0	0	1	18
Human chorionic gonadotropin decreased	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	3
Human chorionic gonadotropin increased	0	0	0	0	0	0	0	7	0	0	0	0	0	0	0	0	0	7
Human chorionic gonadotropin positive	0	0	0	1	0	0	0	2	0	0	0	0	0	0	0	0	0	3
Laboratory test abnormal	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Pregnancy test positive	0	0	0	0	0	0	0	6	0	0	0	0	0	0	0	1	0	7
Pregnancy test urine positive	0	0	0	1	0	0	2	38	0	0	0	0	0	0	0	1	2	40
Respiratory rate increased	0	0	0	0	0	20	0	0	0	0	0	0	0	1	0	0	0	21
Urine output decreased	0	0	0	0	0	8	0	0	0	0	0	0	0	1	0	0	0	9
Volume blood decreased	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Weight decreased	0	0	0	0	1	2	0	0	0	0	0	0	0	2	0	0	1	4
Weight increased	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	2
White blood cell count increased	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Injury, poisoning and procedural complications (24)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	1	42	278	17	77	3	84	0	0	2	261	2	8	0	21	66	730
Abortion induced incomplete	0	0	31	224	0	0	1	38	0	0	0	210	0	0	0	18	32	490
Circumstance or information capable of leading to medication error	0	0	0	0	2	23	0	0	0	0	0	0	0	1	0	0	2	24
Contusion	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Exposure during pregnancy	0	0	2	2	0	0	2	10	0	0	0	0	0	0	0	1	4	13
Exposure via breast milk	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1

Inappropriate schedule of product administration	0	0	0	0	3	10	0	0	0	0	0	0	0	1	0	0	3	11
Incorrect dose administered	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	3
Incorrect route of product administration	0	0	0	0	0	8	0	0	0	0	0	0	0	0	0	0	0	8
Induced abortion failed	0	0	9	52	0	0	0	35	0	0	2	51	0	0	0	2	11	140
Intentional product misuse	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Intercepted product prescribing error	0	0	0	0	1	2	0	0	0	0	0	0	0	0	0	0	1	2
Labelled drug-food interaction medication error	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Maternal exposure during breast feeding	0	0	0	0	0	4	0	0	0	0	0	0	0	0	0	0	0	4
Maternal exposure during pregnancy	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Medication error	0	0	0	0	0	4	0	0	0	0	0	0	0	0	0	0	0	4
Off label use	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Product administration error	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Product dose omission issue	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Product storage error	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1
Product use in unapproved indication	0	0	0	0	6	10	0	0	0	0	0	0	2	3	0	0	8	13
Recalled product administered	0	0	0	0	4	4	0	0	0	0	0	0	0	0	0	0	4	4
Rib fracture	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Underdose	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Uterine perforation	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1

Surgical and medical procedures (6)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	0	22	273	0	0	1	9	0	0	2	331	0	0	0	3	25	616
Evacuation of retained products of conception	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Packed red blood cell transfusion	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	2
Surgery	0	0	7	40	0	0	0	1	0	0	1	48	0	0	0	0	8	89
Transfusion	0	0	0	14	0	0	0	3	0	0	0	3	0	0	0	1	0	21
Uterine dilation and curettage	0	0	15	216	0	0	1	5	0	0	1	278	0	0	0	2	17	501
Uterine dilation and evacuation	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	2

Social circumstances (2)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	4	0	0	1	4	0	0	0	0	0	0	0	3	0	0	1	11
Breast feeding	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Contraindication to medical treatment	0	4	0	0	1	4	0	0	0	0	0	0	0	2	0	0	1	10

Product issues (4)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	0	0	0	5	8	0	0	0	0	0	0	0	0	0	0	5	8
Product complaint	0	0	0	0	3	3	0	0	0	0	0	0	0	0	0	0	3	3
Product packaging quantity issue	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1
Product quality issue	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	3
Product taste abnormal	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1

Total	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	3	79	91	880	85	1889	366	7582	2	11	5	845	2	265	1	1191	555	12742

2.C.2. Cumulative Summary Tabulations of Serious and Non-serious Adverse Reactions from Post-Market experience_MISOPROSTOL

Soc Meddra / Pt	Spontaneous Serious Unlisted		Spontaneous Serious Listed		Spontaneous Non Serious Unlisted		Spontaneous Non Serious Listed		Solicited Serious Unlisted		Solicited Serious Listed		Solicited Non Serious Unlisted		Solicited Non Serious Listed		Total	
Infections and infestations (25)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	2	4	32	0	13	2	63	2	2	0	8	0	6	0	14	8	140
Abortion infected	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	2
Amniotic cavity infection	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	1	1
Bacterial infection	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Bacterial vaginosis	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	2
Bronchitis	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Candida infection	0	0	0	0	0	0	0	6	0	0	0	0	0	0	0	0	0	6
Chlamydial infection	0	1	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	3
Cystitis	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Endometritis	0	0	4	11	0	0	0	1	0	0	0	3	0	0	0	2	4	17
Genital herpes	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Infection	0	0	0	9	0	0	2	40	0	0	0	4	0	0	0	9	2	62
Influenza	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	3
Laryngitis	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Lower respiratory tract infection	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Nasopharyngitis	0	0	0	0	0	5	0	0	0	0	0	0	0	3	0	0	0	8
Ovarian abscess	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Pelvic inflammatory disease	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
Sepsis	0	0	0	6	0	0	0	0	0	0	0	0	0	0	0	0	0	6
Septic shock	0	0	0	1	0	0	0	0	1	1	0	1	0	0	0	0	1	3
Tonsillitis	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Toxic shock syndrome	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	2
Urinary tract infection	0	0	0	2	0	0	0	7	0	0	0	0	0	0	0	1	0	10
Uterine infection	0	0	0	0	0	0	0	4	0	0	0	0	0	0	0	0	0	4
Vaginal infection	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1

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2.C.2. Cumulative Summary Tabulations of Serious and Non-serious Adverse Reactions from Post-Market experience_MISOPROSTOL

Viral infection	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Neoplasms benign, malignant and	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Uterine leiomyoma	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Blood and lymphatic system	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	0	0	1	0	0	0	5	0	0	0	1	0	1	0	1	0	9
Anaemia	0	0	0	1	0	0	0	5	0	0	0	0	0	0	0	1	0	7
Blood loss anaemia	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1
Lymphadenopathy	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Immune system disorders (3)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	1	0	5	0	0	1	2	0	0	0	0	0	0	0	2	1	10
Drug hypersensitivity	0	0	0	1	0	0	1	1	0	0	0	0	0	0	0	0	1	2
Hypersensitivity	0	0	0	4	0	0	0	1	0	0	0	0	0	0	0	2	0	7
Rheumatoid arthritis	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Metabolism and nutrition disorders (8)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	1	2	0	0	1	20	0	0	0	0	0	0	0	0	0	0	2	22
Decreased appetite	0	0	0	0	0	11	0	0	0	0	0	0	0	0	0	0	0	11
Dehydration	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	3
Food craving	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Hyperglycaemia	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Hypophagia	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Hypovolaemia	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Iron deficiency	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	2
Polydipsia	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1
Psychiatric disorders (15)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	7	0	0	0	12	0	15	0	0	0	0	0	1	0	0	0	35
Anxiety	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Autoscopy	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Depressed mood	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Depression	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	3

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2.C.2. Cumulative Summary Tabulations of Serious and Non-serious Adverse Reactions from Post-Market experience_MISOPROSTOL

Depression suicidal	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Hallucination	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Insomnia	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Irritability	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Libido increased	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Mood altered	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Nervousness	0	0	0	0	0	0	0	15	0	0	0	0	0	0	0	0	0	15
Nightmare	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Panic reaction	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Paranoia	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Suicidal ideation	0	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4

Nervous system disorders (20)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	12	1	10	9	114	1	130	0	0	0	1	0	20	0	14	11	301
Burning sensation	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Cerebral ischaemia	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Consciousness fluctuating	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Disturbance in attention	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Dysarthria	0	0	0	0	2	2	0	0	0	0	0	0	0	0	0	0	2	2
Dysstasia	0	0	0	0	1	2	0	0	0	0	0	0	0	0	0	0	1	2
Dystonia	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Headache	0	0	1	1	0	0	1	90	0	0	0	0	0	0	0	11	2	102
Hypoaesthesia	0	1	0	0	0	18	0	0	0	0	0	0	0	0	0	0	0	19
Lethargy	0	0	0	0	0	51	0	0	0	0	0	0	0	7	0	0	0	58
Loss of consciousness	0	5	0	9	0	0	0	3	0	0	0	0	0	2	0	3	0	22
Migraine	0	0	0	0	0	7	0	0	0	0	0	0	0	2	0	0	0	9
Paraesthesia	0	1	0	0	1	18	0	0	0	0	0	0	0	3	0	0	1	22
Parosmia	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Seizure	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
Sensory loss	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Slow speech	0	0	0	0	2	2	0	0	0	0	0	0	0	0	0	0	2	2
Somnolence	0	0	0	0	2	7	0	0	0	0	0	0	0	4	0	0	2	11
Speech disorder	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1

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2.C.2. Cumulative Summary Tabulations of Serious and Non-serious Adverse Reactions from Post-Market experience_MISOPROSTOL

Tremor	0	0	0	0	1	3	0	37	0	0	0	1	0	0	0	0	1	41
Eye disorders (7)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	0	0	3	1	16	0	5	0	0	0	0	0	3	0	1	1	28
Blindness unilateral	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Eye pain	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Eye swelling	0	0	0	2	0	0	0	5	0	0	0	0	0	0	0	1	0	8
Ocular hyperaemia	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Swelling of eyelid	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Vision blurred	0	0	0	0	1	7	0	0	0	0	0	0	0	0	0	0	1	7
Visual impairment	0	0	0	0	0	7	0	0	0	0	0	0	0	2	0	0	0	9
Ear and labyrinth disorders (6)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	1	0	0	1	7	0	1	0	0	0	0	0	0	0	0	1	9
Deafness	0	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	2
Ear pain	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	3
Ear pruritus	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Hyperacusis	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Hypoacusis	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Tinnitus	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Cardiac disorders (10)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	8	0	4	0	39	0	0	0	0	0	0	0	5	0	0	0	56
Acute myocardial infarction	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Arteriospasm coronary	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Cardiac arrest	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
Cardiac disorder	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Cardiac failure	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Cardiac flutter	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Cardiomyopathy	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Palpitations	0	1	0	0	0	37	0	0	0	0	0	0	0	4	0	0	0	42
Tachycardia	0	2	0	0	0	2	0	0	0	0	0	0	0	1	0	0	0	5

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Ventricular fibrillation	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1

Vascular disorders (15)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	1	4	10	76	1	4	85	2011	0	0	0	44	0	0	0	496	97	2635
Dizziness	0	0	0	4	0	0	15	492	0	0	0	2	0	0	0	65	15	563
Dizziness exertional	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Dizziness postural	0	0	0	0	0	0	0	23	0	0	0	0	0	0	0	2	0	25
Flushing	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	1	0	3
Haematoma	0	0	0	0	1	2	0	0	0	0	0	0	0	0	0	0	1	2
Haemodynamic instability	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Haemorrhage	0	0	2	19	0	0	31	421	0	0	0	13	0	0	0	262	33	715
Hot flush	0	0	0	0	0	0	0	19	0	0	0	0	0	0	0	2	0	21
Hypertension	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Hypotension	0	0	0	4	0	0	1	6	0	0	0	0	0	0	0	0	1	10
Neurogenic shock	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2
Peripheral coldness	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Presyncope	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	3
Syncope	0	0	6	19	0	0	1	30	0	0	0	2	0	0	0	6	7	57
Thrombosis	0	1	2	30	0	0	37	1014	0	0	0	27	0	0	0	158	39	1230

Respiratory, thoracic and mediastinal	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	10	0	7	7	163	0	3	0	0	0	0	0	12	0	1	7	196
Asthma	0	0	0	2	0	0	0	1	0	0	0	0	0	0	0	0	0	3
Cough	0	0	0	0	0	10	0	0	0	0	0	0	0	0	0	0	0	10
Dry throat	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Dysphonia	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	2
Dyspnoea	0	4	0	1	5	115	0	0	0	0	0	0	0	3	0	0	5	123
Hyperventilation	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Lung disorder	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Nasal congestion	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Oropharyngeal discomfort	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Oropharyngeal pain	0	0	0	0	2	16	0	0	0	0	0	0	0	6	0	0	2	22
Painful respiration	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2

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Paranasal sinus hypersecretion	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Pharyngeal swelling	0	0	0	4	0	0	0	2	0	0	0	0	0	0	0	1	0	7
Productive cough	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Pulmonary oedema	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Respiration abnormal	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Rhinorrhoea	0	0	0	0	0	5	0	0	0	0	0	0	0	0	0	0	0	5
Sneezing	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Tachypnoea	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Throat irritation	0	1	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	3
Throat tightness	0	1	0	0	0	1	0	0	0	0	0	0	0	2	0	0	0	4
Gastrointestinal disorders (41)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	1	7	3	31	3	123	67	1137	0	0	0	12	0	18	0	182	74	1510
Abdominal discomfort	0	0	0	0	0	0	0	9	0	0	0	0	0	0	0	5	0	14
Abdominal distension	0	0	0	0	0	55	0	0	0	0	0	0	0	13	0	0	0	68
Abdominal pain	0	0	1	11	0	0	12	238	0	0	0	2	0	0	0	49	13	300
Abdominal pain lower	0	0	0	3	0	0	4	97	0	0	0	1	0	0	0	15	4	116
Abdominal pain upper	0	0	0	0	0	0	3	32	0	0	0	0	0	0	0	2	3	34
Abdominal tenderness	0	0	0	0	0	0	0	11	0	0	0	0	0	0	0	3	0	14
Anal haemorrhage	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Anorectal discomfort	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Constipation	0	0	0	0	0	20	0	0	0	0	0	0	0	0	0	0	0	20
Diarrhoea	0	0	0	1	0	0	2	105	0	0	0	0	0	0	0	13	2	119
Diarrhoea haemorrhagic	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Dry mouth	0	0	0	0	0	10	0	0	0	0	0	0	0	1	0	0	0	11
Dyspepsia	0	0	0	0	0	0	1	5	0	0	0	0	0	0	0	0	1	5
Dysphagia	0	0	0	0	1	7	0	0	0	0	0	0	0	0	0	0	1	7
Eructation	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1

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Gastric dilatation	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Gastrointestinal motility disorder	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Gastrointestinal pain	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Gingival blister	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Gingival pain	0	0	0	0	1	2	0	0	0	0	0	0	0	1	0	0	1	3
Gingival swelling	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Glossodynia	0	0	0	0	0	1	0	0	0	0	0	0	0	2	0	0	0	3
Haematemesis	1	6	0	0	0	4	0	0	0	0	0	0	0	0	0	0	1	10
Haemoperitoneum	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Haemorrhoids	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	2
Lip pruritus	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Lip swelling	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	2
Mouth swelling	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	2
Mouth ulceration	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Nausea	0	0	1	2	0	0	19	306	0	0	0	5	0	0	0	42	20	355
Odynophagia	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Oral mucosal erythema	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Oral pain	0	0	0	0	0	4	0	0	0	0	0	0	0	0	0	0	0	4
Proctalgia	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Retching	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	2
Salivary hypersecretion	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1
Swollen tongue	0	0	0	3	0	0	0	6	0	0	0	0	0	0	0	1	0	10
Tongue discomfort	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Tongue oedema	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Toothache	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Vomiting	0	0	1	10	0	1	26	319	0	0	0	4	0	0	0	52	27	386

Hepatobiliary disorders (1)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1

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Liver injury	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Skin and subcutaneous tissue disorders	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	1	0	4	1	132	3	58	0	0	0	0	0	12	0	1	4	208
Acne	0	0	0	0	0	4	0	0	0	0	0	0	0	2	0	0	0	6
Blister	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Cold sweat	0	1	0	0	0	33	0	0	0	0	0	0	0	0	0	0	0	34
Erythema	0	0	0	0	0	0	0	4	0	0	0	0	0	0	0	0	0	4
Hyperhidrosis	0	0	0	0	0	88	0	0	0	0	0	0	0	9	0	0	0	97
Night sweats	0	0	0	0	0	4	0	0	0	0	0	0	0	0	0	0	0	4
Petechiae	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Pruritus	0	0	0	0	0	0	0	25	0	0	0	0	0	0	0	0	0	25
Rash	0	0	0	1	0	0	2	15	0	0	0	0	0	0	0	1	2	17
Rash erythematous	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Rash macular	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Rash papular	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Rash pruritic	0	0	0	1	0	0	0	3	0	0	0	0	0	0	0	0	0	4
Skin discolouration	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Skin irritation	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Skin tightness	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Sweating increased	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1
Swelling face	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	2
Urticaria	0	0	0	1	0	0	1	5	0	0	0	0	0	0	0	0	1	6
Musculoskeletal and connective tissue disorders	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	6	0	2	4	168	22	520	0	1	0	7	0	21	0	62	26	787
Arthralgia	0	1	0	0	0	16	0	0	0	0	0	0	0	2	0	0	0	19
Back pain	0	2	0	0	3	90	0	0	0	0	0	0	0	14	0	0	3	106
Coccydynia	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Flank pain	0	0	0	0	0	7	0	0	0	0	0	0	0	1	0	0	0	8
Groin pain	0	0	0	0	0	2	0	0	0	0	0	0	0	1	0	0	0	3
Intervertebral disc protrusion	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
Joint stiffness	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Joint swelling	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1

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Limb discomfort	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	2
Muscle spasms	0	0	0	2	0	5	22	519	0	0	0	7	0	0	0	62	22	595
Muscle tightness	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Muscular weakness	0	0	0	0	0	2	0	0	0	0	0	0	0	1	0	0	0	3
Musculoskeletal chest pain	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	2
Musculoskeletal stiffness	0	0	0	0	1	2	0	0	0	0	0	0	0	0	0	0	1	2
Myalgia	0	0	0	0	0	19	0	0	0	0	0	0	0	0	0	0	0	19
Neck pain	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	3
Pain in extremity	0	1	0	0	0	15	0	0	0	0	0	0	0	1	0	0	0	17
Pain in jaw	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Pubic pain	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Renal and urinary disorders (14)	Interval 0	Cumulative 2	Interval 0	Cumulative 0	Interval 0	Cumulative 40	Interval 0	Cumulative 0	Interval 0	Cumulative 0	Interval 0	Cumulative 0	Interval 0	Cumulative 5	Interval 0	Cumulative 0	Interval 0	Cumulative 47
Bladder discomfort	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	3
Chromaturia	0	0	0	0	0	3	0	0	0	0	0	0	0	1	0	0	0	4
Dysuria	0	1	0	0	0	16	0	0	0	0	0	0	0	2	0	0	0	19
Hypertonic bladder	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Micturition disorder	0	0	0	0	0	2	0	0	0	0	0	0	0	1	0	0	0	3
Micturition frequency decreased	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Micturition urgency	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	3
Oliguria	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Pollakiuria	0	0	0	0	0	2	0	0	0	0	0	0	0	1	0	0	0	3
Renal injury	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Renal pain	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Urinary retention	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Urine abnormality	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	3
Urine odour abnormal	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	3
Pregnancy, puerperium and perinatal	Interval 0	Cumulative 3	Interval 0	Cumulative 1	Interval 1	Cumulative 2	Interval 0	Cumulative 222	Interval 0	Cumulative 0	Interval 0	Cumulative 2	Interval 0	Cumulative 0	Interval 0	Cumulative 40	Interval 1	Cumulative 270

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2.C.2. Cumulative Summary Tabulations of Serious and Non-serious Adverse Reactions from Post-Market experience_MISOPROSTOL

Abortion incomplete	0	0	0	0	0	0	0	5	0	0	0	0	0	0	0	0	0	5
Cervical dilatation	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1
Morning sickness	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	2
Neonatal disorder	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Pregnancy with injectable contraceptive	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Retained products of conception	0	0	0	1	0	0	0	214	0	0	0	2	0	0	0	40	0	257
Ruptured ectopic pregnancy	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
Uterine hypertonus	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Reproductive system and breast disorders	Interval 0	Cumulative 4	Interval 4	Cumulative 94	Interval 5	Cumulative 406	Interval 59	Cumulative 1607	Interval 0	Cumulative 4	Interval 1	Cumulative 149	Interval 0	Cumulative 76	Interval 0	Cumulative 140	Interval 69	Cumulative 2480
Adnexa uteri pain	0	0	0	0	0	0	1	3	0	0	0	0	0	0	0	0	1	3
Amenorrhoea	0	0	0	0	0	21	0	0	0	0	0	0	0	2	0	0	0	23
Breast discharge	0	0	0	0	0	4	0	0	0	0	0	0	0	0	0	0	0	4
Breast discomfort	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
Breast pain	0	0	0	0	0	0	0	12	0	0	0	0	0	0	0	5	0	17
Breast swelling	0	0	0	0	0	5	0	0	0	0	0	0	0	1	0	0	0	6
Breast tenderness	0	0	0	0	0	0	0	26	0	0	0	0	0	0	0	10	0	36
Cervix disorder	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Dysmenorrhoea	0	0	0	0	0	5	0	0	0	0	0	0	0	3	0	0	0	8
Dyspareunia	0	0	0	0	1	2	0	0	0	0	0	0	0	0	0	0	1	2
Endometrial thickening	0	0	0	0	0	6	0	0	0	0	0	0	0	0	0	0	0	6
Endometriosis	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2

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2.C.2. Cumulative Summary Tabulations of Serious and Non-serious Adverse Reactions from Post-Market experience_MISOPROSTOL

Enlarged clitoris	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Genital blister	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Genital discomfort	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Genital rash	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Heavy menstrual bleeding	0	0	0	0	0	17	1	1	0	0	0	0	0	6	0	0	1	24
Hypomenorrhoea	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Labia enlarged	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Menstruation delayed	0	0	0	0	1	3	0	0	0	0	0	0	0	5	0	0	1	8
Menstruation irregular	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Nipple pain	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Ovarian cyst	0	0	0	0	0	2	0	0	0	0	0	0	0	2	0	0	0	4
Ovarian cyst ruptured	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Pelvic discomfort	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	2
Pelvic pain	0	0	0	1	0	0	0	49	0	0	0	0	0	0	0	20	0	70
Pruritus genital	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Suppressed lactation	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Uterine cervical pain	0	0	0	0	0	0	1	3	0	0	0	0	0	0	0	0	1	3
Uterine pain	0	0	0	0	0	0	0	13	0	0	0	0	0	0	0	0	0	13
Uterine spasm	0	0	0	0	0	0	0	4	0	0	0	0	0	0	0	0	0	4
Uterine tenderness	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Vaginal discharge	0	0	0	0	2	258	0	0	0	4	0	0	0	55	0	0	2	317
Vaginal disorder	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Vaginal haemorrhage	0	0	4	92	0	0	56	1483	0	0	1	149	0	0	0	103	61	1827
Vaginal odour	0	1	0	0	0	60	0	0	0	0	0	0	0	2	0	0	0	63

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2.C.2. Cumulative Summary Tabulations of Serious and Non-serious Adverse Reactions from Post-Market experience_MISOPROSTOL

Vulval disorder	0	0	0	0	0	6	0	0	0	0	0	0	0	0	0	0	0	6
Vulvovaginal discomfort	0	0	0	0	1	2	0	0	0	0	0	0	0	0	0	0	1	2
Vulvovaginal inflammation	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Vulvovaginal pain	0	0	0	0	0	4	0	0	0	0	0	0	0	0	0	0	0	4
Vulvovaginal pruritus	0	0	0	0	0	0	0	7	0	0	0	0	0	0	0	0	0	7
Vulvovaginal swelling	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Congenital, familial and genetic	Interval 0	Cumulative 0	Interval 0	Cumulative 1	Interval 0	Cumulative 0	Interval 0	Cumulative 0	Interval 0	Cumulative 0	Interval 0	Cumulative 0	Interval 0	Cumulative 0	Interval 0	Cumulative 0	Interval 0	Cumulative 1
Moebius II syndrome	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
General disorders and administration	Interval 0	Cumulative 4	Interval 4	Cumulative 40	Interval 16	Cumulative 393	Interval 51	Cumulative 1269	Interval 0	Cumulative 3	Interval 0	Cumulative 19	Interval 0	Cumulative 67	Interval 0	Cumulative 183	Interval 71	Cumulative 1978
Administration site pain	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Asthenia	0	0	0	0	1	101	0	0	0	2	0	0	0	22	0	0	1	125
Chest discomfort	0	0	0	0	0	6	0	0	0	0	0	0	0	0	0	0	0	6
Chest pain	0	2	0	0	0	7	0	0	0	0	0	0	0	2	0	0	0	11
Chills	0	0	1	3	0	0	0	119	0	0	0	1	0	0	0	20	1	143
Cyst	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Discomfort	0	0	0	0	1	11	0	0	0	0	0	0	0	2	0	0	1	13
Drug ineffective	0	0	0	3	0	0	4	13	0	0	0	0	0	0	0	0	4	16
Drug interaction	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Drug resistance	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Facial pain	0	0	0	0	1	2	0	0	0	0	0	0	0	0	0	0	1	2
Fatigue	0	0	0	1	0	7	2	111	0	0	0	2	0	0	0	25	2	146
Feeling cold	0	0	0	1	0	0	1	87	0	0	0	0	0	0	0	6	1	94
Feeling hot	0	0	0	1	0	0	1	100	0	0	0	0	0	0	0	8	1	109
Hunger	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Hyperhidrosis	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Influenza like illness	0	0	0	0	0	15	0	0	0	0	0	0	0	4	0	0	0	19
Lethargy	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1

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2.C.2. Cumulative Summary Tabulations of Serious and Non-serious Adverse Reactions from Post-Market experience_MISOPROSTOL

Malaise	0	0	0	0	11	86	0	0	0	1	0	0	0	30	0	0	11	117
Mass	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Pain	0	0	1	22	0	135	33	591	0	0	0	12	0	4	0	94	34	858
Pallor	0	0	0	1	0	2	1	56	0	0	0	2	0	0	0	4	1	65
Peripheral swelling	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Pyrexia	0	0	1	5	0	0	9	143	0	0	0	2	0	0	0	23	10	173
Sensation of foreign body	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Sluggishness	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Suprapubic pain	0	0	0	0	0	0	0	4	0	0	0	0	0	0	0	0	0	4
Swelling	0	0	0	0	0	2	0	0	0	0	0	0	0	1	0	0	0	3
Swelling face	0	0	0	1	0	0	0	6	0	0	0	0	0	0	0	0	0	7
Tenderness	0	0	0	0	0	0	0	5	0	0	0	0	0	0	0	0	0	5
Therapeutic response decreased	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Thirst	0	0	0	0	0	7	0	0	0	0	0	0	0	2	0	0	0	9
Treatment failure	0	0	1	2	0	0	0	33	0	0	0	0	0	0	0	3	1	38
Ulcer	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1
Investigations (23)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	8	0	3	3	53	3	66	0	0	0	0	0	5	0	5	6	140
Blood glucose increased	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Blood iron decreased	0	1	0	0	0	4	0	0	0	0	0	0	0	0	0	0	0	5
Blood pressure decreased	0	0	0	0	0	0	1	2	0	0	0	0	0	0	0	0	1	2
Blood pressure diastolic abnormal	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Blood urine present	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Body temperature increased	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	2
Haemoglobin decreased	0	0	0	1	0	0	0	7	0	0	0	0	0	0	0	2	0	10
Heart rate abnormal	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	2

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2.C.2. Cumulative Summary Tabulations of Serious and Non-serious Adverse Reactions from Post-Market experience_MISOPROSTOL

Heart rate decreased	0	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	2
Heart rate increased	0	1	0	0	1	16	0	0	0	0	0	0	0	0	0	0	1	17
Human chorionic gonadotropin decreased	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	3
Human chorionic gonadotropin increased	0	0	0	0	0	0	0	7	0	0	0	0	0	0	0	0	0	7
Human chorionic gonadotropin positive	0	0	0	1	0	0	0	2	0	0	0	0	0	0	0	0	0	3
Laboratory test abnormal	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Oxygen saturation decreased	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Pregnancy test positive	0	0	0	0	0	0	0	6	0	0	0	0	0	0	0	1	0	7
Pregnancy test urine positive	0	0	0	1	0	0	2	38	0	0	0	0	0	0	0	1	2	40
Respiratory rate increased	0	0	0	0	0	20	0	0	0	0	0	0	0	1	0	0	0	21
Urine output decreased	0	0	0	0	0	3	0	0	0	0	0	0	0	1	0	0	0	4
Volume blood decreased	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Weight decreased	0	0	0	0	1	2	0	0	0	0	0	0	0	2	0	0	1	4
Weight increased	0	1	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	3
White blood cell count increased	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2

Injury, poisoning and procedural complications	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	3	39	278	40	185	3	80	0	0	2	260	2	54	0	19	86	879

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2.C.2. Cumulative Summary Tabulations of Serious and Non-serious Adverse Reactions from Post-Market experience_MISOPROSTOL

Abortion induced incomplete	0	0	31	226	0	0	1	38	0	0	0	210	0	0	0	18	32	492
Circumstance or information capable of leading to medication error	0	0	0	0	2	24	0	0	0	0	0	0	0	1	0	0	2	25
Contusion	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Dental restoration failure	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Duplicate therapy error	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Exposure during pregnancy	0	0	0	0	0	0	2	9	0	0	0	0	0	0	0	0	2	9
Exposure via breast milk	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Foetal exposure during pregnancy	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Inappropriate schedule of product administration	0	0	0	0	12	42	0	0	0	0	0	0	0	37	0	0	12	79
Incorrect dose administered	0	0	0	0	5	24	0	0	0	0	0	0	0	7	0	0	5	31
Incorrect product administration duration	0	0	0	0	2	2	0	0	0	0	0	0	0	0	0	0	2	2
Incorrect route of product administration	0	0	0	0	2	25	0	0	0	0	0	0	0	1	0	0	2	26
Induced abortion failed	0	0	8	52	0	0	0	31	0	0	2	50	0	0	0	1	10	134

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2.C.2. Cumulative Summary Tabulations of Serious and Non-serious Adverse Reactions from Post-Market experience_MISOPROSTOL

Intentional product misuse	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	3
Intercepted product prescribing error	0	0	0	0	4	10	0	0	0	0	0	0	0	0	0	0	4	10
Maternal exposure during breast feeding	0	0	0	0	0	4	0	0	0	0	0	0	0	0	0	0	0	4
Maternal exposure during pregnancy	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Medication error	0	0	0	0	0	4	0	0	0	0	0	0	0	0	0	0	0	4
Off label use	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	3
Product administration error	0	0	0	0	0	4	0	0	0	0	0	0	0	0	0	0	0	4
Product dispensing error	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Product prescribing error	0	0	0	0	1	3	0	0	0	0	0	0	0	0	0	0	1	3
Product storage error	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1
Product use in unapproved indication	0	0	0	0	6	24	0	0	0	0	0	0	2	5	0	0	8	29
Product use issue	0	0	0	0	1	2	0	0	0	0	0	0	0	0	0	0	1	2
Recalled product administered	0	0	0	0	4	4	0	0	0	0	0	0	0	0	0	0	4	4
Rib fracture	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Tendon rupture	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Underdose	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Uterine perforation	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Wrong dose	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1

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2.C.2. Cumulative Summary Tabulations of Serious and Non-serious Adverse Reactions from Post-Market experience_MISOPROSTOL

Wrong product administered	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Wrong schedule	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Surgical and medical procedures (7)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	0	22	271	0	1	1	8	0	0	2	328	0	0	0	4	25	612
Evacuation of retained products of conception	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Intra-uterine contraceptive device insertion	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Packed red blood cell transfusion	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	2
Surgery	0	0	7	37	0	0	0	0	0	0	1	47	0	0	0	1	8	85
Transfusion	0	0	0	14	0	0	0	3	0	0	0	3	0	0	0	1	0	21
Uterine dilation and curettage	0	0	15	217	0	0	1	5	0	0	1	276	0	0	0	2	17	500
Uterine dilation and evacuation	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	2
Social circumstances (3)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	4	0	0	5	47	0	0	0	0	0	0	0	7	0	0	5	58
Breast feeding	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Contraindication to medical treatment	0	4	0	0	1	4	0	0	0	0	0	0	0	2	0	0	1	10
Refusal of treatment by patient	0	0	0	0	4	43	0	0	0	0	0	0	0	4	0	0	4	47
Product issues (5)	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	0	0	0	0	11	33	0	0	0	0	0	0	0	0	0	0	11	33
Product complaint	0	0	0	0	6	15	0	0	0	0	0	0	0	0	0	0	6	15

Document 6

2.C.2. Cumulative Summary Tabulations of Serious and Non-serious Adverse Reactions from Post-Market experience_MISOPROSTOL

Product packaging issue	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1
Product packaging quantity issue	0	0	0	0	4	13	0	0	0	0	0	0	0	0	0	0	4	13
Product physical issue	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Product quality issue	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	3

Total	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	3	91	87	863	109	1971	298	7202	2	10	5	831	2	313	0	1165	506	12446

Document 6

Appendix 3. Tabular Summary of Safety Signals

Not applicable (see section 15)

Appendix 4a. Listing of all the MAH-sponsored interventional and non-interventional trials with the primary aim of identifying characterising or quantifying a safety hazard or confirming the safety profile of the medicinal product

Not applicable

Appendix 4B. Listing of all the MAH-sponsored non-interventional studies with the primary aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product or measuring the effectiveness of risk management measures

Not applicable

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AUSTRALIAN PRODUCT INFORMATION
MS-2-STEP
(Mifepristone and Misoprostol)
Tablets

It is very important that all patients receiving these medications are followed up by a ~~medical~~ healthcare practitioner, preferably the prescriber, to ensure that the medication has been effective. Even if no adverse events have occurred all patients must receive follow-up 14 to 21 days after taking mifepristone. Read the **Section *4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE*** carefully**.**

This document refers to the use of ***MS-2 Step***, which consists of Mifepristone Linepharma 200 mg tablet and GyMiso® misoprostol 200 microgram tablets in combination. These medicines are indicated in females of childbearing age for the medical termination of an intrauterine pregnancy, up to 63 days of gestation. The Mifepristone Linepharma 200 mg tablet component of this therapy is also used to treat another condition. For information about the treatment of the other condition, refer to the full Product Information for Mifepristone Linepharma 200 mg tablet individual product (AUST R 175671).

1 NAME OF THE MEDICINE

Mifepristone and Misoprostol

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

MS-2 Step is a composite pack containing:

Mifepristone Linepharma

Each tablet contains 200 mg of mifepristone.

For the full list of excipients, see **Section 6.1 LIST OF EXCIPIENTS**.

GyMiso®

Each tablet contains 200 micrograms of misoprostol as a 1% dispersion of misoprostol-hypromellose. Misoprostol is a clear, colourless or yellowish oily liquid.

For the full list of excipients, see **Section 6.1 LIST OF EXCIPIENTS**.

3 PHARMACEUTICAL FORM

Mifepristone Linepharma

White to off-white, round biconvex tablets, diameter 11 mm, with “MF” debossed on one side of the tablet.

GyMiso®

White, flat round tablet with “ML” debossed on one side and “200” on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

MS-2 Step is indicated in females of childbearing age for the medical termination of an intrauterine pregnancy, up to 63 days of gestation.

It is recommended that the duration of pregnancy (i.e., up to 63 days gestation) be confirmed by ultrasound. In the event that an ultrasound is not possible, extra caution should be exercised.

Ultrasound is also useful to exclude ectopic pregnancy

4.2 DOSE AND METHOD OF ADMINSTRATION

MS-2 Step is indicated for medical termination of intrauterine pregnancy, up to 63 days of gestation.

The method of administration is as follows:

Mifepristone: 200 mg of mifepristone (1 tablet containing 200 mg) orally, followed 36 to 48 hours later by the administration of GyMiso®.

GyMiso®: 800 micrograms of misoprostol (4 tablets, each tablet containing 200 micrograms) buccally, i.e: kept between the cheek and the gum for 30 minutes before any fragments being swallowed with water.

When ***MS-2 Step*** fails to cause termination of intra-uterine pregnancy, the patient should return to the treating healthcare practitioner ~~doctor~~ for assessment and discussion of treatment options, which may include pregnancy termination by surgery.

Commented [S22]: Rd 2 Clinical Evaluation report (Q1)

No dosage adjustment of misoprostol or mifepristone is necessary with renal or hepatic insufficiency when administered at the recommended doses.

There are no data available on the effect of food intake on the absorption of mifepristone or misoprostol. MS-2 Step should be taken 2 hours before or 2 hours after a meal.

Refer also to **4.3 CONTRAINDICATIONS**, and **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.**

MS-2 Step should only be prescribed by healthcare practitioners ~~doctors~~ with the appropriate qualifications and ~~certified~~ training. Ectopic pregnancy should be excluded, an intrauterine device (IUD) (if present) must be removed, consent must be obtained and patients must have the ability to access 24-hour emergency care if and when required for incomplete abortion or bleeding.

Commented [S22]: MS3: Removal of certification of practitioners

Commented [S22]: Rd 2 Clinical Evaluation Report (Q5)

4.3 CONTRAINDICATIONS

MS-2 Step should not be prescribed in the following situations:

- Lack of access to emergency medical care in the 14 days following start of the treatment (i.e. administration of mifepristone);
- Suspected or confirmed ectopic pregnancy;
- Asthma uncontrolled by therapy;
- Intrauterine device (IUD) in place;
- Uncertainty about gestational age;
- Chronic adrenal failure;
- Concurrent long term corticosteroid therapy;
- Suspected or known haemorrhagic disorders or treatment with anti-coagulants;
- Hypersensitivity to mifepristone, misoprostol (or any prostaglandin), or any of the excipients used in ***MS-2 Step***;
- Pregnancy not confirmed by an ultrasound or biological test such as urine or serum HCG;

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The prescriber must ensure that consent and treatment of the patient is in accordance with the appropriate state or territory legislation.

Commented [s22]: Rd 2 Clinical Evaluation report

If applicable, medical practitioner's advice should be sought in the event that further management of patients with medical comorbidities or adverse events is required.

Take special care in case of suspected acute adrenal failure. In case of suspected acute adrenal failure, dexamethasone administration is recommended (please refer to the dexamethasone Product Information).

Due to the antiglucocorticoid activity of mifepristone, the efficacy of long-term corticosteroid therapy, including inhaled corticosteroids in asthmatic patients, may be decreased during the 3 to 4 days following intake of mifepristone. Therapy should be adjusted.

Rare serious cardiovascular accidents have been reported following administration of prostaglandins including misoprostol. For this reason women with risk factors for cardiovascular disease or established cardiovascular disease should be treated with caution.

Although no epileptic seizures have been reported with misoprostol, some have been reported with prostaglandins and other prostaglandin analogues, and therefore this possibility should be borne in mind in patients with a history of epilepsy.

Bronchospasm may occur with some prostaglandins and prostaglandin analogues. The possibility should be borne in mind in patients with a history of asthma.

Severe cutaneous adverse reactions, including toxic epidermal necrolysis and acute generalised exanthematous pustulosis, have been reported in association with mifepristone (see **Section 4.8 ADVERSE EVENTS (UNDESIRABLE EFFECTS)**). In patients who experience severe cutaneous adverse reactions, treatment with mifepristone should be immediately discontinued. Re-treatment with mifepristone is not recommended.

Cases of skin rash following misoprostol administration were reported by patients in clinical trials. Angioedema of the face, lips, tongue, and/or larynx, including cases of anaphylaxis have been reported in post-market surveillance with the use of mifepristone and misoprostol, including angioedema occurring within an hour of misoprostol intake. Angioedema associated with upper airway swelling may be life threatening. If the tongue, hypopharynx, or larynx has been involved, appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided.

No data is available in patients with inherited porphyria.

In the case of a pregnancy occurring with an intra-uterine device in situ, this device must be removed before administration of Mifepristone Linepharma.

- ***Populations not studied:***

In the absence of specific studies, MS-2 Step is not recommended in patients with:

- Cardiovascular disease
- Hypertensive disease
- Hepatic disease
- Respiratory disease
- Renal disease
- Diabetes
- Severe anaemia
- Malnutrition
- Heavy smokers

Women who are older than 35 years and who also smoke 15+ cigarettes per day should be treated with caution because such patients were generally excluded from clinical trials of mifepristone.

- ***Specific precautions relating to medical termination of an intra-uterine pregnancy:***

- Ectopic pregnancy

Ectopic pregnancy should be excluded and gestation confirmed prior to medical abortion.

- Rhesus alloimmunisation

The use of MS-2 Step requires rhesus determination and hence the prevention of rhesus allo-immunisation.

- Explanation of requirements for the method

This method requires the involvement of the woman who should be informed of the requirements of the medical method, which involves:

- The necessity to take both Mifepristone Linepharma and GyMiso® in sequence according to instructions
- The need for follow-up within 14 to 21 days after intake of Mifepristone Linepharma in order to confirm that the abortion is complete
- The non-negligible risk of failure (see **Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical Trials**) of the medical method which may require termination by another method
- On discharge from the treatment centre all women should be provided with appropriate medications as necessary and be fully counselled regarding the likely signs and symptoms she may experience and have direct access to the treatment centre by telephone or local access

The expulsion may take place before GyMiso® administration (in about 3% of cases). This does not preclude the need for follow-up to confirm complete expulsion.

The following risks related to the medical method must be taken into account and explained to the woman:

- Failures

The non-negligible risk of failure (including continuing pregnancy and incomplete abortion), which occurs in up to 7% of cases prior to 63 days gestation, makes follow up mandatory in order to check that the expulsion is completed. Up to 63 days about 1% women will have continuing pregnancies, the rest needing curettage for other reasons.

Exposure of the fetus to misoprostol or mifepristone increases the risk of developing Moebius syndrome and/or an amniotic band syndrome and/or central nervous system anomalies (see **Section 4.6 FERTILITY, PREGNANCY AND LACTATION - Use in Pregnancy**). A second termination of pregnancy procedure shall be considered. In case of continuation of the pregnancy close monitoring by ultrasound scan must be performed in specialised centres.

In cases of non-complete expulsion, a surgical intervention may be necessary.

- Bleeding

The patient must be informed of the occurrence of prolonged vaginal bleeding (an average of 10 to 16 days after Mifepristone Linepharma and GyMiso® intake) which may be heavy. Bleeding occurs in almost all cases and is not in any way proof of complete expulsion. Persistent bleeding can be the consequence of incomplete expulsion. Bleeding can be large enough to necessitate a blood transfusion, in up to 0.2 % of cases up to 63 days gestation and to lead to a significant decrease in haemoglobin levels.

The patient should be informed not to travel far away from the prescribing centre as long as complete expulsion has not been recorded. She will receive precise instructions as to whom she should contact and where to go, in the event of any problems emerging, particularly in the case of very heavy vaginal bleeding.

As per the Royal College of Obstetricians and Gynaecologists guideline, *(The Care of Women Requesting Induced Abortion, November 2011)*, the following is recommended:

"Following abortion, women should be provided with verbal and written information about:

• symptoms they may experience, emphasising those which would necessitate an urgent medical consultation

• symptoms suggestive of continuing pregnancy.

Independent providers of abortion services should have arrangements in place for referring women to a public hospital emergency department for assessment and admission. ~~A 24-hour telephone helpline number should be available for women to use after abortion if they have any concerns.~~"

"On discharge, all women should be given a letter providing sufficient information about the procedure to allow another practitioner elsewhere to manage any complications".

Commented s22 MS3: Reference to 24-hour telephone helpline removed.

Follow-up must take place within a period of 14 to 21 days after administration of Mifepristone Linepharma to verify by the appropriate means (clinical examination, ultrasound scan, or beta-hCG measurement) that expulsion has been completed and that vaginal bleeding has stopped. In case of persistent bleeding (even light) beyond this follow-up, the disappearance of bleeding should be checked within a few days.

If an ongoing pregnancy is suspected, a further ultrasound scan may be required to evaluate its viability.

Persistence of vaginal bleeding at this point could signify incomplete abortion, or an unnoticed extra-uterine pregnancy, and appropriate treatment should be considered. In the event of an ongoing pregnancy diagnosed after follow-up, termination by another method will be offered to the woman.

Since heavy bleeding requiring haemostatic curettage occurs in up to 5 % of cases during the medical method of pregnancy termination, special care should be given to patients with haemostatic disorders with hypocoagulability, or with anaemia. The decision to use the medical or the surgical method should be decided with specialised consultants according to the type of haemostatic disorder and the level of anaemia.

- Infection

As with other types of abortion, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of mifepristone and misoprostol. No causal relationship between these events and the use of mifepristone and misoprostol has been established. Treating healthcare practitioners~~doctors~~ evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event and immediately seek a medical practitioner's (doctors) advice. In particular, a sustained fever of 38ºC or higher, severe abdominal pain, or pelvic tenderness in the days after a medical abortion may be an indication of infection.

Commented s22 Rd 2 Clinical Evaluation report

A high index of suspicion is needed to rule out sepsis (from e.g. *Clostridium sordellii* or other species e.g. Streptococcus) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhoea) more than 24 hours after taking misoprostol. However, the symptoms of *Clostridium sordellii* infection are sometimes not the usual symptoms of sepsis and very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, haemo-concentration, and general malaise. Therefore, the possibility of sepsis should be considered in all women who are undergoing medical termination and who present with nausea, vomiting, or diarrhoea and weakness with or without abdominal pain. These symptoms, even without a fever, may indicate *Clostridium sordellii* infection. Strong consideration should be given to obtaining a complete blood count in these patients. Significant leukocytosis with a marked left shift and haemo-concentration may be indicative of sepsis. Doctors should consider immediately initiating treatment with antibiotics that includes coverage of anaerobic bacteria such as *Clostridium sordellii*. Most of the reported deaths occurred in women who used vaginally administered misoprostol however deaths following other forms of administration have been reported. No causal relationship between

mifepristone and misoprostol use and an increased risk of infection or death has been established. *Clostridium sordellii* and other infections such as *Streptococcus* and other bacteria have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynaecologic and non-gynaecologic conditions. Reviews have estimated overall serious infection rates after medical abortion at less than 1%.

Use in the elderly

There is no relevant use of ***MS-2 Step*** in the elderly population in the indication.

Paediatric use

Limited data are available for use of ***MS-2 Step*** in women under 18 years of age.

There is no relevant use of ***MS-2 Step*** in the prepubertal paediatric population in the indication. Administration to adolescents less than 18 years of age should be undertaken with caution.

Effects on laboratory tests

There are no known effects of mifepristone or misoprostol on laboratory tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Mifepristone Linepharma

No interaction studies have been performed.

On the basis of mifepristone's metabolism by CYP3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum levels of mifepristone). Furthermore, rifampicin, dexamethasone, St. John's Wort and certain anticonvulsants (phenytoin, phenobarbital (phenobarbitone), carbamazepine) may induce mifepristone metabolism (lowering serum levels of mifepristone).

Based on *in vitro* information showing that mifepristone acts as a mechanism-based inhibitor of CYP3A4, co-administration of mifepristone may lead to an increase in serum levels of drugs that are CYP3A4 substrates. Due to the irreversible nature of the CYP binding and the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP3A4 substrates and have narrow therapeutic range, including some agents used during general anaesthesia.

GyMiso®

Misoprostol has no known drug interactions. No induction of the hepatic cytochrome P-450 enzyme system has been observed. The serum protein binding of misoprostol acid was not affected by indometacin, ranitidine, digoxin, phenylbutazone, warfarin, diazepam, methyldopa, propranolol, triamterene, cimetidine, paracetamol, ibuprofen, chlorpropamide and hydrochlorothiazide. With salicylic acid (300 µg/mL), the protein binding of misoprostol was lowered from 84 to 52% which is not considered clinically significant since the binding of misoprostol acid is not extensive and its elimination half-life is very short.

In laboratory studies, misoprostol has no significant effect on the cytochrome P450 linked hepatic mixed function oxidase system, and therefore should not affect the metabolism of theophylline, warfarin, benzodiazepines or other drugs normally metabolised by this system. No drug interactions have been attributed to misoprostol in extensive clinical trials. As such, other drugs would be unlikely to interfere with misoprostol's metabolism in either normal or hepatically-impaired patients.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

During clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses.

Mifepristone Linepharma

Mifepristone inhibited oestrus cycling in rats at oral doses of 0.3-1 mg/kg/day (less that the clinical dose adjusted for body surface area) in a 3-week study. This was reversed over the following 2-3 weeks and no subsequent effects on reproductive performance were found.

GyMiso®

In fertility studies in rats in which treated females were mated with treated males, increased pre-implantation losses were observed with misoprostol at oral doses greater than 1 mg/kg/day (11 times the recommended human dose, on a mg/m^2 basis). Post-implantation loss was also increased at 10 mg/kg/day (114 times the recommended human dose, on a mg/m^2 basis).

Use in pregnancy

Mifepristone Linepharma

In animals, the abortifacient effect of mifepristone precludes the proper assessment of any teratogenic effect of the molecule.

Fetal skull/brain malformations, presumed to be related to treatment, have been observed in rabbits and monkeys, but not mice or rats, treated with sub-abortive doses of mifepristone. These most likely occurred secondary to mifepristone's effect on the uterus due to antagonism of progesterone.

Delayed development of the righting reflex and slight inhibition of locomotor development were observed in rats when administered mifepristone at the high-dose level (1 mg/kg/day) from day 15 of gestation to the end of the lactation period (postnatal day 21).

A review of births from 105 pregnancies exposed during first trimester of pregnancy to mifepristone alone (46 cases) or to both mifepristone and misoprostol (59 cases) has recently been published. There were 94 live births (90.4%) and 10 (9.6%) miscarriages (including one with major malformation). Elective termination of pregnancy was performed after the subsequent diagnosis of trisomy 21 in one case. The overall rate of major congenital malformations was 4.2% (95% CI: 1.2 – 10.4%), with two cases among 38 patients exposed to mifepristone alone and two cases among 57 patients exposed to both mifepristone and misoprostol. In conclusion, this unique prospective study found that the rate of major malformations after exposure to mifepristone during the first trimester of pregnancy is only slightly higher than the expected 2 – 3% rate in the general population. Nevertheless, data in humans are still too limited to determine whether the molecule is a human teratogen.

GyMiso®

Use of misoprostol has been associated with birth defects. In a few cases where misoprostol was self-administered (orally or vaginally) in order to induce an abortion, the following deleterious effects of misoprostol have been suggested: malformations of limbs, of fetal movements and of cranial nerves (hypomimia, abnormalities in suckling, deglutition, and eye movements). To date, a risk of malformation cannot be excluded.

Reproductive toxicity studies in animals showed embryotoxicity (increased resorptions) with oral doses of 1 mg/kg/day in rabbits, 10 mg/kg/day in rats, and 20 mg/kg in mice when treatment occurred during the period of organogenesis. An increased incidence of skeletal abnormalities was observed with an oral dose of 1 mg/kg/day in rabbits (possibly due to maternal toxicity) while an increased incidence of cleft palate was seen at a single oral dose

of 30 mg/kg in mice (28 and 170 times the recommended human dose, on a mg/m^2 body surface area basis, respectively).

Failure of pregnancy termination (continuing pregnancy)

Use in pregnancy has been associated with an increased risk of birth defects/malformations for ongoing pregnancies exposed to mifepristone and misoprostol or misoprostol alone, compared to control group. In particular, prenatal exposure to misoprostol has been associated with Moebius syndrome (congenital facial paralysis leading to hypomimia, troubles of sucking and deglutition and eye movements, with or without limb defects) and with amniotic band syndrome (limb deformities/ amputations, especially clubfoot, acheiria, oligodactyly, cleft palate inter alia), and central nervous system anomalies (cerebral and cranial anomalies such as anencephaly, hydrocephaly, cerebellar hypoplasia, neural tube defects).

Women considering medical termination of pregnancy should be precisely counselled on the risks to their fetus if an abortion failure occurs and a second termination of pregnancy procedure is not desirable.

MS-2 Step

As a consequence of the above information on mifepristone and misoprostol:

- Women should be informed that due to the risk of failure of the medical method of pregnancy termination and to the unknown risk to the fetus, follow-up is very important (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).
- Should a failure of the medical method be diagnosed at follow-up (viable ongoing pregnancy), and should the patient still agree, pregnancy termination should be completed by another method.

Should the patient wish to continue with her pregnancy, she should be appropriately counselled as to the risk of birth defects. In that event of continuation of the pregnancy, careful ultra-sonographic monitoring of the pregnancy should be carried out.

To avoid the potential exposure of a subsequent pregnancy to MS-2 Step it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after administration of ***MS-2 Step***.

Use in lactation

Mifepristone is a lipophilic compound and may theoretically be excreted in the mother's breast milk. However, limited data are available. Misoprostol is rapidly metabolised in the mother to misoprostol acid, which is biologically active and is excreted in breast milk. This could cause undesirable effects such as diarrhoea in breast feeding infants. ***MS-2 Step*** use should be avoided during breast-feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most frequent undesirable effects which are observed during treatment with ***MS-2 Step*** are the following:

- Gastrointestinal disorders: nausea (transient and mild), vomiting, diarrhoea, abdominal pain.
- Reproductive system disorders: very frequent uterine contractions observed in the hours following the intake of the misoprostol component of the MS-2 Step pack; vaginal bleeding, sometimes heavy and prolonged (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

- General disorders: headache, dizziness, and chills and fever. (Because castor oil is an excipient of the misoprostol component of the ***MS-2 Step*** pack, digestive symptoms (nausea, vomiting, abdominal pain) can be observed).

The adverse events reported with mifepristone and a prostaglandin analogue such as GyMiso®, classified according to frequency and system organ class, are summarised as shown in Table 1~~Table 1~~.

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Table 1: Adverse Events for the Combined Use of Mifepristone and Misoprostol

MedDRA	Adverse events (frequency)				
System Organ Class	**Very common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1000 to < 1/100**	**Rare ≥ 1/10000 to < 1/1000 and very rare (< 1/10000)***	**Unknown frequency**
Infections and infestations			Infection	Toxic shock syndrome	
Neoplasms benign, malignant and unspecified				Elevated alpha-foeto protein Elevated carcinoembryonic antigen	
Blood and lymphatic system disorders				Thrombotic thrombocytopenic purpura Thrombocytopenia Induced systemic lupus erythematosus	
Psychiatric disorders				Mania	
Nervous system disorders	Headache Dizziness			Epilepsy Neurogenic tinnitus	
Eye disorders				Ophthalmoplegia	
Cardiac disorders				Myocardial infarction Induced Adam-Stokes syndrome Arrhythmia	
Vascular disorders			Hot flush Hypotension (0.25%)	Superficial thrombophlebitis	
Respiratory, thoracic and mediastinal disorders				Bronchospasm Induced bronchial asthma	

Table 1: **Adverse Events for the Combined Use of Mifepristone and Misoprostol**

MedDRA	**Adverse events (frequency)**				
System Organ Class	**Very common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1000 to < 1/100**	**Rare ≥ 1/10000 to < 1/1000 and very rare (< 1/10000)***	**Unknown frequency**
Gastrointestinal disorders	Nausea Vomiting Diarrhoea Gastric discomfort Abdominal pain	Cramping, light or moderate		Gastric bleeding Necrotising pancreatitis	
Hepatobiliary disorders				Abnormal liver function tests Hepatic failure Hepatorenal failure	
Skin and subcutaneous tissue disorders			Skin rash / pruritus	Urticarial reaction Toxic epidermal necrolysis Erythema nodosum Angioedema*	Acute generalized exanthematous pustulosis
Musculoskeletal and connective tissue disorders				Limb spasm	
Renal and urinary disorders				Renal failure	
Pregnancy, puerperium and perinatal conditions	Uterine contractions or cramping (10 to 45%) in the hours following prostaglandin intake.	Heavy bleeding occurs in about 5% of the cases and may require haemostatic curettage in up to 1.4% of the cases. Fetal malformations		Hydatiform mole Ectopic pregnancy Amniotic band syndrome Gestational trophoblastic tumor Uteroplacental apoplexy	
Reproductive system and breast disorders	Vaginal bleeding Uterine spasm	Prolonged post-abortion bleeding Spotting Severe haemorrhage Endometritis Breast tenderness Heavy bleeding	Haemorrhagic shock Salpingitis	Bilateral adnexal mass Intrauterine adhesion Ovarian cyst rupture Breast abscess Haematosalpynx Uterine rupture	

Table 1: **Adverse Events for the Combined Use of Mifepristone and Misoprostol**					
MedDRA	**Adverse events (frequency)**				
System Organ Class	**Very common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1000 to < 1/100**	**Rare ≥ 1/10000 to < 1/1000 and very rare (< 1/10000)***	**Unknown frequency**
General disorders and administration site conditions	Fatigue Chill / fever	Fainting		Anaphylaxis Periorbital edema Vagal symptoms	

*Including occasional case reports

- Post-marketing experience indicates that death can occur as a result of medical termination of pregnancy (although this is a very rare outcome, <1 in 100,000). The reported deaths were due to sepsis (fatal toxic shock syndrome) associated with *Clostridium sordellii*, which also occurs in association with childbirth and spontaneous termination. The symptoms of *Clostridium sordellii* infection are sometimes not the usual symptoms of sepsis. Therefore, the possibility of sepsis should be considered in all women who are undergoing medical termination and who present with nausea, vomiting, or diarrhoea and weakness, with or without abdominal pain. These symptoms, even without a fever, may indicate *Clostridium sordellii* infection. Strong consideration should be given to obtaining a complete blood count in these patients. Significant leukocytosis with a marked left shift and haemo-concentration may be indicative of sepsis. Doctors should consider immediately initiating treatment with antibiotics that includes coverage of anaerobic bacteria such as *Clostridium sordellii*. Refer to **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**.

- Bleeding is an almost constant part of the procedure, whatever the prostaglandin analogue used, and at any pregnancy term, although it is usually more abundant when pregnancy age increases. It can occur after mifepristone alone. When heavy, it usually reflects incomplete abortion and is observed in approximately 3 to 12% of cases, depending on the pregnancy age and the prostaglandin analogue used, and needs specific treatment. It can necessitate a blood transfusion in up to 0.2% of cases. It can be prolonged for several days after prostaglandin analogue administration and sometimes leads to a decrease in haemoglobin levels. This potentially severe complication justifies that after intake (i) follow-up takes place approximately 14 to 21 days after Mifepristone Linepharma administration to ensure that expulsion is complete with no persisting bleeding and (ii) until follow-up has taken place, the woman remains close to a facility where she can be treated at any moment in case of severe or prolonged bleeding. Refer to **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**.

The issue of the outcome of persisting pregnancy in the case of failure of the medical method remains incompletely solved; a risk of malformation attributable to mifepristone or to prostaglandin analogues such as misoprostol cannot be excluded, and women should be adequately counselled in such a situation. Another fact to take into consideration is the possibility of a pregnancy persisting in the form of an ectopic pregnancy, since evidence suggests that the method does not appear able to terminate an ectopic pregnancy.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems and to MS Health at 1300 515 883.

4.9 OVERDOSE

Mifepristone Linepharma

No case of overdose has been reported.

In the event of massive ingestion signs of adrenal failure might occur. Signs of acute intoxication may require specialist treatment including the administration of dexamethasone.

GyMiso®

The toxic dose of misoprostol in humans has not been determined. Cumulative total daily doses of 1600 micrograms have been tolerated, with only symptoms of gastrointestinal discomfort reported.

Clinical signs that may indicate an overdose are sedation, tremor, convulsions, dyspnoea, abdominal pain, diarrhoea, fever, palpitations, hypotension or bradycardia. Hypertension and tachycardia have also been reported following overdoses. Overdose in pregnancy has resulted in uterine contractions with fetal death.

There is no specific antidote. Treatment should be symptomatic and supportive. Consider administration of activated charcoal in the event of a potentially toxic ingestion. Activated charcoal may reduce absorption of misoprostol if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Mifepristone Linepharma

Pharmacotherapeutic group: Other Sex Hormone and Modulator of the Reproductive function/ Antiprogestogen. ATC code: GO3XB01

Mifepristone is a synthetic steroid with an antiprogestational action as a result of competition with progesterone at the progesterone receptors.

Mifepristone binds to human progesterone receptors with nanomolar affinity. In animals, oral administration was shown to inhibit the action of endogenous or exogenous progesterone in multiple species (rat, mouse, rabbit, dog and monkey). This action is manifested in the form of pregnancy termination.

In women at doses of greater than or equal to 1 mg/kg, mifepristone antagonises the endometrial and myometrial effects of progesterone. During pregnancy it sensitises the myometrium to the contraction inducing action of prostaglandins. While clinical data have demonstrated that mifepristone facilitates dilatation of the cervix, no data are available to indicate that this results in a lowering of the rate of early or late complications to the dilatation procedure.

In the event of an early termination of pregnancy, the combination of a prostaglandin analogue used in a sequential regimen after mifepristone leads to an increase in the success rate and accelerates the expulsion of the conceptus.

Mifepristone binds to the glucocorticoid receptor with affinity comparable to that for the progesterone receptor. Full inhibition of the action of dexamethasone was evident in rats at oral doses 0.5-1.1 times the human dose adjusted for body surface area. In man the

antiglucocorticoid action is manifested at a dose equal to or greater than 4.5 mg/kg by a compensatory elevation of ACTH and cortisol.

Mifepristone also has some anti-androgenic activity. In toxicological studies in rats and monkeys up to a duration of 6 months, mifepristone produced effects related to its antihormonal (antiprogesterone, antiglucocorticoid and antiandrogenic) activity.

GyMiso®

Pharmacotherapeutic group: Other gynecological medicines – prostaglandins. ATC code: G02AD06

Misoprostol is a synthetic analogue of prostaglandin E1. At the recommended dosages, misoprostol induces contractions of the smooth muscle fibers in the myometrium and relaxation of the uterine cervix. The uterotonic properties of misoprostol should facilitate cervical opening and evacuation of intrauterine debris.

In the event of an early termination of pregnancy, the combination of GyMiso® used in a sequential regimen after mifepristone leads to an increase in the success rate and accelerates the expulsion of the conceptus.

Pharmacodynamic studies in early pregnancy have found an increase in uterine tone around 8 minutes after oral and 40 minutes after buccal misoprostol, with sustained contractions achieved by a mean of around 90 minutes and uterine activity peaking prior to 5 hours. Following oral administration uterine activity rises earlier than other routes, but is lower overall. Pretreatment with mifepristone has previously been shown to increase uterine contractility in response to misoprostol.

Clinical trials

Clinical efficacy of early medical abortion is defined as complete abortion without surgical intervention, regardless of the reason for the intervention, which may include continuing pregnancy, missed or incomplete abortion, prolonged or heavy vaginal bleeding or a woman's request.

An open-label single-group prospective trial performed in Mexico by Gynuity Healthcare, USA, involving 971 women available for efficacy treated with 200 mg mifepristone followed by 800 micrograms misoprostol administered buccally indicated that efficacy was 98.0, 96.8 and 95.9% for women with gestational age 49 days and below, 50-56 days and 57-63 days, respectively. In these 3 gestational age groups, the rate of surgical evacuation was 2.0, 3.2 and 4.1% respectively. In this study 25 women received a second dose of misoprostol, in each case, a dose of 800 micrograms by the buccal route. Of those 25, 20 had a successful outcome with medication alone, 4 had a surgical intervention and 1 woman did not return for follow up. In this study, bleeding occurred in all women independent of outcome, and was judged as more than expected in 27.1% of the women.

In an Authorised Prescribers Program in Australia in 2012 that included 7,166 women, efficacy was 97.4% for women with gestational age <49 days, and 95.2% for women with gestational age of 49-63 days. The rate of incomplete termination requiring aspiration was: <49 days: 2.3%; 49-63 days: 4.8%. The rate of ongoing pregnancies was: <49 days: 0.3%; 49-63 days: 0.6%. Bleeding was considered as an adverse event in 0.24% of women, independent of pregnancy age.

Studies published in the literature have reported mifepristone and oral or buccal misoprostol regimens. In one study of 966 patients[1] with pregnancies up to gestational age of 63 days, randomised to 200 mg mifepristone followed 24-36 hours later by 800 micrograms of misoprostol orally or buccally, reported efficacy rates were 91.3% for the oral and 96.2% for the buccal group (RR 0.95, 95% CI 0.92-0.98, p=0.003).

[1] Winikoff B et al. Obstetr Gynecol 2008, 1303-10

Studies published on the combination of mifepristone 200 mg and misoprostol 800 micrograms buccally, and reporting outcomes by gestational age, encompass 399 women with gestational ages 50 – 56 days and 344 women with gestational ages 57 – 63[2][3][4][5][6][7] days. Efficacy ranged from 86.5 to 98.5% in women with gestational age 50 – 56 days and from 93.0 to 100% in those with gestational age 57 – 63 days. In these studies, the rate of ongoing pregnancies ranged from 0 to 7.1% in women with gestational age 50 – 56 days and from 0 to 2.3% in those with gestational age 57 – 63 days.

Literature data provides information on the bleeding and expulsion pattern after termination of pregnancy with mifepristone and misoprostol: approximately half of women start to bleed before prostaglandin administration. Median bleeding time is 10 to 16 days. Bleeding is judged more or much more abundant than usual menses for 2 to 3 days after prostaglandin. In studies where it was measured, there was a slight but significant decrease in haemoglobin level after compared to baseline. In one study blood loss was quantified: the median blood loss was 83 mL and 5.4% of women had a blood loss above 200 mL. Expulsion usually takes place within 3 hours after misoprostol in approximately half of the women, and within 4 hours after misoprostol in approximately 50 to 90% of women.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Mifepristone Linepharma

After oral administration of a single dose of 200 mg, mifepristone is rapidly absorbed. The peak concentration of 2.3 to 2.7 mg/L is reached after 0.75 hours (mean of 49 subjects). The half-life of mifepristone is 36.5 to 38.3 hours.

Mifepristone shows non-linear pharmacokinetics. Following the distribution phase the elimination is at first slow, with a half-life of approximately 12 to 72 hours, and then the concentration is more rapidly reduced with a half-life of 18 hours. With radio-receptor analysis, the final half-life is shown to be up to 90 hours, including all mifepristone metabolites that can bind to progesterone receptors.

After administration of low doses of mifepristone (20 mg orally or intravenously), the absolute bioavailability is 69%.

GyMiso®

When administered orally, misoprostol is rapidly absorbed and metabolised. Peak concentrations around 1.1 ng/mL were reached about 15 minutes after a 400 µg dose in the fasting state. Plasma concentrations of its main degradation metabolite, misoprostol acid, reach their peak of 2 - 2.5 ng/mL after a 2 µg/kg oral dose within approximately 30 minutes and rapidly decline thereafter. As a result, uterine contractility increases and then plateaus after about one hour. Absorption is almost complete, measured at levels between 64 - 73% from urinary data.

For a single oral administration of 800 micrograms misoprostol (4 tablets of 200 micrograms GyMiso®), AUC_{0-t} was 1.9709 ± 0.8130 hr.ng/mL, $AUC_{0-\infty}$ was 2.0192 ± 0.8032 hr.ng/mL and C_{max} was 2.6830 ± 1.2161 ng/mL. For a single buccal administration of 800 micrograms misoprostol (4 tablets of 200 micrograms GyMiso®), AUC_{0-t} was 1.9095 ± 0.2909 hr.ng/mL, $AUC_{0-\infty}$ was 2.0726 ± 0.3578 hr.ng/mL and C_{max} was 1.3611 ± 0.3436 ng/mL. For a single sublingual administration of 800 micrograms misoprostol (4 tablets of 200 micrograms

[2] Chong et al 2012 Contraception 86, 251–256
[3] Fjerstad et al 2009 Contraception 80, 282-286
[4] Boersma et al 2011 Eur J of Contraception & Reproductive Health Care 16, 61-66
[5] Ngoc et al 2011 Contraception 83, 410 – 417
[6] Blum et al 2012 Int J Gynecol Obstetr 118, 166 - 171
[7] WHO 2000 Br J Obstetr Gynecol 107, 524-30

GyMiso®), AUC_{0-t} was 3.0574 ± 0.9872 hr.ng/mL, $AUC_{0-\infty}$ was 3.2094 ±1.0417 hr.ng/mL and C_{max} was 2.4391 ± 1.1567 ng/mL. For log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}, there were statistically significant differences between 3 treatment groups (p = 0.0159, 0.0162 and 0.0083, respectively). Sublingual administration of misoprostol had a higher $AUC_{0-\infty}$ compared with buccal and oral administration which indicated bioavailability was higher by the sublingual route. Misoprostol sublingual and oral administration resulted in higher C_{max} compared with buccal. The C_{max} of buccal administration was achieved later compared with other routes of administration. No difference was found when comparing oral, sublingual and buccal half-lives (p= 0.4495).

Distribution

Mifepristone Linepharma

In plasma, mifepristone is 98% bound to plasma proteins: albumin and principally alpha-1-acid glycoprotein (AAG), to which binding is saturable. Due to this specific binding, the volume of distribution and plasma clearance of mifepristone are inversely proportional to the plasma concentration of AAG.

GyMiso®

Serum protein binding of labeled misoprostol acid was studied in man and was similar in young (81-88%) and elderly (81-89%) subjects. Accumulation in erythrocytes was not seen.

Metabolism

Mifepristone Linepharma

N mono- and di-demethylation and terminal hydroxylation of the 17-propynyl chain are primary metabolic pathways of hepatic oxidative metabolism. Metabolites are detectable in plasma 1 hour after ingestion of mifepristone. Plasma AUC for the dominant metabolite, monodemethylated mifepristone, is approximately double that of the unchanged mifepristone at the clinical dose, and this metabolite retains significant affinity for the progesterone receptor. The other metabolites also display some progesterone receptor affinity (approximately 10 to 15% that of mifepristone). The metabolites may contribute to the pharmacological effects of mifepristone.

In vitro CYP3A4 appears as the isoenzyme primarily responsible for mifepristone demethylation and hydroxylation in human liver microsomes. CYP3A4 substrates progesterone and midazolam inhibited metabolite formation by up to 77%. Other isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1) had apparently no action on mifepristone metabolism.

GyMiso®

Metabolism of misoprostol to misoprostol acid is rapid with no intact misoprostol found in plasma consistent with an *in vitro* half-life of 6.4 minutes for de-esterification of misoprostol in human plasma at 37ºC. Elimination of misoprostol and its metabolites is also rapid with a plasma elimination half-life of 35 minutes.

Excretion

Mifepristone Linepharma

After administration of 600 mg radiolabelled mifepristone, 10% of the total radioactivity was recovered in urine and 90% in faeces.

GyMiso®

The liver is the primary site of metabolism and between 1-4% of misoprostol acid is excreted in the urine.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Mifepristone Linepharma

Mifepristone has been evaluated in tests for mutagenicity in bacterial, yeast and mammalian cells; gene conversion in yeast; unscheduled DNA synthesis in HeLa cells; and for clastogenicity *in vitro* (Chinese hamster ovary cells) and in vivo (mouse bone marrow micronucleus test). No evidence of genotoxicity was observed.

GyMiso®

Misoprostol has been evaluated in tests for mutagenicity in bacterial, yeast and mammalian cells; and for clastogenicity *in vitro* (Chinese hamster ovary cells) and *in vivo* (mouse bone marrow micronucleus test). No evidence of genotoxicity was observed.

Carcinogenicity

Mifepristone Linepharma

No long-term animal carcinogenicity studies have been conducted with mifepristone. Based on the negative genotoxicity results, findings in general repeat-dose toxicity studies and considering the pattern of clinical use, mifepristone is not predicted to pose a particular carcinogenic risk.

GyMiso®

The potential carcinogenicity of misoprostol has been evaluated in both mice and rats. There was no evidence of an effect of misoprostol on tumour occurrence or incidence in rats receiving oral doses up to 2.4 mg/kg/day for 24 months. Similarly, there was no effect of misoprostol on tumour occurrence or incidence in mice receiving oral doses up to 16 mg/kg/day for 21 months. These doses are at least 27 times the recommended human dose, on a mg/m^2 body surface area basis.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mifepristone Linepharma 200 mg tablet contains the following excipients: maize starch, povidone, microcrystalline cellulose, colloidal anhydrous silica and magnesium stearate.

GyMiso® contains the following excipients: hypromellose, microcrystalline cellulose, sodium starch glycollate type A and hydrogenated castor oil.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Do not use after the expiry date printed on the carton labels of the composite pack and the individual components.

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C, keep in the original container to protect from light.

Keep out of reach of children.

Mifepristone Linepharma

Keep in the original green carton in order to protect from light

GyMiso®

Keep in the original purple carton

6.5 NATURE AND CONTENTS OF CONTAINER

Each ***MS-2 Step*** composite pack consists of:

- 1 green carton containing Mifepristone Linepharma 200 mg tablet packaged in a PVC/PVDC/Aluminium blister. Pack size of 1 tablet.
- 1 purple carton containing GyMiso® misoprostol 200 microgram tablet packaged in a dual-faced Aluminium blister. Pack size of 4 tablets (2 tablets per blister).

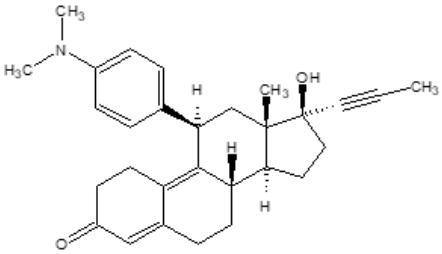
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Mifepristone

Chemical structure



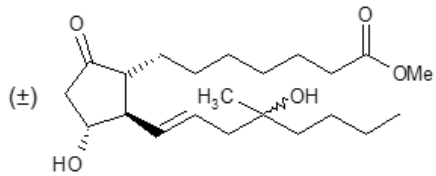
Molecular formula: $C_{29}H_{35}NO_2$ Molecular weight: 429.6

CAS number

CAS Registry Number: 84371-65-3

GyMiso®

Chemical Structure



Molecular formula:$C_{22}H_{38}O_5$ Molecular weight: 382.5

CAS number

CAS Registry Number: 59122-46-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8 SPONSOR

MS Health Pty Ltd
Suite 60, 278 Church Street,
Richmond, VIC, Australia, 3121
Ph: 1300 515 883

MS-2 Step® is a registered trademark of MSI Reproductive Choices (UK). Mifepristone Linepharma and GyMiso® are licensed from Linepharma International Limited (UK).

9 DATE OF FIRST APPROVAL

4 June 2014

10 DATE OF REVISION

~~23rd August 2022~~TBC

11 SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
~~4.3~~	~~Additional contraindications added to align with CCDS~~
~~4.4~~	~~Additional precautions added to align with CCDS~~
~~4.8~~	~~Arrhythmia and Fetal malformations added as an additional AE~~
~~8~~	~~Sponsor contact number added and trademark statement updated~~
~~All~~	~~Editorial changes made throughout PI.~~
Black box and 4.2	Medical practitioner /doctor changed to healthcare practitioner

4.2	Certification of doctors removed
4.4	Reference to 24-hour help line in guideline removed and instructions for further medical advice added.

AUSTRALIAN PRODUCT INFORMATION

MS-2-STEP

(Mifepristone and Misoprostol)

Tablets

It is very important that all patients receiving these medications are followed up by a healthcare practitioner, preferably the prescriber, to ensure that the medication has been effective. Even if no adverse events have occurred all patients must receive follow-up 14 to 21 days after taking mifepristone. Read the **Section *4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE*** carefully*.*

This document refers to the use of ***MS-2 Step***, which consists of Mifepristone Linepharma 200 mg tablet and GyMiso® misoprostol 200 microgram tablets in combination. These medicines are indicated in females of childbearing age for the medical termination of an intrauterine pregnancy, up to 63 days of gestation. The Mifepristone Linepharma 200 mg tablet component of this therapy is also used to treat another condition. For information about the treatment of the other condition, refer to the full Product Information for Mifepristone Linepharma 200 mg tablet individual product (AUST R 175671).

1 NAME OF THE MEDICINE

Mifepristone and Misoprostol

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

MS-2 Step is a composite pack containing:

Mifepristone Linepharma

Each tablet contains 200 mg of mifepristone.

For the full list of excipients, see **Section 6.1 LIST OF EXCIPIENTS**.

GyMiso®

Each tablet contains 200 micrograms of misoprostol as a 1% dispersion of misoprostol-hypromellose. Misoprostol is a clear, colourless or yellowish oily liquid.

For the full list of excipients, see **Section 6.1 LIST OF EXCIPIENTS**.

3 PHARMACEUTICAL FORM

Mifepristone Linepharma

White to off-white, round biconvex tablets, diameter 11 mm, with “MF” debossed on one side of the tablet.

GyMiso®

White, flat round tablet with “ML” debossed on one side and “200” on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

MS-2 Step is indicated in females of childbearing age for the medical termination of an intrauterine pregnancy, up to 63 days of gestation.

It is recommended that the duration of pregnancy (i.e., up to 63 days gestation) be confirmed by ultrasound. In the event that an ultrasound is not possible, extra caution should be exercised.

Ultrasound is also useful to exclude ectopic pregnancy

4.2 DOSE AND METHOD OF ADMINSTRATION

MS-2 Step is indicated for medical termination of intrauterine pregnancy, up to 63 days of gestation.

The method of administration is as follows:

Mifepristone: 200 mg of mifepristone (1 tablet containing 200 mg) orally, followed 36 to 48 hours later by the administration of GyMiso®.

GyMiso®: 800 micrograms of misoprostol (4 tablets, each tablet containing 200 micrograms) buccally, i.e: kept between the cheek and the gum for 30 minutes before any fragments being swallowed with water.

When ***MS-2 Step*** fails to cause termination of intra-uterine pregnancy, the patient should return to the treating healthcare practitioner for assessment and discussion of treatment options, which may include pregnancy termination by surgery.

No dosage adjustment of misoprostol or mifepristone is necessary with renal or hepatic insufficiency when administered at the recommended doses.

There are no data available on the effect of food intake on the absorption of mifepristone or misoprostol. MS-2 Step should be taken 2 hours before or 2 hours after a meal.

Refer also to **4.3 CONTRAINDICATIONS**, and **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.**

MS-2 Step should only be prescribed by healthcare practitioners with the appropriate qualifications and training. Ectopic pregnancy should be excluded, an intrauterine device (IUD) (if present) must be removed, consent must be obtained and patients must have the ability to access 24-hour emergency care if and when required for incomplete abortion or bleeding.

4.3 CONTRAINDICATIONS

MS-2 Step should not be prescribed in the following situations:

- Lack of access to emergency medical care in the 14 days following start of the treatment (i.e. administration of mifepristone);
- Suspected or confirmed ectopic pregnancy;
- Asthma uncontrolled by therapy;
- Intrauterine device (IUD) in place;
- Uncertainty about gestational age;
- Chronic adrenal failure;
- Concurrent long term corticosteroid therapy;
- Suspected or known haemorrhagic disorders or treatment with anti-coagulants;
- Hypersensitivity to mifepristone, misoprostol (or any prostaglandin), or any of the excipients used in ***MS-2 Step****;*
- Pregnancy not confirmed by an ultrasound or biological test such as urine or serum HCG;

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The prescriber must ensure that consent and treatment of the patient is in accordance with the appropriate state or territory legislation.

If applicable, medical practitioner's advice should be sought in the event that further management of patients with medical comorbidities or adverse events is required.

Take special care in case of suspected acute adrenal failure. In case of suspected acute adrenal failure, dexamethasone administration is recommended (please refer to the dexamethasone Product Information).

Due to the antiglucocorticoid activity of mifepristone, the efficacy of long-term corticosteroid therapy, including inhaled corticosteroids in asthmatic patients, may be decreased during the 3 to 4 days following intake of mifepristone. Therapy should be adjusted.

Rare serious cardiovascular accidents have been reported following administration of prostaglandins including misoprostol. For this reason women with risk factors for cardiovascular disease or established cardiovascular disease should be treated with caution.

Although no epileptic seizures have been reported with misoprostol, some have been reported with prostaglandins and other prostaglandin analogues, and therefore this possibility should be borne in mind in patients with a history of epilepsy.

Bronchospasm may occur with some prostaglandins and prostaglandin analogues. The possibility should be borne in mind in patients with a history of asthma.

Severe cutaneous adverse reactions, including toxic epidermal necrolysis and acute generalised exanthematous pustulosis, have been reported in association with mifepristone (see **Section 4.8 ADVERSE EVENTS (UNDESIRABLE EFFECTS))**. In patients who experience severe cutaneous adverse reactions, treatment with mifepristone should be immediately discontinued. Re-treatment with mifepristone is not recommended.

Cases of skin rash following misoprostol administration were reported by patients in clinical trials. Angioedema of the face, lips, tongue, and/or larynx, including cases of anaphylaxis have been reported in post-market surveillance with the use of mifepristone and misoprostol, including angioedema occurring within an hour of misoprostol intake. Angioedema associated with upper airway swelling may be life threatening. If the tongue, hypopharynx, or larynx has been involved, appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided**.**

No data is available in patients with inherited porphyria.

In the case of a pregnancy occurring with an intra-uterine device in situ, this device must be removed before administration of Mifepristone Linepharma.

- ***Populations not studied:***

In the absence of specific studies, MS-2 Step is not recommended in patients with:

- Cardiovascular disease
- Hypertensive disease
- Hepatic disease
- Respiratory disease
- Renal disease
- Diabetes
- Severe anaemia
- Malnutrition
- Heavy smokers

Women who are older than 35 years and who also smoke 15+ cigarettes per day should be treated with caution because such patients were generally excluded from clinical trials of mifepristone.

- ***Specific precautions relating to medical termination of an intra-uterine pregnancy:***

- Ectopic pregnancy

Ectopic pregnancy should be excluded and gestation confirmed prior to medical abortion.

- Rhesus alloimmunisation

The use of MS-2 Step requires rhesus determination and hence the prevention of rhesus allo-immunisation.

- Explanation of requirements for the method

This method requires the involvement of the woman who should be informed of the requirements of the medical method, which involves:

- The necessity to take both Mifepristone Linepharma and GyMiso® in sequence according to instructions
- The need for follow-up within 14 to 21 days after intake of Mifepristone Linepharma in order to confirm that the abortion is complete
- The non-negligible risk of failure (see **Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical Trials**) of the medical method which may require termination by another method
- On discharge from the treatment centre all women should be provided with appropriate medications as necessary and be fully counselled regarding the likely signs and symptoms she may experience and have direct access to the treatment centre by telephone or local access

The expulsion may take place before GyMiso® administration (in about 3% of cases). This does not preclude the need for follow-up to confirm complete expulsion.

The following risks related to the medical method must be taken into account and explained to the woman:

- Failures

The non-negligible risk of failure (including continuing pregnancy and incomplete abortion), which occurs in up to 7% of cases prior to 63 days gestation, makes follow up mandatory in order to check that the expulsion is completed. Up to 63 days about 1% women will have continuing pregnancies, the rest needing curettage for other reasons.

Exposure of the fetus to misoprostol or mifepristone increases the risk of developing Moebius syndrome and/or an amniotic band syndrome and/or central nervous system anomalies (see **Section 4.6 FERTILITY, PREGNANCY AND LACTATION - Use in Pregnancy**). A second termination of pregnancy procedure shall be considered. In case of continuation of the pregnancy close monitoring by ultrasound scan must be performed in specialised centres.

In cases of non-complete expulsion, a surgical intervention may be necessary.

- Bleeding

The patient must be informed of the occurrence of prolonged vaginal bleeding (an average of 10 to 16 days after Mifepristone Linepharma and GyMiso® intake) which may be heavy. Bleeding occurs in almost all cases and is not in any way proof of complete expulsion. Persistent bleeding can be the consequence of incomplete expulsion. Bleeding can be large enough to necessitate a blood transfusion, in up to 0.2 % of cases up to 63 days gestation and to lead to a significant decrease in haemoglobin levels.

The patient should be informed not to travel far away from the prescribing centre as long as complete expulsion has not been recorded. She will receive precise instructions as to whom she should contact and where to go, in the event of any problems emerging, particularly in the case of very heavy vaginal bleeding.

As per the Royal College of Obstetricians and Gynaecologists guideline, *(The Care of Women Requesting Induced Abortion, November 2011)*, the following is recommended:

"Following abortion, women should be provided with verbal and written information about:

• symptoms they may experience, emphasising those which would necessitate an urgent medical consultation

• symptoms suggestive of continuing pregnancy.

Independent providers of abortion services should have arrangements in place for referring women to a public hospital emergency department for assessment and admission. "

"On discharge, all women should be given a letter providing sufficient information about the procedure to allow another practitioner elsewhere to manage any complications".

Follow-up must take place within a period of 14 to 21 days after administration of Mifepristone Linepharma to verify by the appropriate means (clinical examination, ultrasound scan, or beta-hCG measurement) that expulsion has been completed and that vaginal bleeding has stopped. In case of persistent bleeding (even light) beyond this follow-up, the disappearance of bleeding should be checked within a few days.

If an ongoing pregnancy is suspected, a further ultrasound scan may be required to evaluate its viability.

Persistence of vaginal bleeding at this point could signify incomplete abortion, or an unnoticed extra-uterine pregnancy, and appropriate treatment should be considered. In the event of an ongoing pregnancy diagnosed after follow-up, termination by another method will be offered to the woman.

Since heavy bleeding requiring haemostatic curettage occurs in up to 5 % of cases during the medical method of pregnancy termination, special care should be given to patients with haemostatic disorders with hypocoagulability, or with anaemia. The decision to use the medical or the surgical method should be decided with specialised consultants according to the type of haemostatic disorder and the level of anaemia.

o Infection

As with other types of abortion, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of mifepristone and misoprostol. No causal relationship between these events and the use of mifepristone and misoprostol has been established. Treating healthcare practitioners evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event and immediately seek a medical practitioner's (doctors) advice. In particular, a sustained fever of 38ºC or higher, severe abdominal pain, or pelvic tenderness in the days after a medical abortion may be an indication of infection.

A high index of suspicion is needed to rule out sepsis (from e.g. *Clostridium sordellii* or other species e.g. Streptococcus) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhoea) more than 24 hours after taking misoprostol. However, the symptoms of *Clostridium sordellii* infection are sometimes not the usual symptoms of sepsis and very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, haemo-concentration, and general malaise. Therefore, the possibility of sepsis should be considered in all women who are undergoing medical termination and who present with nausea, vomiting, or diarrhoea and weakness with or without abdominal pain. These symptoms, even without a fever, may indicate *Clostridium sordellii* infection. Strong consideration should be given to obtaining a complete blood count in these patients. Significant leukocytosis with a marked left shift and haemo-concentration may be indicative of sepsis. Doctors should consider immediately initiating treatment with antibiotics that includes coverage of anaerobic bacteria such as *Clostridium sordellii*. Most of the reported deaths occurred in women who used vaginally administered misoprostol however deaths following other forms of administration have been reported. No causal relationship between mifepristone and misoprostol use and an increased risk of infection or death has been

established. *Clostridium sordellii* and other infections such as *Streptococcus* and other bacteria have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynaecologic and non-gynaecologic conditions. Reviews have estimated overall serious infection rates after medical abortion at less than 1%.

Use in the elderly

There is no relevant use of ***MS-2 Step*** in the elderly population in the indication.

Paediatric use

Limited data are available for use of ***MS-2 Step*** in women under 18 years of age.

There is no relevant use of ***MS-2 Step*** in the prepubertal paediatric population in the indication. Administration to adolescents less than 18 years of age should be undertaken with caution.

Effects on laboratory tests

There are no known effects of mifepristone or misoprostol on laboratory tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Mifepristone Linepharma

No interaction studies have been performed.

On the basis of mifepristone's metabolism by CYP3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum levels of mifepristone). Furthermore, rifampicin, dexamethasone, St. John's Wort and certain anticonvulsants (phenytoin, phenobarbital (phenobarbitone), carbamazepine) may induce mifepristone metabolism (lowering serum levels of mifepristone).

Based on *in vitro* information showing that mifepristone acts as a mechanism-based inhibitor of CYP3A4, co-administration of mifepristone may lead to an increase in serum levels of drugs that are CYP3A4 substrates. Due to the irreversible nature of the CYP binding and the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP3A4 substrates and have narrow therapeutic range, including some agents used during general anaesthesia.

GyMiso®

Misoprostol has no known drug interactions. No induction of the hepatic cytochrome P-450 enzyme system has been observed. The serum protein binding of misoprostol acid was not affected by indometacin, ranitidine, digoxin, phenylbutazone, warfarin, diazepam, methyldopa, propranolol, triamterene, cimetidine, paracetamol, ibuprofen, chlorpropamide and hydrochlorothiazide. With salicylic acid (300 µg/mL), the protein binding of misoprostol was lowered from 84 to 52% which is not considered clinically significant since the binding of misoprostol acid is not extensive and its elimination half-life is very short.

In laboratory studies, misoprostol has no significant effect on the cytochrome P450 linked hepatic mixed function oxidase system, and therefore should not affect the metabolism of theophylline, warfarin, benzodiazepines or other drugs normally metabolised by this system. No drug interactions have been attributed to misoprostol in extensive clinical trials. As such, other drugs would be unlikely to interfere with misoprostol's metabolism in either normal or hepatically-impaired patients.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

During clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses.

Mifepristone Linepharma

Mifepristone inhibited oestrus cycling in rats at oral doses of 0.3-1 mg/kg/day (less that the clinical dose adjusted for body surface area) in a 3-week study. This was reversed over the following 2-3 weeks and no subsequent effects on reproductive performance were found.

GyMiso®

In fertility studies in rats in which treated females were mated with treated males, increased pre-implantation losses were observed with misoprostol at oral doses greater than 1 mg/kg/day (11 times the recommended human dose, on a mg/m^2 basis). Post-implantation loss was also increased at 10 mg/kg/day (114 times the recommended human dose, on a mg/m^2 basis).

Use in pregnancy

Mifepristone Linepharma

In animals, the abortifacient effect of mifepristone precludes the proper assessment of any teratogenic effect of the molecule.

Fetal skull/brain malformations, presumed to be related to treatment, have been observed in rabbits and monkeys, but not mice or rats, treated with sub-abortive doses of mifepristone. These most likely occurred secondary to mifepristone's effect on the uterus due to antagonism of progesterone.

Delayed development of the righting reflex and slight inhibition of locomotor development were observed in rats when administered mifepristone at the high-dose level (1 mg/kg/day) from day 15 of gestation to the end of the lactation period (postnatal day 21).

A review of births from 105 pregnancies exposed during first trimester of pregnancy to mifepristone alone (46 cases) or to both mifepristone and misoprostol (59 cases) has recently been published. There were 94 live births (90.4%) and 10 (9.6%) miscarriages (including one with major malformation). Elective termination of pregnancy was performed after the subsequent diagnosis of trisomy 21 in one case. The overall rate of major congenital malformations was 4.2% (95% CI: 1.2 – 10.4%), with two cases among 38 patients exposed to mifepristone alone and two cases among 57 patients exposed to both mifepristone and misoprostol. In conclusion, this unique prospective study found that the rate of major malformations after exposure to mifepristone during the first trimester of pregnancy is only slightly higher than the expected 2 – 3% rate in the general population. Nevertheless, data in humans are still too limited to determine whether the molecule is a human teratogen.

GyMiso®

Use of misoprostol has been associated with birth defects. In a few cases where misoprostol was self-administered (orally or vaginally) in order to induce an abortion, the following deleterious effects of misoprostol have been suggested: malformations of limbs, of fetal movements and of cranial nerves (hypomimia, abnormalities in suckling, deglutition, and eye movements). To date, a risk of malformation cannot be excluded.

Reproductive toxicity studies in animals showed embryotoxicity (increased resorptions) with oral doses of 1 mg/kg/day in rabbits, 10 mg/kg/day in rats, and 20 mg/kg in mice when treatment occurred during the period of organogenesis. An increased incidence of skeletal abnormalities was observed with an oral dose of 1 mg/kg/day in rabbits (possibly due to maternal toxicity) while an increased incidence of cleft palate was seen at a single oral dose

of 30 mg/kg in mice (28 and 170 times the recommended human dose, on a mg/m^2 body surface area basis, respectively).

Failure of pregnancy termination (continuing pregnancy)

Use in pregnancy has been associated with an increased risk of birth defects/malformations for ongoing pregnancies exposed to mifepristone and misoprostol or misoprostol alone, compared to control group. In particular, prenatal exposure to misoprostol has been associated with Moebius syndrome (congenital facial paralysis leading to hypomimia, troubles of sucking and deglutition and eye movements, with or without limb defects) and with amniotic band syndrome (limb deformities/ amputations, especially clubfoot, acheiria, oligodactyly, cleft palate inter alia), and central nervous system anomalies (cerebral and cranial anomalies such as anencephaly, hydrocephaly, cerebellar hypoplasia, neural tube defects).

Women considering medical termination of pregnancy should be precisely counselled on the risks to their fetus if an abortion failure occurs and a second termination of pregnancy procedure is not desirable.

MS-2 Step

As a consequence of the above information on mifepristone and misoprostol:

- Women should be informed that due to the risk of failure of the medical method of pregnancy termination and to the unknown risk to the fetus, follow-up is very important (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).
- Should a failure of the medical method be diagnosed at follow-up (viable ongoing pregnancy), and should the patient still agree, pregnancy termination should be completed by another method.

Should the patient wish to continue with her pregnancy, she should be appropriately counselled as to the risk of birth defects. In that event of continuation of the pregnancy, careful ultra-sonographic monitoring of the pregnancy should be carried out.

To avoid the potential exposure of a subsequent pregnancy to MS-2 Step it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after administration of ***MS-2 Step***.

Use in lactation

Mifepristone is a lipophilic compound and may theoretically be excreted in the mother's breast milk. However, limited data are available. Misoprostol is rapidly metabolised in the mother to misoprostol acid, which is biologically active and is excreted in breast milk. This could cause undesirable effects such as diarrhoea in breast feeding infants. ***MS-2 Step*** use should be avoided during breast-feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most frequent undesirable effects which are observed during treatment with ***MS-2 Step*** are the following:

- Gastrointestinal disorders: nausea (transient and mild), vomiting, diarrhoea, abdominal pain.
- Reproductive system disorders: very frequent uterine contractions observed in the hours following the intake of the misoprostol component of the MS-2 Step pack; vaginal bleeding, sometimes heavy and prolonged (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

- General disorders: headache, dizziness, and chills and fever. (Because castor oil is an excipient of the misoprostol component of the ***MS-2 Step*** pack, digestive symptoms (nausea, vomiting, abdominal pain) can be observed).

The adverse events reported with mifepristone and a prostaglandin analogue such as GyMiso®, classified according to frequency and system organ class, are summarised as shown in Table 1.

Table 1: **Adverse Events for the Combined Use of Mifepristone and Misoprostol**

MedDRA	**Adverse events (frequency)**				
System Organ Class	**Very common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1000 to < 1/100**	**Rare ≥ 1/10000 to < 1/1000 and very rare (< 1/10000)***	**Unknown frequency**
Infections and infestations			Infection	Toxic shock syndrome	
Neoplasms benign, malignant and unspecified				Elevated alpha-foeto protein Elevated carcinoembryonic antigen	
Blood and lymphatic system disorders				Thrombotic thrombocytopenic purpura Thrombocytopenia Induced systemic lupus erythematosus	
Psychiatric disorders				Mania	
Nervous system disorders	Headache Dizziness			Epilepsy Neurogenic tinnitus	
Eye disorders				Ophthalmoplegia	
Cardiac disorders				Myocardial infarction Induced Adam-Stokes syndrome Arrhythmia	
Vascular disorders			Hot flush Hypotension (0.25%)	Superficial thrombophlebitis	
Respiratory, thoracic and mediastinal disorders				Bronchospasm Induced bronchial asthma	

Table 1: Adverse Events for the Combined Use of Mifepristone and Misoprostol					
MedDRA	**Adverse events (frequency)**				
System Organ Class	**Very common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1000 to < 1/100**	**Rare ≥ 1/10000 to < 1/1000 and very rare (< 1/10000)***	**Unknown frequency**
Gastrointestinal disorders	Nausea Vomiting Diarrhoea Gastric discomfort Abdominal pain	Cramping, light or moderate		Gastric bleeding Necrotising pancreatitis	
Hepatobiliary disorders				Abnormal liver function tests Hepatic failure Hepatorenal failure	
Skin and subcutaneous tissue disorders			Skin rash / pruritus	Urticarial reaction Toxic epidermal necrolysis Erythema nodosum Angioedema*	Acute generalized exanthematous pustulosis
Musculoskeletal and connective tissue disorders				Limb spasm	
Renal and urinary disorders				Renal failure	
Pregnancy, puerperium and perinatal conditions	Uterine contractions or cramping (10 to 45%) in the hours following prostaglandin intake.	Heavy bleeding occurs in about 5% of the cases and may require haemostatic curettage in up to 1.4% of the cases. Fetal malformations		Hydatiform mole Ectopic pregnancy Amniotic band syndrome Gestational trophoblastic tumor Uteroplacental apoplexy	
Reproductive system and breast disorders	Vaginal bleeding Uterine spasm	Prolonged post-abortion bleeding Spotting Severe haemorrhage Endometritis Breast tenderness Heavy bleeding	Haemorrhagic shock Salpingitis	Bilateral adnexal mass Intrauterine adhesion Ovarian cyst rupture Breast abscess Haematosalpynx Uterine rupture	

Table 1: Adverse Events for the Combined Use of Mifepristone and Misoprostol					
MedDRA	**Adverse events (frequency)**				
System Organ Class	**Very common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1000 to < 1/100**	**Rare ≥ 1/10000 to < 1/1000 and very rare (< 1/10000)***	**Unknown frequency**
General disorders and administration site conditions	Fatigue Chill / fever	Fainting		Anaphylaxis Periorbital edema Vagal symptoms	

*Including occasional case reports

- Post-marketing experience indicates that death can occur as a result of medical termination of pregnancy (although this is a very rare outcome, <1 in 100,000). The reported deaths were due to sepsis (fatal toxic shock syndrome) associated with *Clostridium sordellii*, which also occurs in association with childbirth and spontaneous termination. The symptoms of *Clostridium sordellii* infection are sometimes not the usual symptoms of sepsis. Therefore, the possibility of sepsis should be considered in all women who are undergoing medical termination and who present with nausea, vomiting, or diarrhoea and weakness, with or without abdominal pain. These symptoms, even without a fever, may indicate *Clostridium sordellii* infection. Strong consideration should be given to obtaining a complete blood count in these patients. Significant leukocytosis with a marked left shift and haemo-concentration may be indicative of sepsis. Doctors should consider immediately initiating treatment with antibiotics that includes coverage of anaerobic bacteria such as *Clostridium sordellii*. Refer to **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**.

- Bleeding is an almost constant part of the procedure, whatever the prostaglandin analogue used, and at any pregnancy term, although it is usually more abundant when pregnancy age increases. It can occur after mifepristone alone. When heavy, it usually reflects incomplete abortion and is observed in approximately 3 to 12% of cases, depending on the pregnancy age and the prostaglandin analogue used, and needs specific treatment. It can necessitate a blood transfusion in up to 0.2% of cases. It can be prolonged for several days after prostaglandin analogue administration and sometimes leads to a decrease in haemoglobin levels. This potentially severe complication justifies that after intake (i) follow-up takes place approximately 14 to 21 days after Mifepristone Linepharma administration to ensure that expulsion is complete with no persisting bleeding and (ii) until follow-up has taken place, the woman remains close to a facility where she can be treated at any moment in case of severe or prolonged bleeding. Refer to **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**.

The issue of the outcome of persisting pregnancy in the case of failure of the medical method remains incompletely solved; a risk of malformation attributable to mifepristone or to prostaglandin analogues such as misoprostol cannot be excluded, and women should be adequately counselled in such a situation. Another fact to take into consideration is the possibility of a pregnancy persisting in the form of an ectopic pregnancy, since evidence suggests that the method does not appear able to terminate an ectopic pregnancy.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems and to MS Health at 1300 515 883.

4.9 OVERDOSE

Mifepristone Linepharma

No case of overdose has been reported.

In the event of massive ingestion signs of adrenal failure might occur. Signs of acute intoxication may require specialist treatment including the administration of dexamethasone.

GyMiso®

The toxic dose of misoprostol in humans has not been determined. Cumulative total daily doses of 1600 micrograms have been tolerated, with only symptoms of gastrointestinal discomfort reported.

Clinical signs that may indicate an overdose are sedation, tremor, convulsions, dyspnoea, abdominal pain, diarrhoea, fever, palpitations, hypotension or bradycardia. Hypertension and tachycardia have also been reported following overdoses. Overdose in pregnancy has resulted in uterine contractions with fetal death.

There is no specific antidote. Treatment should be symptomatic and supportive. Consider administration of activated charcoal in the event of a potentially toxic ingestion. Activated charcoal may reduce absorption of misoprostol if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Mifepristone Linepharma

Pharmacotherapeutic group: Other Sex Hormone and Modulator of the Reproductive function/ Antiprogestogen. ATC code: GO3XB01

Mifepristone is a synthetic steroid with an antiprogestational action as a result of competition with progesterone at the progesterone receptors.

Mifepristone binds to human progesterone receptors with nanomolar affinity. In animals, oral administration was shown to inhibit the action of endogenous or exogenous progesterone in multiple species (rat, mouse, rabbit, dog and monkey). This action is manifested in the form of pregnancy termination.

In women at doses of greater than or equal to 1 mg/kg, mifepristone antagonises the endometrial and myometrial effects of progesterone. During pregnancy it sensitises the myometrium to the contraction inducing action of prostaglandins. While clinical data have demonstrated that mifepristone facilitates dilatation of the cervix, no data are available to indicate that this results in a lowering of the rate of early or late complications to the dilatation procedure.

In the event of an early termination of pregnancy, the combination of a prostaglandin analogue used in a sequential regimen after mifepristone leads to an increase in the success rate and accelerates the expulsion of the conceptus.

Mifepristone binds to the glucocorticoid receptor with affinity comparable to that for the progesterone receptor. Full inhibition of the action of dexamethasone was evident in rats at oral doses 0.5-1.1 times the human dose adjusted for body surface area. In man the

antiglucocorticoid action is manifested at a dose equal to or greater than 4.5 mg/kg by a compensatory elevation of ACTH and cortisol.

Mifepristone also has some anti-androgenic activity. In toxicological studies in rats and monkeys up to a duration of 6 months, mifepristone produced effects related to its antihormonal (antiprogesterone, antiglucocorticoid and antiandrogenic) activity.

GyMiso®

Pharmacotherapeutic group: Other gynecological medicines – prostaglandins. ATC code: G02AD06

Misoprostol is a synthetic analogue of prostaglandin E1. At the recommended dosages, misoprostol induces contractions of the smooth muscle fibers in the myometrium and relaxation of the uterine cervix. The uterotonic properties of misoprostol should facilitate cervical opening and evacuation of intrauterine debris.

In the event of an early termination of pregnancy, the combination of GyMiso® used in a sequential regimen after mifepristone leads to an increase in the success rate and accelerates the expulsion of the conceptus.

Pharmacodynamic studies in early pregnancy have found an increase in uterine tone around 8 minutes after oral and 40 minutes after buccal misoprostol, with sustained contractions achieved by a mean of around 90 minutes and uterine activity peaking prior to 5 hours. Following oral administration uterine activity rises earlier than other routes, but is lower overall. Pretreatment with mifepristone has previously been shown to increase uterine contractility in response to misoprostol.

Clinical trials

Clinical efficacy of early medical abortion is defined as complete abortion without surgical intervention, regardless of the reason for the intervention, which may include continuing pregnancy, missed or incomplete abortion, prolonged or heavy vaginal bleeding or a woman's request.

An open-label single-group prospective trial performed in Mexico by Gynuity Healthcare, USA, involving 971 women available for efficacy treated with 200 mg mifepristone followed by 800 micrograms misoprostol administered buccally indicated that efficacy was 98.0, 96.8 and 95.9% for women with gestational age 49 days and below, 50-56 days and 57-63 days, respectively. In these 3 gestational age groups, the rate of surgical evacuation was 2.0, 3.2 and 4.1% respectively. In this study 25 women received a second dose of misoprostol, in each case, a dose of 800 micrograms by the buccal route. Of those 25, 20 had a successful outcome with medication alone, 4 had a surgical intervention and 1 woman did not return for follow up. In this study, bleeding occurred in all women independent of outcome, and was judged as more than expected in 27.1% of the women.

In an Authorised Prescribers Program in Australia in 2012 that included 7,166 women, efficacy was 97.4% for women with gestational age <49 days, and 95.2% for women with gestational age of 49-63 days. The rate of incomplete termination requiring aspiration was: <49 days: 2.3%; 49-63 days: 4.8%. The rate of ongoing pregnancies was: <49 days: 0.3%; 49-63 days: 0.6%. Bleeding was considered as an adverse event in 0.24% of women, independent of pregnancy age.

Studies published in the literature have reported mifepristone and oral or buccal misoprostol regimens. In one study of 966 patients[1] with pregnancies up to gestational age of 63 days, randomised to 200 mg mifepristone followed 24-36 hours later by 800 micrograms of misoprostol orally or buccally, reported efficacy rates were 91.3% for the oral and 96.2% for the buccal group (RR 0.95, 95% CI 0.92-0.98, p=0.003).

[1] Winikoff B et al. Obstetr Gynecol 2008, 1303-10

Studies published on the combination of mifepristone 200 mg and misoprostol 800 micrograms buccally, and reporting outcomes by gestational age, encompass 399 women with gestational ages 50 – 56 days and 344 women with gestational ages 57 – 63[2][3][4][5][6][7] days. Efficacy ranged from 86.5 to 98.5% in women with gestational age 50 – 56 days and from 93.0 to 100% in those with gestational age 57 – 63 days. In these studies, the rate of ongoing pregnancies ranged from 0 to 7.1% in women with gestational age 50 – 56 days and from 0 to 2.3% in those with gestational age 57 – 63 days.

Literature data provides information on the bleeding and expulsion pattern after termination of pregnancy with mifepristone and misoprostol: approximately half of women start to bleed before prostaglandin administration. Median bleeding time is 10 to 16 days. Bleeding is judged more or much more abundant than usual menses for 2 to 3 days after prostaglandin. In studies where it was measured, there was a slight but significant decrease in haemoglobin level after compared to baseline. In one study blood loss was quantified: the median blood loss was 83 mL and 5.4% of women had a blood loss above 200 mL. Expulsion usually takes place within 3 hours after misoprostol in approximately half of the women, and within 4 hours after misoprostol in approximately 50 to 90% of women.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Mifepristone Linepharma

After oral administration of a single dose of 200 mg, mifepristone is rapidly absorbed. The peak concentration of 2.3 to 2.7 mg/L is reached after 0.75 hours (mean of 49 subjects). The half-life of mifepristone is 36.5 to 38.3 hours.

Mifepristone shows non-linear pharmacokinetics. Following the distribution phase the elimination is at first slow, with a half-life of approximately 12 to 72 hours, and then the concentration is more rapidly reduced with a half-life of 18 hours. With radio-receptor analysis, the final half-life is shown to be up to 90 hours, including all mifepristone metabolites that can bind to progesterone receptors.

After administration of low doses of mifepristone (20 mg orally or intravenously), the absolute bioavailability is 69%.

GyMiso®

When administered orally, misoprostol is rapidly absorbed and metabolised. Peak concentrations around 1.1 ng/mL were reached about 15 minutes after a 400 µg dose in the fasting state. Plasma concentrations of its main degradation metabolite, misoprostol acid, reach their peak of 2 - 2.5 ng/mL after a 2 µg/kg oral dose within approximately 30 minutes and rapidly decline thereafter. As a result, uterine contractility increases and then plateaus after about one hour. Absorption is almost complete, measured at levels between 64 - 73% from urinary data.

For a single oral administration of 800 micrograms misoprostol (4 tablets of 200 micrograms GyMiso®), AUC_{0-t} was 1.9709 ± 0.8130 hr.ng/mL, $AUC_{0-\infty}$ was 2.0192 ± 0.8032 hr.ng/mL and C_{max} was 2.6830 ± 1.2161 ng/mL. For a single buccal administration of 800 micrograms misoprostol (4 tablets of 200 micrograms GyMiso®), AUC_{0-t} was 1.9095 ± 0.2909 hr.ng/mL, $AUC_{0-\infty}$ was 2.0726 ± 0.3578 hr.ng/mL and C_{max} was 1.3611 ± 0.3436 ng/mL. For a single sublingual administration of 800 micrograms misoprostol (4 tablets of 200 micrograms

[2] Chong et al 2012 Contraception 86, 251–256
[3] Fjerstad et al 2009 Contraception 80, 282-286
[4] Boersma et al 2011 Eur J of Contraception & Reproductive Health Care 16, 61-66
[5] Ngoc et al 2011 Contraception 83, 410 – 417
[6] Blum et al 2012 Int J Gynecol Obstetr 118, 166 - 171
[7] WHO 2000 Br J Obstetr Gynecol 107, 524-30

GyMiso®), AUC_{0-t} was 3.0574 ± 0.9872 hr.ng/mL, $AUC_{0-\infty}$ was 3.2094 ±1.0417 hr.ng/mL and C_{max} was 2.4391 ± 1.1567 ng/mL. For log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}, there were statistically significant differences between 3 treatment groups (p = 0.0159, 0.0162 and 0.0083, respectively). Sublingual administration of misoprostol had a higher $AUC_{0-\infty}$ compared with buccal and oral administration which indicated bioavailability was higher by the sublingual route. Misoprostol sublingual and oral administration resulted in higher C_{max} compared with buccal. The C_{max} of buccal administration was achieved later compared with other routes of administration. No difference was found when comparing oral, sublingual and buccal half-lives (p= 0.4495).

Distribution

Mifepristone Linepharma

In plasma, mifepristone is 98% bound to plasma proteins: albumin and principally alpha-1-acid glycoprotein (AAG), to which binding is saturable. Due to this specific binding, the volume of distribution and plasma clearance of mifepristone are inversely proportional to the plasma concentration of AAG.

GyMiso®

Serum protein binding of labeled misoprostol acid was studied in man and was similar in young (81-88%) and elderly (81-89%) subjects. Accumulation in erythrocytes was not seen.

Metabolism

Mifepristone Linepharma

N mono- and di-demethylation and terminal hydroxylation of the 17-propynyl chain are primary metabolic pathways of hepatic oxidative metabolism. Metabolites are detectable in plasma 1 hour after ingestion of mifepristone. Plasma AUC for the dominant metabolite, monodemethylated mifepristone, is approximately double that of the unchanged mifepristone at the clinical dose, and this metabolite retains significant affinity for the progesterone receptor. The other metabolites also display some progesterone receptor affinity (approximately 10 to 15% that of mifepristone). The metabolites may contribute to the pharmacological effects of mifepristone.

In vitro CYP3A4 appears as the isoenzyme primarily responsible for mifepristone demethylation and hydroxylation in human liver microsomes. CYP3A4 substrates progesterone and midazolam inhibited metabolite formation by up to 77%. Other isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1) had apparently no action on mifepristone metabolism.

GyMiso®

Metabolism of misoprostol to misoprostol acid is rapid with no intact misoprostol found in plasma consistent with an *in vitro* half-life of 6.4 minutes for de-esterification of misoprostol in human plasma at 37ºC. Elimination of misoprostol and its metabolites is also rapid with a plasma elimination half-life of 35 minutes.

Excretion

Mifepristone Linepharma

After administration of 600 mg radiolabelled mifepristone, 10% of the total radioactivity was recovered in urine and 90% in faeces.

GyMiso®

The liver is the primary site of metabolism and between 1-4% of misoprostol acid is excreted in the urine.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Mifepristone Linepharma

Mifepristone has been evaluated in tests for mutagenicity in bacterial, yeast and mammalian cells; gene conversion in yeast; unscheduled DNA synthesis in HeLa cells; and for clastogenicity *in vitro* (Chinese hamster ovary cells) and in vivo (mouse bone marrow micronucleus test). No evidence of genotoxicity was observed.

GyMiso®

Misoprostol has been evaluated in tests for mutagenicity in bacterial, yeast and mammalian cells; and for clastogenicity *in vitro* (Chinese hamster ovary cells) and *in vivo* (mouse bone marrow micronucleus test). No evidence of genotoxicity was observed.

Carcinogenicity

Mifepristone Linepharma

No long-term animal carcinogenicity studies have been conducted with mifepristone. Based on the negative genotoxicity results, findings in general repeat-dose toxicity studies and considering the pattern of clinical use, mifepristone is not predicted to pose a particular carcinogenic risk.

GyMiso®

The potential carcinogenicity of misoprostol has been evaluated in both mice and rats. There was no evidence of an effect of misoprostol on tumour occurrence or incidence in rats receiving oral doses up to 2.4 mg/kg/day for 24 months. Similarly, there was no effect of misoprostol on tumour occurrence or incidence in mice receiving oral doses up to 16 mg/kg/day for 21 months. These doses are at least 27 times the recommended human dose, on a mg/m^2 body surface area basis.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mifepristone Linepharma 200 mg tablet contains the following excipients: maize starch, povidone, microcrystalline cellulose, colloidal anhydrous silica and magnesium stearate.

GyMiso® contains the following excipients: hypromellose, microcrystalline cellulose, sodium starch glycollate type A and hydrogenated castor oil.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Do not use after the expiry date printed on the carton labels of the composite pack and the individual components.

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C, keep in the original container to protect from light.

Keep out of reach of children.

Mifepristone Linepharma

Keep in the original green carton in order to protect from light

GyMiso®

Keep in the original purple carton

6.5 NATURE AND CONTENTS OF CONTAINER

Each ***MS-2 Step*** composite pack consists of:

- 1 green carton containing Mifepristone Linepharma 200 mg tablet packaged in a PVC/PVDC/Aluminium blister. Pack size of 1 tablet.
- 1 purple carton containing GyMiso® misoprostol 200 microgram tablet packaged in a dual-faced Aluminium blister. Pack size of 4 tablets (2 tablets per blister).

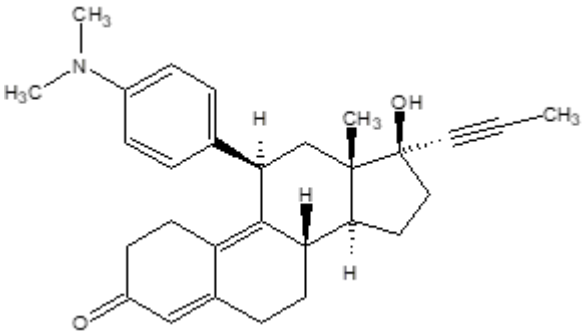
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Mifepristone

Chemical structure



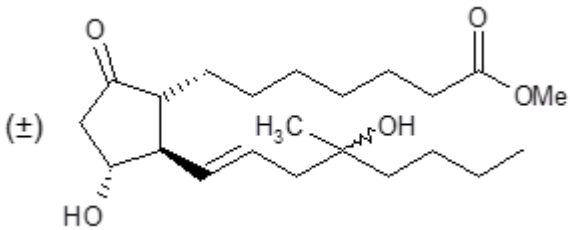
Molecular formula: $C_{29}H_{35}NO_2$ Molecular weight: 429.6

CAS number

CAS Registry Number: 84371-65-3

GyMiso®

Chemical Structure



Molecular formula:$C_{22}H_{38}O_5$ Molecular weight: 382.5

CAS number

CAS Registry Number: 59122-46-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8 SPONSOR

MS Health Pty Ltd
Suite 60, 278 Church Street,
Richmond, VIC, Australia, 3121

Ph: 1300 515 883MS-2 Step® is a registered trademark of MSI Reproductive Choices (UK). Mifepristone Linepharma and GyMiso® are licensed from Linepharma International Limited (UK).

9 DATE OF FIRST APPROVAL

4 June 2014

10 DATE OF REVISION

TBC

11 SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
Black box and 4.2	Medical practitioner /doctor changed to healthcare practitioner
4.2	Certification of doctors removed
4.4	Reference to 24-hour help line in guideline removed and instructions for further medical advice added.

MS-2 Step® GyMiso®

Document 6

Consumer Medicine Information (CMI) summary

The full CMI on the next page has more details. If you are worried about using this medicine, speak to your healthcare practitioner (doctor, nurse or pharmacist).

WARNING: Important safety information is provided in a boxed warning in the full CMI. Read before using this medicine.

1. Why am I using MS-2 Step GyMiso®?

MS-2 Step GyMiso® contains the active ingredient misoprsotol. MS-2 Step GyMiso® is used to terminate pregnancy when given in combination with another medicine called Mifepristone Linepharma.

For more information, see Section 1. Why am I using MS-2 Step GyMiso®? in the full CMI.

2. What should I know before I use MS-2 Step GyMiso®?

Do not use if you have ever had an allergic reaction to misoprostol or any of the ingredients listed at the end of the CMI.

Talk to your healthcare practitioner if you have any other medical conditions, take any other medicines, or are pregnant or plan to become pregnant or are breastfeeding.

For more information, see Section 2. What should I know before I use MS-2 Step GyMiso®? in the full CMI.

3. What if I am taking other medicines?

Some medicines may interfere with MS-2 Step GyMiso® and affect how it works.

A list of these medicines is in Section 3. What if I am taking other medicines? in the full CMI.

4. How do I use MS-2 Step GyMiso®?

- MS-2 Step GyMiso® is usually taken 36-48 hours after you have taken MS – 2 Step Mifepristone Linepharma tablet. You will need to take the four MS-2 Step GyMiso® tablets in one dose.
- MS-2 Step GyMiso® should be taken by holding the tablets in your mouth, between the cheek and gum (buccal method), for 30 minutes before swallowing any fragments with water. It is recommended to that MS-2 Step GyMiso® should be taken on an empty stomach before or after a meal.

More instructions can be found in Section 4. How do I use MS-2 Step GyMiso®? in the full CMI.

5. What should I know while using MS-2 Step GyMiso®?

Things you should do	• Remind any doctor, nurse, dentist or pharmacist you visit that you are using MS-2 Step GyMiso® • MS-2 Step GyMiso® tablets must be taken only after taking the MS – 2 Step Mifepristone Linepharma tablet provided in the MS-2 Step pack. • It is important to keep all healthcare practitioner appointments so that your progress can be checked
Things you should not do	• Do not travel away from home during the time that you are bleeding so that you can visit your doctor or clinic if necessary.
Driving or using machines	• Be careful before you drive or use any machines or tools until you know how MS-2 Step GyMiso® affects you.
Drinking alcohol	• Tell your healthcare practitioner if you drink alcohol.
Looking after your medicine	• MS-2 Step GyMiso® should be stored within the MS-2 Step composite pack and be kept in a cool and dry place where the temperature stays below 25 degrees C • Keep MS -2 Step where children cannot reach it

For more information, see Section 5. What should I know while using while using MS-2 Step GyMiso®? in the full CMI.

6. Are there any side effects?

The common side effects include headache, spotting, cramps, breast tenderness, fainting, abdominal discomfort, vomiting, diarrhea, fever. Serious side effects include prolonged heavy vaginal bleeding, infections that can be potentially life threatening, ongoing abdominal pain, or feeling unwell or feeling weak, with or without a fever.

For more information, including what to do if you have any side effects, see Section 6. Are there any side effects? in the full CMI.

Document 6

WARNING: It is very important that all patients receiving this medication are followed up by a healthcare practitioner, preferably the prescriber, to ensure that the medication has been effective. Even if no adverse events have occurred all patients must receive follow-up 14 to 21 days after taking mifepristone.

MS-2 Step® GyMiso®

Active ingredient: *misoprostol*

Consumer Medicine Information (CMI)

MS-2 Step is a composite pack product containing Mifepristone Linepharma 200 mg tablet and GyMiso® misoprostol 200 microgram tablets (this medicine in the purple box).

Mifepristone Linepharma = mifepristone

GyMiso® = misoprostol

GyMiso® misoprostol 200 microgram tablets must be taken only after having taken the mifepristone tablet.

This leaflet provides important information about using MS-2 Step GyMiso®. **You should also speak to your doctor, nurse or pharmacist if you would like further information or if you have any concerns or questions about using MS-2 Step GyMiso®.**

Where to find information in this leaflet:

1. Why am I using MS-2 Step GyMiso®

MS-2 Step GyMiso® contains the active ingredient misoprostol. MS-2 Step GyMiso® belongs to a group of medicines called prostaglandins. It acts like prostaglandin E_1. MS-2 Step GyMiso® induces contractions of the smooth muscle and relaxation of the cervix. These properties help open the cervix and push out the contents of the uterus.

MS-2 Step GyMiso® can therefore be used to terminate a pregnancy. It is given in combination with another medicine called Mifepristone Linepharma (in the green box), which blocks progesterone, a hormone that is needed for pregnancy to continue. Both medicines are contained within the MS-2 Step pack, and they are recommended for termination of pregnancy up to 63 days after the first day of your last menstrual period.

Ask your healthcare practitioner if you have any questions about why MS-2 Step has been prescribed for you.

2. What should I know before I use MS-2 Step® GyMiso®

Warnings

Do not use MS-2 Step GyMiso® if:

- you are allergic to misoprostol, mifepristone (or any prostaglandin) or any of the ingredients listed at the end of this leaflet.
- Always check the ingredients to make sure you can use this medicine.
- your doctor suspects an ectopic pregnancy (the egg is implanted outside the womb)
- you are using an intrauterine contraceptive device. It should be removed first.
- your pregnancy has not been confirmed by aan ultrasound scan or biological test such as urine or serum HCG
- the first day of your last period was more than 63 days ago, unless tests have been done to confirm the age of the pregnancy is no more than 63 days
- you are pregnant and wish to carry your pregnancy to term
- you have not taken, first, the mifepristone tablet
- you suffer from chronic adrenal failure
- you suffer from severe disease where it is necessary to take steroids (e.g. asthma uncontrolled by treatment)
- you have known or suspected hypocoagulation diseases
- you are on anticoagulant therapy

If you are under 18 years of age, you should only take MS-2 Step GyMiso® if advised to do so by your doctor. There is limited information on the use of MS-2 Step GyMiso® in adolescents less than 18 years of age.

Check with your healthcare practitioner if you:

- have any other medical conditions:
  - heart or cardiovascular disease
  - epilepsy
  - asthma
  - porphyria
  - kidney problems
  - liver problems
  - malnutrition
  - problems with your adrenal glands
  - anaemia

  - blood disorders which lead to difficulty in clotting
- if you are taking anticoagulants
- if you are taking corticosteroids including inhaled corticosteroids for the treatment of asthma
- if you have an intra uterine device (IUD), as this needs to be removed
- take any medicines for any other condition

If you are not sure whether you should be given this medicine, talk to your healthcare practitioner.

Your healthcare practitioner will give you more information about what to expect with medical abortion, the risks and side effects, when you need to seek advice or help, and contact numbers for 24 hours assistance.

During treatment, you may be at risk of developing certain side effects. It is important you understand these risks and how to monitor for them. See additional information under Section 6. Are there any side effects?

Pregnancy and breastfeeding

Check with your healthcare practitioner if you are pregnant or intend to become pregnant.

You should not be given MS-2 Step GyMiso® if:

- your healthcare practitioner suspects an ectopic pregnancy (the egg is implanted outside the womb)
- your pregnancy has not been confirmed by a pregnancy test or an ultrasound scan
- you are pregnant and wish to carry your pregnancy to term

Talk to your healthcare practitioner if you are breastfeeding or intend to breastfeed.

MS-2 Step GyMiso® should not be taken if you are breastfeeding.

3. What if I am taking other medicines?

Tell your healthcare practitioner if you are taking any other medicines, including any medicines, vitamins or supplements that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines may interfere with MS-2 Step GyMiso® and affect how it works.
Different medicines may be affected by MS-2 Step GyMiso® or may affect how well it works. You may need to be given different amounts of your medicines, or you may need to be given different medicines.

Your healthcare practitioner may have more information on medicines to be careful with or avoid while being treated with MS-2 Step GyMiso®.

Check with your healthcare practitioner if you are not sure about what medicines, vitamins or supplements you are taking and if these affect MS-2 Step GyMiso®.

4. How do I use MS-2 Step GyMiso®?

How much to take

- Your healthcare practitioner will tell you how many tablets you need to take and when to take them. MS-2 Step GyMiso® is usually taken 36 to 48 hours after you have taken the MS-2 Step Mifepristone Linepharma tablet. You will need to take the four MS-2 Step GyMiso® tablets (misoprostol 800 micrograms) which are in the purple box. These are taken as four tablets in one dose.

When to take

- It is necessary to take the MS-2 Step Mifepristone Linepharma tablet first and then, 36 to 48 hours later, take the MS-2 Step GyMiso® tablets. This must be done in this order for the medicines to work.
- It is recommended that MS-2 Step GyMiso® should be taken on an empty stomach 2 hours before or after a meal.

How to take

- MS-2 Step GyMiso® should be taken by holding the tablets in your mouth, between the cheek and gum (buccal method), for 30 minutes before swallowing any fragments with water.

If you forget to use MS-2 Step GyMiso®

Contact your healthcare practitioner immediately if you forget to take MS-2 Step GyMiso® tablets and it has been more than 48 hours after you have taken a MS-2 Step Mifepristone Linepharma tablet.

If you use too much MS-2 Step GyMiso®

MS-2 Step GyMiso® is prescribed for you by your healthcare practitioner. An overdose is not likely to occur. Ask your healthcare practitioner if you have any concerns. If you think that you have used too much MS-2 Step GyMiso®, you may need urgent medical attention.

You should immediately:

- phone the Poisons Information Centre (**by calling 13 11 26**), or
- contact your doctor, or
- go to the Emergency Department at your nearest hospital.

You should do this even if there are no signs of discomfort or poisoning.

5. What should I know while using MS-2 Step GyMiso®?

Things you should do

- After you taken MS-2 Step GyMiso® tablets, you should stay at home and rest for 3 hours. Vaginal bleeding will occur and the pregnancy may be expelled within a few hours of taking MS-2 Step GyMiso® or during the next few days. The bleeding lasts on average for 10 to 16 days and may be heavy.

- **It is very important that you have follow up with your healthcare practitioner 14 to 21 days after you take MS – 2 Step Mifepristone Linepharma, to ensure that the termination was complete, because incomplete termination will increase the risk of serious infection or bleeding.**
- In some cases treatment with MS-2 Step may not result in a termination of pregnancy. You must keep all of your doctor's appointments so that your progress can be checked. This is very important.
- If treatment with MS-2 Step does not work, a termination can be arranged using another method.
- If treatment with MS-2 Step does not work and you wish to keep your pregnancy, it is not known if mifepristone can cause harm to your baby. It is believed, though, that MS-2 Step GyMiso® can cause harm to your baby. You need to tell your doctor or nurse about MS-2 Step so that they can carefully monitor your pregnancy.
- If you are Rhesus negative, the use of MS-2 Step requires that your doctor take measures to prevent Rhesus factor sensitization, along with the general measures taken during any pregnancy termination.
- Using contraceptives: It is possible for you to become pregnant again immediately after the pregnancy termination is completed. As some effects of misoprostol and mifepristone may still be present after taking MS-2 Step, it is recommended that you avoid getting pregnant again before your next menstrual period.

Call your healthcare practitioner straight away:

- If bleeding does not occur, it is very important that you contact your doctor immediately. For some patients, the healthcare practitioner may prescribe a repeat dose of MS-2 Step GyMiso®or a termination can be arranged using another method.
- In case of heavy and prolonged bleeding, you should contact your doctor immediately in order to schedule an appointment.
- In rare cases, a termination can occur after you take the MS -2 Step Mifepristone Linepharma tablet but before you take MS-2 Step GyMiso®. It is essential that you are checked to confirm that a complete termination has occurred. If this occurs, you should contact your doctor immediately in order to schedule an appointment.

Remind any doctor, nurse, dentist or pharmacist you visit that you are using MS–2 Step GyMiso®.

Things you should not do

- It is recommended that you do not travel away from home during the time that you are bleeding so that you can visit your doctor or clinic if necessary

Driving or using machines

Be careful before you drive or use any machines or tools until you know how MS-2 Step GyMiso® affects you.

Drinking alcohol

Tell your healthcare practitioner if you drink alcohol.

Looking after your medicine

- MS-2 Step GyMiso® should be stored within the MS-2 Step pack
- Store below 25 degrees C.
- Store in the original packaging.

Follow the instructions in the carton on how to take care of your medicine properly.

Store it in a cool dry place away from moisture, heat or sunlight; for example, do not store it:

- in the bathroom or near a sink, or
- in the car or on window sills.

Keep it where young children cannot reach it.

Getting rid of any unwanted medicine

If you no longer need to use this medicine or it is out of date, take it to any pharmacy for safe disposal.

Do not use this medicine after the expiry date.

6. Are there any side effects?

All medicines can have side effects. If you do experience any side effects, most of them are minor and temporary. However, some side effects may need medical attention.

See the information below and, if you need to, ask your healthcare practitioner if you have any further questions about side effects.

Less serious side effects

Less serious side effects	What to do
Gastrointestinal upset • Nausea • Vomiting • Diarrhoea **Tiredness related** • Fainting • Dizziness • Fatigue • Headache **Vagina related** • Vaginal bleeding • Spotting **Pain related** • Abdominal discomfort • Abdominal pain • Cramps • Breast tenderness **Skin related** • Hot flushes • Skin rashes or itching **Infection related** • Chills and /or fever	**Speak to your doctor if you have any of these less serious side effects and they worry you.**

Serious side effects

Serious side effects	What to do
Bleeding related • Vaginal bleeding usually starts a few hours after taking misoprostol tablets. Bleeding can occur for 10 to 16 days and it is usual for bleeding to be heavier than a normal period for 2 to 3 days. Contact your doctor immediately if you find you have very heavy bleeding and have soaked more than 2 pads per hour over 2 hours. **Infection related** • Serious infections are very rare in a medical termination of pregnancy and can be potentially life threatening. If you have symptoms occurring more than 24 hours after taking misoprostol or ongoing abdominal pain, or feeling unwell, or feeling weak, with or without a fever you should contact your doctor without delay.	**Call your doctor straight away, or go straight to the Emergency Department at your nearest hospital if you notice any of these serious side effects.**

Tell your healthcare practitioner if you notice anything else that may be making you feel unwell.

Other side effects not listed here may occur in some people.

Reporting side effects

After you have received medical advice for any side effects you experience, you can report side effects to the Therapeutic Goods Administration online at www.tga.gov.au/reporting-problems. By reporting side effects, you can help provide more information on the safety of this medicine.

Always make sure you speak to your healthcare practitioner before you decide to stop taking any of your medicines.

7. Product details

This medicine is only available with a prescription.

What MS-2 Step GyMiso® contains

Active ingredient (main ingredient)	misoprostol
Other ingredients (inactive ingredients)	Hydrogenated castor oil Hypermellose Microcrystalline cellulose Sodium starch glycollate type A
Potential allergens	No

Do not take this medicine if you are allergic to any of these ingredients.

What MS-2 Step GyMiso® looks like

MS-2 Step GyMiso® is presented in a box containing a blister pack of 4 white, round, flat tablets with ML on one side and 200 on the other.

Each tablet contains 200 micrograms of misoprostol. There is one GyMiso® pack in each MS-2 Step pack.

Australian registration number: AUST R 210574.

Who distributes MS-2 Step GyMiso®

MS-2 Step is supplied in Australia by:

MS Health Pty Ltd

Suite 60, 278 Church Street,

Richmond, VIC, Australia, 3121.

Ph: 1300 515 883

GyMiso® is licensed from Linepharma International Ltd, UK

MS-2 Step® is a registered trademark of MSI Reproductive Choices (UK). Mifepristone Linepharma and GyMiso® are licensed from Linepharma International Limited (UK).

This leaflet was updated in April 2023.

MS-2 Step® Mifepristone Linepharma

Document 6

Consumer Medicine Information (CMI) summary

The full CMI on the next page has more details. If you are worried about using this medicine, speak to your healthcare practitioner (doctor, nurse or pharmacist).

WARNING: Important safety information is provided in a boxed warning in the full CMI. Read before using this medicine.

1. Why am I using MS -2 Step Mifepristone Linepharma?

MS-2 Step® is a composite pack product containing Mifepristone Linepharma 200 mg tablet and GyMiso® misoprostol 200 microgram tablets. MS -2 Step Mifepristone Linepharma contains the active ingredient mifepristone. MS -2 Step Mifepristone Linepharma is used to terminate a pregnancy up to 63 days after your last menstrual period when given in combination with MS - 2 Step GyMiso®.

For more information, see Section 1. Why am I using MS -2 Step Mifepristone Linepharma? in the full CMI.

2. What should I know before I use MS -2 Step Mifepristone Linepharma?

Do not use if you have ever had an allergic reaction to mifepristone or any of the ingredients listed at the end of the CMI.

Talk to your healthcare practitioner if you have any other medical conditions, take any other medicines, or are pregnant or plan to become pregnant or are breastfeeding. For more information, see Section 2. What should I know before I use MS -2 Step Mifepristone Linepharma? in the full CMI.

3. What if I am taking other medicines?

Some medicines may interfere with MS -2 Step Mifepristone Linepharma and affect how it works.

A list of these medicines is in Section 3. What if I am taking other medicines? in the full CMI.

4. How do I use MS -2 Step Mifepristone Linepharma?

MS -2 Step Mifepristone Linepharma tablet should be taken first and then, 36 to 48 hours later, take the MS - 2 Step GyMiso® tablets. The MS -2 Step Mifepristone Linepharma tablet should be swallowed with water. It is recommended that the MS -2 Step Mifepristone Linepharma tablet should be taken on an empty stomach 2 hours before or 2 hours after a meal.

More instructions can be found in Section 4. How do I use MS -2 Step Mifepristone Linepharma? in the full CMI.

5. What should I know while using MS -2 Step Mifepristone Linepharma?

Things you should do	• Remind any doctor, nurse, dentist or pharmacist you visit that you are using MS -2 Step Mifepristone Linepharma. • Contact your healthcare practitioner immediately if you forget to take the dose of MS - 2 Step GyMiso® tablets in the purple box, and it is greater than 48 hours after you have taken MS -2 Step Mifepristone Linepharma tablet. • It is important to have a follow up with your doctor 14-21 days after you take MS -2 Step Mifepristone Linepharma
Things you should not do	• Do not take grapefruit juice when you are treated with MS – 2 Step Mifepristone Linepharma. • Do not travel away from home during the time that you are bleeding so that you can visit your doctor if necessary.
Driving or using machines	Be careful before you drive or use any machines or tools until you know how MS - 2 Step Mifepristone Linepharma affects you.
Drinking alcohol	Tell your healthcare practitioner (doctor, nurse or pharmacist) if you drink alcohol.
Looking after your medicine	• MS - 2 Step Mifepristone Linepharma should be stored within the MS - 2 Step composite pack and be kept in a cool and dry place where the temperature stays below 25 degrees C • Keep MS -2 Step where children cannot reach it

For more information, see Section 5. What should I know while using MS – 2 Step Mifepristone Linepharma? in the full CMI.

6. Are there any side effects?

The common side effects include headache, spotting, cramps, breast tenderness, fainting. Serious side effects include serious skin reactions, prolonged heavy vaginal bleeding, infections that can be potentially life threatening, ongoing abdominal pain. For more information, including what to do if you have any side effects, see Section 6. Are there any side effects? in the full CMI.

WARNING: It is very important that all patients receiving this medication are followed up by a healthcare practitioner, preferably the prescriber, to ensure that the medication has been effective. Even if no adverse events have occurred all patients must receive follow-up 14 to 21 days after taking MS -2 Step Mifepristone Linepharma.

MS – 2 Step® Mifepristone Linepharma

Active ingredient: *mifepristone*

Consumer Medicine Information (CMI)

MS-2 Step is a composite pack product containing Mifepristone Linepharma 200 mg tablet and GyMiso® misoprostol 200 microgram tablets (this medicine in the purple box).

Mifepristone Linepharma = mifepristone

GyMiso® = misoprostol

This leaflet provides important information about using MS -2 Step Mifepristone Linepharma contained within the MS-2 Step pack. **You should also speak to your doctor, nurse or pharmacist if you would like further information or if you have any concerns or questions about using MS -2 Step Mifepristone Linepharma.**

Where to find information in this leaflet:

1. Why am I using MS -2 Step Mifepristone Linepharma?

MS -2 Step Mifepristone Linepharma contains the active ingredient mifepristone. Mifepristone is an anti-hormone. It acts by blocking the effects of progesterone, a hormone which is needed for pregnancy to continue.

MS -2 Step Mifepristone Linepharma can therefore be used to terminate a pregnancy. It is given in combination with another medicine called misoprostol a prostaglandin analogue.

Both medicines are contained within the ***MS-2 Step*** pack, and they are recommended for the termination of pregnancy up to 63 days after your last menstrual period.

Ask your healthcare practitioner (doctor, nurse or pharmacist) if you have any questions about why MS-2 Step has been prescribed for you.

2. What should I know before I use MS -2 Step Mifepristone Linepharma?

Warnings

Do not use MS -2 Step Mifepristone Linepharma if:

- you are allergic to mifepristone, or any of the ingredients listed at the end of this leaflet. Some of the symptoms of an allergic reaction may include:
  - Reddish circular patches on the trunk
  - Skin peeling
  - Ulcers of mouth, throat, nose, genitals, and eyes.
- Always check the ingredients to make sure you can use this medicine.
- you are unable to access to emergency medical care in the next 14 days
- your doctor suspects an ectopic pregnancy (the egg is implanted outside the womb)
- if you have an intra-uterine device (IUD), as this needs to be removed.
- your pregnancy has not been confirmed by an ultrasound scan or biological test such as urine or serum HCG
- the first day of your last period was more than 63 days ago, unless tests have been done to confirm the age of the pregnancy is no more than 63 days
- you are pregnant and wish to carry your pregnancy to term
- you suffer from chronic adrenal failure
- you suffer from severe disease where it is necessary to take steroids (e.g. asthma uncontrolled by treatment)
- you have known or suspected hypocoagulation diseases
- you are on anticoagulant therapy
- you are allergic to prostaglandins. This is because of the need to use a prostaglandin analogue in combination with mifepristone.

If you are under 18 years of age, you should only take mifepristone if advised to do so by your doctor. There is limited information on the use of mifepristone in adolescents under 18 years of age.

Check with your healthcare practitioner if you:

- have any other medical conditions such as:
  - kidney problems

- liver problems
- malnutrition
- problems with your adrenal glands
- heart or cardiovascular disease
- anaemia
- blood disorders which lead to difficulty in clotting
- asthma
- epilepsy
- porphyria
- are taking anticoagulants
- are taking long term corticosteroids including inhaled corticosteroids for the treatment of asthma

Serious skin reactions including toxic epidermal necrolysis and acute generalized exanthematous pustulosis have been reported in association with mifepristone treatment. Stop using the Mifepristone Linepharma 200 mg tablet and seek medical attention immediately if you notice any of the symptoms described under the 'Side Effects' section. If you get a serious skin reaction you should not use mifepristone again in the future.

During treatment, you may be at risk of developing certain side effects. It is important you understand these risks and how to monitor for them. See additional information under Section 6. Are there any side effects?

Pregnancy and breastfeeding

Check with your healthcare practitioner if you are pregnant or intend to become pregnant.

Do not use MS -2 Step Mifepristone Linepharma if:

- your healthcare practitioner suspects an ectopic pregnancy (the egg is implanted outside the womb)
- your pregnancy has not been confirmed by a pregnancy test or an ultrasound scan
- the first day of your last period was more than 63 days ago, unless tests have been done to confirm the age of the pregnancy is no more than 63 days
- you are pregnant and wish to carry your pregnancy to term

Talk to your healthcare practitioner if you are breastfeeding or intend to breastfeed. MS -2 Step Mifepristone Linepharma should not be taken if you are breast-feeding.

3. What if I am taking other medicines?

Tell your healthcare practitioner if you are taking any other medicines, including any medicines, vitamins or supplements that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines may interfere with MS -2 Step Mifepristone Linepharma and affect how it works. These include:

- corticosteroids including inhaled corticosteroids for the treatment of asthma
- ketoconazole or itraconazole, medicines used to treat fungal infections
- erythromycin or rifampicin, antibiotics for treating infections
- St John's Wort, a natural remedy used to treat mild depression
- phenytoin, phenobarbitone, carbamazepine, medicines used to treat epilepsy

These medicines may be affected by MS -2 Step Mifepristone Linepharma or may affect how well it works. You may need to be given different amounts of your medicines, or you may need to be given different medicines.

Grapefruit juice should not be taken when you are treated with MS -2 Step Mifepristone Linepharma.

4. How do I use MS – 2 Step Mifepristone Linepharma?

How much to take

- Your healthcare practitioner will tell you how many tablets you need to take and when to take them.
- The usual dose of MS – 2 Step Mifepristone Linepharma is 200 mg (one tablet) in the green box.

When to take

- It is necessary to take the MS -2 Step Mifepristone Linepharma tablet first and then, 36 to 48 hours later, take the MS - 2 Step GyMiso® tablets. This must be done in this order for the medicines to work.
- It is recommended that the MS -2 Step Mifepristone Linepharma tablet should be taken on an empty stomach - 2 hours before or 2 hours after a meal.

How to take

- The MS -2 Step Mifepristone Linepharma tablet should be swallowed with water.

Vaginal bleeding usually starts 1 to 2 days after taking the mifepristone tablet.

36 to 48 hours after taking the mifepristone tablet you need to take misoprostol tablets as directed by your doctor or given to you by your healthcare practitioner.

If you forget to take your dose of *MS - 2 Step GyMiso®*

Contact your healthcare practitioner immediately if you forget to take the dose of MS - 2 Step GyMiso® tablets in the purple box, and it is greater than 48 hours after you have taken MS -2 Step Mifepristone Linepharma tablet.

If you use too much MS – 2 Step Mifepristone Linepharma

MS – 2 Step Mifepristone Linepharma is available as a single tablet pack, and it is prescribed for you by your healthcare practitioner. An overdose is not likely to occur. Ask your doctor or healthcare practitioner if you have any

concerns. If you think that you have used too much MS – 2 Step Mifepristone Linepharma, you may need urgent medical attention.

You should immediately:

- phone the Poisons Information Centre

(by calling 13 11 26), or

- contact your doctor, or
- go to the Emergency Department at your nearest hospital.

You should do this even if there are no signs of discomfort or poisoning.

5. What should I know while using MS – 2 Step Mifepristone Linepharma?

Things you must do

- After you take MS - 2 Step GyMiso® tablets, you should stay at home and rest for 3 hours. Some women may be at a clinic for this part of the treatment. Vaginal bleeding will usually occur and the pregnancy may be expelled within a few hours of taking MS - 2 Step GyMiso® or during the next few days. The bleeding lasts on average for 10 to 16 days and may be heavy.In some cases, treatment with MS-2 Step may not result in a termination of pregnancy. You must keep all of your clinic appointments so that your progress can be checked. This is very important.
- If treatment with MS-2 Step does not work, a termination can be arranged using another method.
- If treatment with MS-2 Step does not work and you wish to keep your pregnancy, it is not known if MS - 2 Step Mifepristone Linepharma can cause harm to your baby. It is believed, though, MS - 2 Step GyMiso® can cause harm to your baby. You need to tell your doctor or nurse about MS-2 Step so that they can carefully monitor your pregnancy.

If you are Rhesus negative, the use of *MS-2 Step* requires that your doctor will take measures to prevent Rhesus factor sensitization, along with the general measures taken during any pregnancy termination. **It is very important that you have follow up with your doctor or healthcare practitioner 14 to 21 days after you take MS - 2 Step Mifepristone Linepharma, to ensure that the termination was complete because incomplete termination will increase the risk of serious infection or bleeding**.

In case of heavy and prolonged bleeding, you should contact your doctor or clinic immediately to get advice and care.

Using contraceptives: It is possible for you to become pregnant again immediately after the pregnancy termination is completed. As some effects of misoprostol and mifepristone may still be present after taking MS-2 Step, it is recommended that you avoid getting pregnant again before your next menstrual period.

Tell your doctor if you are a smoker.

Call your healthcare practitioner straight away:

- In case of heavy and prolonged bleeding, you should contact your healthcare practitioner or clinic immediately to get advice and care.
  In a few cases, a termination can occur after you take MS -2 Step Mifepristone Linepharma but before you take MS - 2 Step GyMiso®. It is essential that you are checked to confirm that a complete termination has occurred. If this occurs, you should contact your doctor immediately in order to schedule an appointment.

Remind any doctor, nurse, dentist or pharmacist you visit that you are using MS-2 Step as it may interact with other medicines or anaesthetics they may use.

Things you should not do

- It is recommended that you do not travel away from home during the time that you are bleeding so that you can visit your doctor or clinic if necessary

Driving or using machines

Be careful before you drive or use any machines or tools until you know how MS - 2 Step Mifepristone Linepharma affects you.

Drinking alcohol

Tell your healthcare practitioner if you drink alcohol.

Looking after your medicine

- MS - 2 Step Mifepristone Linepharma should be stored within the MS-2 Step pack
- Store below 25 degrees C.
- Store in the original packaging.

Follow the instructions in the carton on how to take care of your medicine properly.

Store it in a cool dry place away from moisture, heat or sunlight; for example, do not store it:

- in the bathroom or near a sink, or
- in the car or on window sills.

Keep it where young children cannot reach it.

Getting rid of any unwanted medicine

If you no longer need to use this medicine or it is out of date, take it to any pharmacy for safe disposal.

Do not use this medicine after the expiry date.

6. Are there any side effects?

All medicines can have side effects. If you do experience any side effects, most of them are minor and temporary. However, some side effects may need medical attention.

See the information below and, if you need to, ask your healthcare practitioner if you have any further questions about side effects.

Less serious side effects

Less serious side effects	What to do
Gastrointestinal upset • Nausea • Vomiting • Diarrhoea **Tiredness related** • Fainting • Dizziness • Fatigue • Headache **Vagina related** • Vaginal bleeding which may be heavy or prolonged • Spotting **Pain related** • Abdominal discomfort • Abdominal pain • Cramps • Breast tenderness **Skin related** • Hot flushes • Skin rashes or itching **Infection related** • Chills and /or fever	**Speak to your doctor if you have any of these less serious side effects and they worry you.**

Serious side effects

Serious side effects	What to do
Skin related • Serious skin reactions include reddish circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. • These serious skin rashes are rare and can be preceded by fever and flu-like symptoms. A red, scaly widespread rash with bumps under the skin and blisters accompanied by fever may appear at the initiation of treatment. **Bleeding related** • Vaginal bleeding usually starts a few hours after taking MS – 2 Step GyMiso® tablets. Bleeding can occur for 10 to 16 days, and it is usual for bleeding to be heavier than a normal period for 2 to 3 days. Contact your doctor immediately if you find you have very heavy bleeding and have soaked more than 2 pads per hour over 2 hours. **Infection related** • Serious infections are very rare in a medical termination of pregnancy and can be potentially life threatening. If you have symptoms more than 24 hours after taking MS – 2 Step GyMiso® or ongoing abdominal pain, or feeling unwell or feeling weak, with or without a fever, you should contact your doctor without delay.	**Call your doctor straight away, or go straight to the Emergency Department at your nearest hospital if you notice any of these serious side effects.**

Tell your healthcare practitioner if you notice anything else that may be making you feel unwell.

Other side effects not listed here may occur in some people.

Reporting side effects

After you have received medical advice for any side effects you experience, you can report side effects to the Therapeutic Goods Administration online at www.tga.gov.au/reporting-problems. By reporting side effects, you can help provide more information on the safety of this medicine.

Always make sure you speak to your healthcare practitioner before you decide to stop taking any of your medicines.

7. Product details

This medicine is only available with a prescription.

What MS – 2 Step Mifepristone Linepharma contains

Active ingredient (main ingredient)	mifepristone
Other ingredients (inactive ingredients)	colloidal anhydrous silica magnesium stearate maize starch microcrystalline cellulose povidone
Potential allergens	No

The tablets do not contain gluten, lactose, tartrazine or any azo dyes.

Do not take this medicine if you are allergic to any of these ingredients.

What MS - 2 Step Mifepristone Linepharma looks like

The MS - 2 Step Mifepristone Linepharma tablet is a white to off white, round tablet, with MF embossed on one side of the tablet. Each tablet contains 200 mg of mifepristone. MS - 2 Step Mifepristone Linepharma is in a blister pack of one tablet. There is one Mifepristone Linepharma pack in each MS-2 Step pack.

Australian registration number: AUST R 210574

Who distributes MS - 2 Step Mifepristone Linepharma

MS-2 Step is supplied in Australia by:

MS Health Pty Ltd

Suite 60, 278 Church Street,

Richmond, VIC, Australia, 3121.

Ph: 1300 515 883 MS-2 Step® is a registered trademark of MSI

Reproductive Choices (UK). Mifepristone

Linepharma and GyMiso® are licensed from

Linepharma International Limited (UK).

This leaflet was prepared in April 2023.

PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**MIFEGYMISO**

Mifepristone tablet
Tablet, mifepristone 200 mg, oral administration
Progesterone receptor modulator

and

Misoprostol tablets
Tablets (4), misoprostol 200 mcg (each),
buccal administration
Prostaglandin

Medical Termination of Pregnancy

Sponsor:
Linepharma International Limited
16, Upper Woburn Place,
London, WC1H 0BS
United Kingdom

Date of Initial Authorization:
JUL. 29, 2015

Date of Revision:
MAY. 02, 2023

Importer and distributor in Canada:
Linepharma International Inc.
402-21 St Clair Ave E
Toronto, Ontario
M4T 1L9

Submission Control No: 270410

RECENT MAJOR LABEL CHANGES

3 SERIOUS WARNINGS AND PRECAUTIONS BOX	06/2022
4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations	05/2023
7 WARNINGS AND PRECAUTIONS, Skin	06/2022
7 WARNINGS AND PRECAUTIONS, Skin	12/2022

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Mifegymiso (mifepristone tablet/misoprostol tablets) is indicated for:

- medical termination of a developing intra-uterine pregnancy with a gestational age up to 63 days as measured from the first day of the Last Menstrual Period (LMP) in a presumed 28-day cycle.

Mifegymiso is not intended for routine use as a contraceptive.

1.1 Pediatrics

Pediatrics (<15 years of age): There are insufficient data in patients less than 15 years old to establish efficacy and safety. Mifegymiso is not indicated in the prepubertal population.

Pediatrics (>15 and <18 years of age): Compared to adults, patients less than 18 years of age reported vomiting and pain more frequently (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

1.2 Geriatrics

Geriatrics (>65 years of age): Mifegymiso is not indicated in post-menopausal women.

2 CONTRAINDICATIONS

Mifegymiso should not be prescribed to patients who:

- have a confirmed or suspected ectopic pregnancy;
- have an intrauterine device (IUD) in place;
- have unconfirmed gestational age;
- have chronic adrenal failure;
- are on concurrent long term systemic corticosteroid therapy;
- have haemorrhagic disorders or using concurrent anticoagulation therapy;
- have inherited porphyria;
- have uncontrolled asthma;
- have known hypersensitivity to mifepristone, misoprostol, other prostaglandins, or any of the excipients used in Mifegymiso. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- It is important that all patients be followed by a health professional 7 to 14 days after taking mifepristone to confirm safety and complete pregnancy termination (see WARNINGS AND PRECAUTIONS, Genitourinary and Monitoring and Laboratory Tests).
- **Risk of infection and sepsis:** Cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of Mifegymiso. Some patients presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. A high index of suspicion is needed to rule out sepsis (from e.g. Clostridium sordellii) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhea) more than 24 hours after taking misoprostol (see WARNINGS AND PRECAUTIONS, Genitourinary).
- **Risk of skin reactions:** Serious skin reactions including toxic epidermal necrolysis and acute generalized exanthematous pustulosis have been reported in association with Mifegymiso treatment (see WARNINGS AND PRECAUTIONS, Skin)
- **Risk of bleeding:** Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. These patients must seek immediate medical attention (see WARNINGS AND PRECAUTIONS, Genitourinary).
- **Embryotoxicity:** Patients should be counselled that once the treatment is started, there are risks of embryotoxicity if the pregnancy is not terminated. Both mifepristone and misoprostol are embryotoxic and have been associated with fetal abnormalities (see NONCLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).
- **Return to fertility**: Patients should be advised of their immediate return to fertility after Mifegymiso administration. To avoid the potential exposure of a subsequent pregnancy to mifepristone and misoprostol, it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive methods should therefore commence as early as possible (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Woman).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Prior to prescribing Mifegymiso, health professionals must:

- Ensure that patients have access to emergency medical care in the 14 days following administration of mifepristone;
- Schedule follow-up 7 to 14 days after patients take mifepristone to confirm complete pregnancy termination;
- Exclude ectopic pregnancy and confirm gestational age by an appropriate method.
- Counsel each patient on the risks and benefits of Mifegymiso, including bleeding, infection and incomplete abortion;
- Obtain the patient's informed consent to take the drug.

Mifegymiso should be prescribed by health professionals with adequate knowledge of medical abortion and/or who have completed a Mifegymiso education program.

Before starting Mifegymiso, patients must be informed of the following:

- Mifepristone and misoprostol must be taken in sequence according to instructions.
- Follow-up within 7 to 14 days after intake of mifepristone to confirm pregnancy termination and complete abortion is required.
- Return to fertility is expected immediately after Mifegymiso administration and reliable contraceptive methods should be started as early as possible.
- Failure of Mifegymiso may require surgical termination of pregnancy (see CLINICAL TRIALS).
- Signs and symptoms they may experience.
- How to access emergency medical care by telephone or local access.

Mifegymiso should be prescribed by health professionals with adequate knowledge of medical abortion and/or who have completed a Mifegymiso education program

Each patient should be provided with a printed copy of the Mifegymiso Patient Medication Information and a Patient Information Card. The Patient Information Card should be completed by the health professional. These documents as well as a consent form can be obtained and/or ordered from www.linepharma.ca or by phone at 1-877-230-4227. The Mifegymiso Patient Medication Information and the Patient Information Card are also included in the box.

Hepatic impairment

Mifepristone and its metabolites showed a decrease in both overall peak and exposure in patients with moderate hepatic impairment compared to healthy-matched participants. However, no dose adjustments are recommended in this population (see **Error! Reference source not found. Error! Reference source not found.**, Special Populations and Conditions, Hepatic Insufficiency).

4.2 Recommended Dose and Dosage Adjustment

- 200 mg of mifepristone (1 tablet)
- 800 mcg of misoprostol (4 tablets, each tablet containing 200 mcg)

There are no data available on the effect of food intake on the absorption of mifepristone or misoprostol.

4.3 Administration

Step 1 Mifepristone:

- 200 mg of mifepristone (1 tablet) should be taken orally, followed 24 to 48 hours (1 to 2 days) later by the administration of misoprostol.
- Mifepristone should be administered as directed by the prescribing health professional.

Step 2 Misoprostol:

- 800 mcg of misoprostol (4 tablets, each tablet containing 200 mcg) should be taken in a single intake by buccal route (kept between the cheek and the gum for 30 minutes before any remaining fragments are swallowed with water).

4.4 Missed Dose

Step 1 Mifepristone tablet

Patients should be advised to contact their health professional immediately if they delay or do not take the Mifepristone tablet at the time and date directed by the health professional. This information can be found on the completed Patient Information Card.

Step 2 Misoprostol tablets

Patients should be advised to contact their health professional immediately if they forget to take the Misoprostol tablets and it is more than 48 hours after they have taken the Mifepristone tablet.

If it is less than 48 hours since the patient took Step 1 but after the time and date on the Patient Information Card, clinical trial data indicates that health professionals can instruct patients to take the Misoprostol tablets (Step 2) right away.

5 OVERDOSAGE

Mifepristone

No cases of overdose have been reported.

In the event of massive ingestion of mifepristone signs of adrenal failure may occur. Signs of acute intoxication may require specialist treatment including the administration of dexamethasone.

Misoprostol

Cumulative total daily doses of 1600 mcg have been tolerated, with only symptoms of gastrointestinal discomfort reported.

Possible symptoms of an overdose are sedation, tremor, convulsions, dyspnoea, abdominal pain, diarrhea, fever, palpitations, hypotension or bradycardia. Hypertension and tachycardia have also been reported.

There is no specific antidote. Treatment should be symptomatic and supportive. Consider administration of activated charcoal in the event of a potentially toxic ingestion. Activated charcoal may reduce absorption of misoprostol if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1– Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet, 200 mg Mifepristone	Colloidal silica anhydrous, magnesium stearate, maize starch, microcrystalline cellulose, povidone k30.
Buccal	Tablet, 200 mcg Misoprostol	Hydrogenated castor oil, hypromellose, microcrystalline cellulose, sodium starch glycolate

Description

Mifegymiso (mifepristone tablet/ misoprostol tablets) is a composite pack containing one mifepristone 200 mg tablet and four misoprostol 200 mcg tablets. The two products are provided in two different boxes which are packed together.

Mifepristone 200 mg tablets

Mifepristone tablets are white to off white, round, biconvex with "MF" embossed on one side.

Mifepristone is packaged in a PVC/PVDC/Aluminum blister of 1 tablet presented in a green box of one tablet.

Misoprostol 200 mcg tablets

Misoprostol tablets are white, round flat with "ML" debossed on one side and "200" on the other side.

Misoprostol tablets are packaged in dual-faced aluminum strips and presented in an orange box of four (4) tablets.

7 WARNINGS AND PRECAUTIONS

General

Please see SERIOUS WARNINGS AND PRECAUTIONS BOX.

A patient's ability to comply with the requirements of the regimen, especially the need for a follow-up visit, should be considered prior to administering Mifegymiso.

Patients should be advised to take their Patient Information Card with them if they visit an emergency room or another health professional who did not prescribe Mifegymiso, so that the health professional will be aware that the patient is undergoing a medical abortion.

Rhesus alloimmunisation

The use of Mifegymiso requires measures to prevent rhesus alloimmunisation.

Carcinogenesis and Mutagenesis

See Section NON-CLINICAL TOXICOLOGY for the carcinogenesis and mutagenesis on animals.

Cardiovascular

Rare serious cardiovascular accidents have been reported following administration of prostaglandins including misoprostol. Mifegymiso has not been studied, and is therefore not recommended, in women with cardiovascular disease.

Women with risk factors for cardiovascular disease (hypertension, diabetes or who are over the age of 35 and are heavy smokers) should be treated with caution.

Driving and Operating Machinery

Caution is warranted when driving or operating a vehicle or potentially dangerous machinery. Dizziness, fatigue, headache, and fainting can occur. The side effects diminish after Day 3 and are gone by Day 14. The patient must rest 3 hours after taking the misoprostol tablets.

Endocrine and Metabolism

Patients with suspected acute adrenal failure were excluded from trials and therefore should be treated with caution. If treatment with Mifegymiso is required, therapy should be adjusted. The safety and efficacy have not been studied in women suffering from malnutrition. Treatment with Mifegymiso is therefore not recommended.

Genitourinary

Gestational age should be confirmed by an appropriate method. Ultrasound imaging is recommended before prescribing Mifegymiso when an ectopic pregnancy is suspected or gestational age is uncertain. Health professionals should remain alert to the possibility that a patient who is undergoing a medical abortion could have an undiagnosed ectopic pregnancy, since some of the symptoms of a medical abortion may be similar to those of a ruptured ectopic pregnancy. The presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed Mifegymiso.

Treatment failures

Failures in clinical studies occurred in 2.7 to 5.1% of cases prior to 63 days of gestation (see CLINICAL TRIALS). The rate of failure increases with advancing gestational age. Reasons for failure requiring a surgical termination of pregnancy included persistent non-viable pregnancies, continuing pregnancies and persistent heavy vaginal bleeding. Follow-up is mandatory to ensure that the expulsion is completed.

In the event of an ongoing pregnancy, pregnancy termination should be completed by another method (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Woman). Animal studies have shown that, if a pregnancy continues after exposure to mifepristone or misoprostol, fetal abnormalities may occur (see NONCLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

Bleeding

Bleeding occurs in almost all cases and is not proof of complete expulsion (see CLINICAL TRIALS). Prolonged heavy vaginal bleeding may occur and can be a sign of incomplete expulsion. Bleeding can lead to a significant decrease in hemoglobin levels and may necessitate a blood transfusion.

Persistent bleeding should be monitored closely.

The patient should have access to emergency medical care until complete termination of pregnancy is confirmed at a follow-up visit.

Infections

Cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of mifepristone and misoprostol. A sustained fever of 38oC or higher, severe abdominal pain or pelvic tenderness in the days after a medical abortion may be an indication of infection.

Sepsis (from e.g. Clostridium sordellii or other species e.g. Streptococcus) should be highly suspected if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhea) more than 24 hours after taking misoprostol. However, the symptoms of Clostridium sordellii infection are sometimes not the usual symptoms of sepsis. Very rarely, deaths have been reported. Therefore, the possibility of sepsis should be considered in all women who present with nausea, vomiting, diarrhea and weakness with or without abdominal pain or fever. Strong consideration should be given to obtaining a complete blood count in these patients. Significant

leukocytosis with a marked left shift and hemoconcentration may be indicative of sepsis. Health professionals should consider immediately initiating treatment with antibiotics that include coverage of anaerobic bacteria such as Clostridium sordellii.

Hematologic

Heavy bleeding requiring curettage occurred in some patients in clinical trials. Patients with anemia should be treated with caution. Patients with severe anemia were excluded from clinical trials and administration of Mifegymiso in these patients is not recommended.

Hepatic/Biliary/Pancreatic

The safety and efficacy have not been studied in women suffering from hepatic failure. Treatment with Mifegymiso is therefore not recommended.

Immune

Cases of skin rash following misoprostol administration were reported by patients in clinical trials. Angioedema of the face, lips, tongue, and/or larynx, including cases of anaphylaxis have been reported in post-market surveillance with the use of Mifegymiso, including angioedema occurring within an hour of misoprostol intake. Angioedema associated with upper airway swelling may be life threatening. If the tongue, hypopharynx, or larynx has been involved, appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided.

Monitoring and Laboratory Tests

Follow-up must take place within a period of 7 to 14 days after administration of Mifegymiso to verify that expulsion has been completed (i.e. clinical examination, ultrasound scan or beta-hCG measurement). Persistent bleeding should be monitored closely for a decrease in hemoglobin concentration, hematocrit and red blood cell count.

Neurologic

Seizures have been reported with prostaglandins and prostaglandin analogues, and therefore this possibility should be considered when treating patients with a history of a seizure disorder.

Renal

The safety and efficacy have not been studied in women suffering from renal failure. Treatment with Mifegymiso is therefore not recommended.

Reproductive Health: Female and Male Potential

- **Fertility**

During clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses. To avoid the potential exposure of a subsequent pregnancy to mifepristone and misoprostol, conception should be avoided during the next menstrual cycle. Reliable contraceptive precautions should commence as early as possible after Mifegymiso administration (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women).

- **Teratogenic Risk**

Reproductive studies conducted in rabbits and monkeys have shown that if a pregnancy continues after exposure to mifepristone, abnormalities in fetal skull, brain and developmental markers may occur.

Use of misoprostol has been associated with birth defects. When used alone to induce an abortion, the following effects of misoprostol have been reported: malformations of limbs, abnormalities of fetal

movements and of cranial nerves (hypomimia, abnormalities in suckling, deglutition, and eye movements).

Misoprostol was shown to be embryotoxic in rabbits, rats and mice, when exposure occurred during embryogenesis. There was also an increase in skeletal abnormalities in rabbits and cleft palate in mice.

Respiratory

Due to the antiglucocorticoid activity of mifepristone, the efficacy of corticosteroid therapy, including inhaled corticosteroids, may be decreased temporarily following intake of mifepristone. Therapy should be adjusted.

Bronchospasm may occur with some prostaglandins and prostaglandin analogues. Caution should be exercised in patients with a history of asthma (see CONTRAINDICATIONS).

Skin

Severe cutaneous adverse reactions, including toxic epidermal necrolysis and acute generalised exanthematous pustulosis, have been reported in association with mifepristone (see ADVERSE REACTIONS). In patients who experience severe cutaneous adverse reactions, re-treatment with mifepristone is not recommended.

7.1 Special Populations

7.1.1 Pregnant Women

Mifepristone

A review of births from 105 pregnancies exposed during first trimester of pregnancy to mifepristone alone (46 cases) or to both mifepristone and misoprostol (59 cases) has been published. There were 94 live births (90.4%) and 10 (9.6%) miscarriages (including one with major malformation). Elective termination of pregnancy was performed after the subsequent diagnosis of trisomy 21 in one case. The overall rate of major congenital malformations was 4.2% (95% CI: 1.2 – 10.4%), with two cases among 38 patients exposed to mifepristone alone and two cases among 57 patients exposed to both mifepristone and misoprostol.

Misoprostol

Use of misoprostol has been associated with birth defects. When used alone to induce an abortion, the following effects of misoprostol have been reported: malformations of limbs, abnormalities of fetal movements and of cranial nerves (hypomimia, abnormalities in suckling, deglutition, and eye movements).

Mifegymiso

Due to the risk of failure of the medical method of pregnancy termination and to the unknown risk to the fetus, follow-up is mandatory (see SERIOUS WARNINGS AND PRECAUTIONS BOX).

Should a failure of Mifegymiso be diagnosed at follow-up (viable ongoing pregnancy), it is recommended that pregnancy termination should be completed by another method.

Should the patient wish to continue with the pregnancy, she should be appropriately counselled as to the risk of birth defects and appropriate ultra-sonographic monitoring of the pregnancy should be carried out.

7.1.2 Breast-feeding

Mifegymiso use should be avoided during breast-feeding.

Mifepristone is lipophilic and may be excreted in the mother's milk. Misoprostol is rapidly metabolised in the mother to misoprostol acid, which is biologically active and is excreted in breast milk. This could cause undesirable effects such as diarrhea in breastfeeding infants.

7.1.3 Pediatrics

Pediatrics (<15 years of age): There are insufficient data in patients less than 15 years old to establish efficacy and safety. Mifegymiso is not indicated in the prepubertal population.

Pediatrics (>15 and <18 years of age): Patients 15 to 17 years of age had similar efficacy to that seen in the adult population. More pain than expected was reported more frequently in this population, as well as vomiting, compared with adults (see CLINICAL TRIALS). Careful counselling should be provided to adjust patients' expectations from the procedure and identification of safety issues requiring immediate medical attention.

7.1.4 Geriatrics

Mifegymiso is not indicated in post-menopausal women.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most frequent undesirable effects which were observed during treatment with Mifegymiso were:

- Reproductive system disorders: vaginal bleeding, sometimes heavy and prolonged uterine cramping (see WARNINGS AND PRECAUTIONS, Genitourinary).
- Gastrointestinal disorders: nausea, vomiting, diarrhea and abdominal pain.
- General disorders: headache, dizziness, chills and fever.

Bleeding was occasionally observed after mifepristone alone. Misoprostol administration resulted in vaginal bleeding, abdominal pain and cramping. In some patients, persistent or heavy vaginal bleeding required treatment with intravenous fluids or blood transfusion. On average, bleeding lasted for 11.4 days and was heavier than a normal period for 2.2 days.

Infectious complications, including sometimes fatal sepsis, have been observed. Patients typically presented with abdominal pain or discomfort, fever or general malaise (including weakness, nausea, vomiting or diarrhea) more than 24 hours after taking misoprostol. *Clostridium sordellii* infection was observed in some women without abdominal pain or fever, that progressed rapidly to multi-organ failure and death.

The adverse events reported with Mifegymiso, classified according to frequency and system organ class, are summarized as shown in Table 2.

Table 2: Adverse Events for the Use of Mifepristone and Misoprostol

MedDRA	Adverse events (frequency)		
System Organ Class	**Very common (≥ 1/10)**	**Common (> 1/100 to < 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**
Gastro-intestinal disorders	Nausea; Vomiting; Diarrhea; Gastric discomfort; Abdominal pain	Cramping, light or moderate	
Cardiac disorders			Arrhythmia
Nervous system disorders	Headache		
Reproductive system & breast disorders	Vaginal bleeding; Spotting; Uterine contractions or cramping	Prolonged post-abortion bleeding; Severe hemorrhage; Endometritis; Breast tenderness; Heavy bleeding; Heavy bleeding requiring surgical termination of pregnancy	Hemorrhagic shock; Salpingitis; Heavy bleeding requiring IV fluids or blood transfusion
General disorders and administration site conditions	Fatigue; Chills/fever; Dizziness	Syncope	
Infections and infestations			Infection
Vascular disorders			Hot flush; Hypotension
Respiratory, thoracic and mediastinal disorders			Bronchospasm

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Mifegymiso was studied in three open-label multi-center prospective studies. In these studies, a total of 1,596 women were included in the safety analysis. The mean age of women who received mifepristone and misoprostol was 26.0, 26.7 and 25.4 years for Studies 1, 2 and 3, respectively. Treatment-emergent adverse events reported in clinical trials are reported in Table 3. Nausea and vomiting tended to increase slightly with advancing gestational age.

Table 3: Treatment-Emergent Adverse Events Occurring in Clinical Trials, %

Adverse Events	Study 1	Study 2	Study 3
	N = 212	N = 415	N = 969
Nausea	70.8	66.0	34.2
Vomiting	37.7	40.2	26.4
Diarrhea	36.8	33.7	59.5
Pain	93.4	-	-
Fever	42.9	18.6	45.3
Chills	-	36.9	
Headache	44.3	34.0	13.9
Dizziness	41.5	32.8	13.1
Weakness	55.7	45.1	21.3

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Study results in women less than 18 years of age

Of the 1,000 women enrolled in Study 3, 67 were less than 18 years of age. The reported frequent adverse events are detailed below. Women less than 18 years old reported vomiting more frequently than women 18 years and older.

Table 4: Adverse events by women age, % (N=969)

Adverse Events	< 18 years	≥ 18 years
	N = 67	N = 902
Nausea	29.9	34.5
Vomiting	43.3	25.2
Diarrhea	62.7	59.3
Fever/chills	41.8	45.6
Headache	11.9	14.1
Dizziness	16.4	12.9
Weakness	17.9	21.6

8.5 Post-Market Adverse Reactions

The following adverse reaction have been identified during the post-marketing experience in association with Mifegymiso use.

Skin and subcutaneous tissue disorders: Skin rash/pruritus and acute generalized exanthematous pustulosis.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No interaction studies have been performed with mifepristone and misoprostol.

Mifepristone

In vitro studies and *in vivo* data showed mifepristone to be metabolized by CYP3A4 and that co-administration of other CYP3A4 substrates inhibited metabolite formation. CYP3A4 inhibitors, such as ketoconazole, itraconazole and erythromycin may inhibit mifepristone metabolism, whereas CYP3A4 inducers, such as rifampicin, dexamethasone, and certain anticonvulsants (phenytoin, phenobarbital, carbamazepine), may increase its metabolism.

In vitro studies also showed mifepristone to be a competitive inhibitor of CYP3A4 and, to a lesser extent, of CYPs 1A, 2B, 2D6, and 2E1.

Due to the irreversible nature of the CYP binding and the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP3A4 substrates and have narrow therapeutic range, including some agents used during general anaesthesia.

In an open-label, cross-over, phase 1 DDI Study done in healthy female subjects, the co-administration of mifepristone with rifampicin (strong CYP3A4 inducer) was shown to decrease mifepristone AUC by 6.3-fold, and thus a reduced efficacy may be expected. Therefore, in patients treated with strong or moderate CYP3A4 inducers, a different termination of pregnancy procedure might be warranted. In case of concomitant administration with CYP3A4 inducers, a follow-up appointment with the patient is needed to ensure the pregnancy has completely ended. In the event of method failure, a different termination of pregnancy procedure is to be suggested to the patient.

Due to the antiglucocorticoid activity of mifepristone, the efficacy of corticosteroid therapy, including inhaled corticosteroids, may be temporarily decreased following intake of mifepristone. Therapy should be adjusted.

Misoprostol

Limited studies investigating the metabolism of misoprostol were conducted in the rat. Misoprostol was not found to affect hepatic drug metabolism.

No drug interactions have been attributed to misoprostol in extensive clinical trials.

9.3 Drug-Behavioural Interactions

Mifepristone and misoprostol may cause dizziness, which could have an effect on the ability to drive and use machines.

9.4 Drug-Drug Interactions

Table 5: Established or Potential Drug-Drug Interactions

Mifepristone

Class/Common name	Source of Evidence	Effect	Clinical comment
CYP3A4 inhibitors (such as ketoconazole, itraconazole and erythromycin)	CT	↑ mifepristone plasma concentration	Mifepristone is metabolized by CYP3A4. Co-administration of mifepristone with itraconazole (strong CYP3A4 inhibitor) was shown to increase mifepristone AUC by 2.6-fold. No dose adjustment is recommended when mifepristone is given concomitantly with a CYP3A4 inhibitor, but caution is warranted.
CYP3A4 inducers (such as rifampicin, dexamethasone and certain anticonvulsants (phenytoin, phenobarbital, carbamazepine)	CT	↓ mifepristone plasma concentration	Mifepristone is metabolized by CYP3A4. Co-administration of mifepristone with rifampicin (strong CYP3A4 inducer) was shown to decrease mifepristone AUC by 6.3-fold. Therefore, a reduced efficacy may be expected when mifepristone is co-administered with a strong or moderate CYP3A4 inducer.
Corticosteroid therapy, including inhaled costicosteroids	T	↓ corticosteroid	Mifepristone has antiglucocorticoid activity. The efficacy of corticosteroid therapy may be temporarily decreased following intake of mifepristone. Therapy should be adjusted.
CYP3A4 substrates that have narrow therapeutic range (including some agents used during general anaesthesia)	T		Due to the irreversible nature of the CYP binding and the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Caution should be exercised when mifepristone is administered with drugs that are CYP3A4 substrates and have narrow therapeutic range.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Grapefruit juice may inhibit mifepristone's metabolism, increasing its serum levels.

9.6 Drug-Herb Interactions

The concomitant use of St. John's Wort may increase mifepristone metabolism, lowering its serum levels.

9.7 Drug-Laboratory Test Interactions

There are no known effects of mifepristone or misoprostol on laboratory tests.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

When mifepristone blocks progesterone receptors, the endometrium can no longer sustain the growing embryo. Without the effect of progesterone, the lining of the uterus breaks down, and bleeding begins. Mifepristone also triggers an increase in prostaglandin levels and dilates the cervix, facilitating abortion. Misoprostol then induces contractions of the smooth muscle fibers in the myometrium, relaxation of the uterine cervix and evacuation of intrauterine content.

10.2 Pharmacodynamics

Mifepristone

Mifepristone is an orally active antiprogestogen which acts by competing with progesterone for receptor binding. It also possesses antiglucocorticoid and antiandrogenic activity. It is devoid of estrogenic, antiestrogenic, mineralocorticoid and antimineralocorticoid properties. Its ability to block the action of progesterone on the pregnant uterus provides a medical approach to termination of early pregnancy. In normally menstruating women, the effect of mifepristone depends on the timing of administration. When administered in the first half of the luteal phase, menstrual induction occurs independently of luteolysis; mifepristone administration during the mid-luteal phase produced bleeding within a few days in most women but there was a second bleed at the time of expected menses in about two-thirds. The first episode of bleeding occurred in the presence of elevated progesterone and estrogen concentrations. Administration during the late luteal phase resulted in bleeding within 1 to 3 days, shortening the luteal phase of the treatment cycle and lengthening of the subsequent follicular phase. Administration on the first 3 days of the menstrual cycle had no effect on cycle length but when given in the late follicular phase, mifepristone prolonged the follicular phase by preventing the development of a normal LH surge and delaying the new surge for about 15 days.

In the first trimester of pregnancy, mifepristone induced uterine activity in virtually all women 36 and 48 hours after administration, and increased the sensitivity of myometrium to exogenous prostaglandins (PG). The accompanying increase in decidual $PGF2_{\alpha}$ production was attenuated by indomethacin, but the increase in uterine activity was not: thus, mechanisms other than an increase in decidual PG production contribute to the abortifacient effect of mifepristone. Mifepristone administration also resulted in cervical ripening in pregnant women.

Single doses of mifepristone of 4.5 and 6 mg/kg increase plasma levels of cortisol, ACTH and lipotrophin, and in patients with unresectable meningioma treated with 200 mg mifepristone daily for prolonged periods, increases in plasma cortisol, ACTH and urinary cortisol are maximal at 3 weeks and remain unchanged thereafter. Dosages of mifepristone required to exert antiglucocorticoid effects, which are achieved by disruption of the negative pituitary feedback, are higher than those needed for antiprogestogen activity. In subjects with normal adrenal function, the increase in ACTH produced by

mifepristone compensates for its antiglucocorticoid activity and there have been no reports of acute adrenal insufficiency at dosages used to terminate early pregnancy.

Mifepristone inhibited estrous cycling in rats at oral doses of 0.3-1 mg/kg/day (less than the clinical dose adjusted for body surface area) in a 3-week study. This was reversed over the following 2-3 weeks and no subsequent effects on reproductive performance were found.

Mifepristone binds to human progesterone receptors with nanomolar affinity. In animals, oral administration was shown to inhibit the action of endogenous or exogenous progesterone in multiple species.

In women administered 1 mg/kg or greater, mifepristone antagonises the endometrial and myometrial effects of progesterone. During pregnancy it sensitises the myometrium to the contraction-inducing action of prostaglandins. During the first trimester, administration of mifepristone allows cervical dilatation.

In vitro studies showed mifepristone to also bind to the glucocorticoid and androgen receptors with high affinity, comparable to that for the progesterone receptor. In toxicological studies in rats and monkeys up to a duration of 6 months, mifepristone produced effects related to its antihormonal (antiprogesterone, antiglucocorticoid and antiandrogenic) activity.

In man the antiglucocorticoid action is manifested at a dose equal to or greater than 4.5 mg/kg by a compensatory elevation of ACTH and cortisol.

Misoprostol

Misoprostol is a synthetic analogue of prostaglandin E1. At the recommended dosages, misoprostol induces contractions of the smooth muscle fibers in the myometrium and relaxation of the uterine cervix. The uterotonic properties of misoprostol should facilitate cervical opening and evacuation of intrauterine content. In the event of an early termination of pregnancy, the combination of misoprostol used in a sequential regimen after mifepristone leads to an increase in the success rate and accelerates the expulsion of the conceptus. Among other effects, misoprostol inhibits the acid gastric secretion and increases the digestive peristaltism.

Uterine contractility following administration of misoprostol via the buccal route was investigated with an intrauterine pressure transducer in women seeking termination of pregnancy. Results indicated that the average time to onset of increased tone and first uterine contraction were 41.2 and 67.1 minutes, respectively. Sustained uterine activity was observed on average after 90.0 minutes and peak uterine activity after 264.0 minutes.

In fertility studies in rats in which treated females were mated with treated males, increased pre-implantation losses were observed with misoprostol at oral doses greater than 1 mg/kg/day (11 times the recommended human dose, on a mg/m^2 basis). Post-implantation loss was also increased at 10 mg/kg/day (114 times the recommended human dose, on a mg/m^2 basis).

10.3 Pharmacokinetics

Mifepristone

The pharmacokinetic properties of mifepristone have been studied mostly following oral administration in healthy women, although studies were also conducted in pregnant women and a few male volunteers. Plasma concentrations of mifepristone and its metabolites were measured by radioimmuno- and radioreceptor assays, or high performance liquid chromatography (HPLC), and

pharmacokinetic parameters calculated employing one- and two-compartment models as well as non-compartmental analysis.

The pharmacokinetics of mifepristone and its metabolites are not linear.

Absorption

After oral administration of a single dose of 200 mg, mifepristone is rapidly absorbed. The peak concentration of 2.3 to 2.7 mg/L is reached after 0.75 hours (mean of 49 subjects). The half-life of mifepristone is 36.5 to 38.3 hours.

Following oral administration of single doses of mifepristone 100, 400, 600 and 800 mg to healthy female volunteers maximum plasma concentrations were about 2.5 mg/L (2,500 ng/mL) and differed between the 100 and 800 mg doses only 2 hours after ingestion. After a single 600 mg dose maximum plasma concentration was about 2 mg/L (2,000 ng/mL) at 1.35 hours. High doses of 10 and 25 mg/kg in healthy female and male volunteers produced maximum plasma concentrations of progesterone receptor-reactive material of 5.17 to 7.5 mg/L. Maximum plasma concentrations were attained 0.7 to 1.5 hours after oral administration. The parent drug and its metabolites were still detectable 6 to 7 days after a single dose using HPLC and for 10 days using radioimmunoassay.

Administration of 12.5, 25, 50 or 100 mg twice daily for 4 days to healthy female volunteers resulted in similar plasma concentrations of 1.4 to1.7 mg/L (1,400 to 1,700 ng/mL) at dosages > 50 mg twice daily, and it was suggested that the lack of increase in plasma drug concentration when dosage increased above 50 mg twice daily is partly explained by saturation of □-I-acid glycoprotein (AAG), the serum binding protein for mifepristone in man, which has a binding capacity lower than the therapeutic dose.

Plasma concentration and clinical efficacy: a study conducted in 17 women less than 56 days pregnant who were administered mifepristone 600 mg for termination of pregnancy, found no correlation between clinical efficacy (13 responders) and plasma concentration of mifepristone or circulating metabolites, protein binding, or plasma AAG.

The absolute bioavailability of a low oral dose of 20 mg is 69 %.

Distribution:

Mifepristone is 99% bound to plasma proteins, albumin and α1-acid glycoprotein in man. Binding to the latter protein is saturable, and the drug displays nonlinear kinetics with respect to plasma concentration and clearance. Animal studies found mifepristone to be widely distributed, initially having high extravascular concentration, but shifting to greater erythrocyte concentration over 24 hrs. Studies in pregnant animals have shown mifepristone to cross the placental barrier.

Apparent initial volume of distribution after intravenous administration of mifepristone 280 mg was low (8 L) but at steady state was 25.7 L. The volume of distribution and clearance of mifepristone were inversely proportional to the plasma concentration of AAG, being greater in subjects with low AAG levels, and are dose· and time-dependent. At plasma concentrations of up to 0.8 mg/L mifepristone is about 98 % bound to plasma proteins in the blood. Its binding to erythrocytes is negligible. A value of 94 % was reported at a plasma mifepristone concentration of 5 mg/L. It is considered that AAG is the principal binding protein for mifepristone. When binding to AAG is saturated, mifepristone and its metabolites bind to albumin.

Metabolism:

Metabolism of mifepristone is primarily via pathways involving N-demethylation and terminal hydroxylation of the 17-propynyl chain. In vitro studies have shown that CYP450 3A4 is primarily

responsible for the metabolism. The three major metabolites identified in humans are: (1) N-monodemethylated metabolite, the most widely found in plasma; (2) N-didemethylated mifepristone, which results from the loss of two methyl groups from the 4-dimethylaminophenyl in position 11 ß; and (3) terminal hydroxylation of the 17-propynyl chain.

Metabolites are detectable in plasma 1 hour after ingestion of mifepristone. Their concentrations increase dose-dependently with those of the monodemethylated metabolite sometimes exceeding those of the parent compound. The plasma concentrations of the didemethylated compound rises gradually over the first 10 hours following mifepristone administration. The binding affinity of the metabolites to progesterone receptors is about 10 to 20% of that of mifepristone and it is not known whether they contribute to the pharmacological effects of mifepristone.

Effect of CYP3A4 on the oxidation of mifepristone in human liver microsomes: Using in vitro techniques, it has been demonstrated that human liver microsomes catalyzed the demethylation of mifepristone with mean (+ SD) apparent K_m and V_{max} values of 10.6 + 3.8 µM and 4920 + 1340 pmol/min/mg protein. CYP3A4 substrates progesterone and midazolam inhibited metabolite formation by up to 77 %. Other isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2E1) had apparently no action on mifepristone metabolism. CYP3A4 appears as the isoenzyme primarily responsible for mifepristone demethylation and hydroxylation in human liver microsomes.

Elimination

Elimination of mifepristone is slow at first (50% eliminated between 12 and 72 hours) and then becomes more rapid with a terminal elimination half-life of 18 hours. Mifepristone shows non-linear pharmacokinetics. Eleven days after a 600 mg dose of tritiated compound, 83% of the drug has been accounted for in the feces and 9% in the urine. Serum levels are undetectable at 11 days.

Total plasma clearance of mifepristone was reported to be 3 L/h. Following oral administration of titrated mifepristone to healthy volunteers, 90% of the dose was recovered in the feces over a period of 6 to 7 days. As mifepristone was completely absorbed, the principal route of elimination was biliary. The urinary route was secondary and renal clearance was negligible relative to total clearance.

In studies employing long sampling periods, the elimination half-life of mifepristone was reported to be 24 to 54 hours.

Special Populations and Conditions

- **Hepatic Insufficiency**: A study has been done on 8 women with moderate hepatic impairment versus 8 women with normal hepatic function, treated with a single oral dose of mifepristone 200 mg to assess the mifepristone and its metabolites (N-demethylated metabolite, hydroxylated metabolite and di-demethylated metabolite) pharmacokinetic. The total C_{max} of mifepristone and its metabolites were reduced by half in patients with moderate hepatic impairment compared to normal hepatic function participants. Similarly, the total AUC_{∞} was reduced by 43% and 50% for mifepristone and N-demethylated metabolite in patients with moderate hepatic impairment compared to normal hepatic function participants. This decrease in exposure could be caused by a decrease in absorption and/or protein binding. However, the assessment of mifepristone and its metabolites unbound fractions (0.2 to 6%) could not be performed with enough accuracy to be able to discriminate any significant variation between the two groups. Considering the above, the clinical consequences of 200 mg mifepristone administration in patient with moderate hepatic impairment are still unknown.

Misoprostol

Absorption

When administered orally, misoprostol is rapidly absorbed (T_{max}: 30 minutes) and metabolized. Peak concentrations around 1.1 ng/mL were reached about 15 minutes after a 400 mcg dose in the fasting state. Plasma concentrations of its main degradation metabolite, misoprostol acid, reach their peak of 2 - 2.5 ng/mL after a 2 mcg/kg oral dose within approximately 30 minutes and rapidly decline thereafter. As a result, uterine contractility increases and then plateaus after about one hour. Absorption is almost complete, measured at levels between 64 - 73% from urinary data.

Overall, areas under curve tend to be higher when misoprostol is administered via vaginal, sublingual or buccal routes when compared to oral administration. A study compared the pharmacokinetics of misoprostol (800 mcg) administered either sublingually or buccally in non pregnant women: misoprostol plasma concentrations were higher for the sublingual vs. the buccal route. The misoprostol $AUC_{0–\infty}$ (1,910 vs. 484 pg/mL, sublingual and buccal, respectively, $p<0.04$) and AUC0–4h (1600 vs. 380 pg/mL, sublingual and buccal, respectively, $p<0.03$) were lower when given by the buccal route. Sublingual misoprostol administration achieved a higher C_{max} compared to buccal (1,140 vs. 229 pg/mL, $p<0.03$). No difference was found when comparing sublingual and buccal C_{min} or half-life.

Parametric confidence intervals were used for the evaluation of the relative bioavailability as the ANOVA residuals did not deviate from normal distribution. The following formal preconditions for the evaluation of the relative bioavailability were checked and found to be met.

A terminal elimination half-life of < 2.5 h was observed in all subjects. The wash-out phase of at least 1 week was adequate, corresponding to at least 60 times the apparent terminal disposition half-life in the subjects. A carry over from one treatment to the other thus was methodologically excluded by an adequate wash-out. The ANOVA revealed, correspondingly no significant sequence effect for any of the pharmacokinetic characteristics. Also no period effect occurred.

An adequate portion of the total area under the curve of >80% was covered by measured concentrations in all subjects.

The 90% confidence intervals of the AUC_{0-t} ratio (89.4-101%), $AUC_{0-\infty}$ ratio (90.4- 102%) and C_{max} ratio (83.4-105%) were included by the acceptance range of 80- 125%.

Table 6: Summary of Pharmacokinetic Parameters of Oral Misoprostol 200 mcg Tablets in Healthy Women

	Mean	Median	SD	Q1	Q3
AUC_{0-t} (h*ng/mL)	0.710	0.650	0.247	0.523	0.862
AUC_0 (h*ng/L)	0.746	0.674	0.259	0.545	0.918
C_{max} (ng/mL)	1.10	1.07	0.42	0.871	1.28
MRT (h)	0.776	0.690	0.428	0.589	0.764
T_{max} (h)	0.246	0.250	0.129	0.167	0.333
$T_{1/2}$ (h)	0.581	0.476	0.444	0.379	0.524

Distribution:

Serum protein binding of labeled misoprostol acid was studied in man and was similar in young (81-88%) and elderly (81-89%) subjects. Accumulation in erythrocytes was not seen.

Metabolism:

Metabolism of misoprostol to misoprostol acid is rapid with no intact misoprostol found in plasma consistent with an in vitro half-life of 6.4 minutes for the de-esterification of misoprostol in human plasma at 37°C.

Elimination

Elimination of misoprostol and its metabolites is also rapid with a plasma elimination half-life of 21 minutes in man. 1-4% of misoprostol acid is excreted in the urine.

After administration of radio-labeled misoprostol, approximately 80% of radioactive products are eliminated in the urine and feces, respectively. Approximately 56 % of the product is eliminated in the urine within 8 hours after intake.

11 STORAGE, STABILITY AND DISPOSAL

Mifegymiso should be stored between 15-25°C in its original outer carton in order to protect from light. Keep out of the sight and reach of children.

Storage of mifepristone 200 mg tablet

When separated, mifepristone should be stored between 15-30°C; in the mifepristone (Green) box, in order to protect from light.

Storage of misoprostol 200 mcg tablets

When separated, misoprostol should be stored between 15-25°C; in the misoprostol (Orange) box.

12 SPECIAL HANDLING INSTRUCTIONS

No special handling instructions are required.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

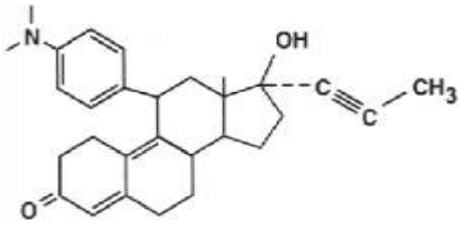
Mifepristone

Proper name: mifepristone

Chemical name: (11β,17β)-11-[4-(Dimethylamino)phenyl]-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one

Molecular formula and molecular mass: $C_{29}H_{35}NO_2$; 429.6 g/mol

Structural formula:



The absolute configuration of the chiral centers is as follows: 8S, 11R, 13S, 14S, 17R.

Physicochemical properties:

The compound is a yellow powder with a melting point of 191-196 °C. It is highly soluble in methanol and methylene chloride, and poorly soluble in water.

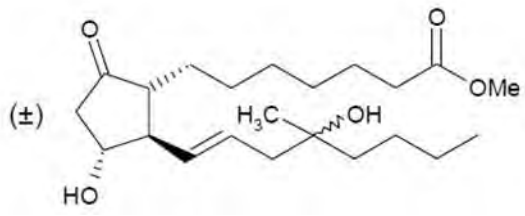
Misoprostol

Proper name: misoprostol

Chemical name: (±)-Methyl (1R,2R,3R)-3-hydroxy-2-[(E)-(4RS)-4-hydroxy-4-methyl-1-octenyl]-5-oxocyclopentaneheptanoate (USP)

Molecular formula and molecular mass: $C_{22}H_{38}O_5$; 382.54g/mol

Structural formula:



The structure of misoprostol contains four chiral centers, the presence of 2^4 = 16 enantiomers is thus possible. Four of the 16 enantiomers comprise misoprostol [methyl (13E)-(±)-11,16- dihydroxy-16-methyl-9-oxoprost-13-en-1-oate], and the other 12 enantiomers comprise Impurity A (8-epi misoprostol), Impurity E (11-epi misoprostol) and Impurity B (12-epi misoprostol) by 4 enantiomers respectively.

Physicochemical properties: Misoprostol is a clear, colorless to yellowish oily liquid. Practically insoluble in water, soluble in ethanol (96%), sparingly soluble in acetonitrile.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Medical Termination of a Developing Intra-Uterine Pregnancy

Study Design and Demographics

Table 7: Summary of patient demographics for clinical trials

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study 1	Open-label, randomized study	200 mg mifepristone tablet oral 800 mcg misoprostol tablet buccal	223	17 years or older Age: ≤ 24 year old: 51.1% 25-29 year old: 19.7% 30-34 year old: 19.7% ≥ 35 year old: 9.4%	F
Study 2	Open-label, randomized study	200 mg mifepristone tablet oral 800 mcg misoprostol tablet buccal	421	17 years or older Age: ≤ 24 year old: 44.9% 25-29 year old: 25.2% 30-34 year old: 16.2% ≥ 35 year old: 13.8%	F
Study 3	Open-label, single arm, prospective study	200 mg mifepristone tablet oral 800 mcg misoprostol tablet buccal	1000	13 years or older Age: ≤ 24 year old: 52.8% 25-29 year old: 21.3% 30-34 year old: 14.6% ≥ 35 year old: 11.4%	F

Study 1 (Middleton et al. 2005)

This study was an open-label trial conducted in two family planning clinics in the United States. Healthy women (N = 223) with an intra-uterine pregnancy up to 56 days since the first day of the last menstrual period (LMP) verified by ultrasonography, requesting a termination of pregnancy received 200 mg oral mifepristone followed after 24 to 72 hours by 800 mcg buccal misoprostol. The efficacy of the procedure was assessed by vaginal ultrasound and adverse events were evaluated during a follow-up visit 4 to 15 days after mifepristone administration.

Study 2 (Winikoff et al. 2008)

This open-label randomized seven-site study conducted in the United States compared the efficacy and safety of 200 mg oral mifepristone followed 24 to 36 hours later by 800 mcg buccal or oral misoprostol for early termination of pregnancy. Healthy women (N = 421) with an intra-uterine pregnancy up to 63 days LMP, determined by clinical examination and/or ultrasonography, were enrolled. The efficacy of

the procedure was established by ultrasonography, and adverse events were assessed during a 7 to 14 days follow-up, after the intake of mifepristone.

Study 3 (Pena et al. 2014)

This open-label single-arm study was conducted in three sites in Mexico. Its objective was to evaluate the safety and efficacy of mifepristone (200 mg oral) followed 24 to 48 hours by misoprostol (800 mcg buccal) for early pregnancy termination. Gestational age was determined by physical examination, menstrual history and ultrasound and 1,000 healthy women with pregnancy up to 63 days LMP were enrolled. Pregnancy termination was confirmed by ultrasound and clinical exam 8 days after study enrollment.

Study Results

Results from the three phase 3 pivotal trials are summarized in Table 8 to Table 12.

Clinical efficacy in the three pivotal trials was defined as complete abortion without surgical intervention. In the three studies, women presenting at follow-up with an on-going viable pregnancy were offered surgical termination of pregnancy. Ultrasound was performed in 96.7% of patients in clinical trials. Women presenting with a persistent gestational sac at first follow-up visit could opt for surgical intervention or wait and follow-up at a next visit for a spontaneous resolution on Day 15 to 36 post-mifepristone. In studies 2 and 3, women with a persistent gestational sac at the first follow-up visit could also choose to receive a second dose of 800 mcg buccal misoprostol. Of the 12 women choosing a second misoprostol dose, 9 had a complete abortion without surgery at next follow-up visit and 3 required a surgical intervention.

Table 8: Outcome of women undergoing medical termination of pregnancy

	Study		
	1 (N = 215)*	**2 (N = 421)**	**3 (N = 971)***
Termination of pregnancy without surgical procedure	**94.9%**	**96.2%**	**97.3%**
≤49 days of gestation	95.1%	97.2%	98.0%
50-56 days of gestation	94.3%	95.7%	96.8%
56-63 days of gestation		94.8%	95.9%
Surgical termination of pregnancy:	5.1%	3.8%	2.7%
Indication for surgery:			
Incomplete abortion	4.2%	-	-
Persistent gestational sac	-	1.0%	0.2%
Ongoing viable pregnancy	0.9%	1.0%	0.6%
Persistent heavy bleeding	-	1.9%**	1.6%
Abdominal Pain	-	-	0.2%
Patient lost to follow-up	8	47	29

* Patients were mistakenly enrolled (1 in Study 1, 56-63 days of gestation and 2 in Study 3, ≥ 64 days of gestation [data not presented])

** Medically necessary (e.g. excessive bleeding)

The results from the three trials indicate that a regimen of 200 mg oral mifepristone followed by 800 mcg buccal misoprostol is efficient for the termination of a pregnancy with a gestational age of 63 days or less. Stratification of the efficacy by age and ethnicity revealed no clinically meaningful difference in termination of pregnancy outcome. In trials 2 and 3, patients with a gravidity of 4 or more tended to

have a higher failure rate in the 50 to 63 days of gestational age group (failure rate 3.1-3.4% vs 6.3%, in women with gravidity of 1-3 (N = 465) or 4 and over (N = 142)), but not in women with a gestation of 49 days or less (failure rate 1.9-2.5% vs 2.3% in women with gravidity of 1-3 (N = 592) or 4 and over (N = 172)).

Table 9: Total bleeding time from treatment and type of bleeding, in days: mean ± SD, median (range)

	Study		
	1 (N = 212)	**2 (N = 414)**	**3 (N = 969)**
Total bleeding time	NA	11.4 ± 4.0, 12 (0-37)	NA
Type of bleeding			
Heavy bleeding	2.3±2.1, 2 (0-15)	2.2 ± 2.2, 2 (0-15)	NA
Normal bleeding	5.2±3.0, 5 (0-14)	4.5 ± 3.0, 4 (0-15)	NA
Spotting	3.8±2.6, 4 (0-12)	4.8 ± 3.4, 4 (0-14)	NA

N/A = not available

One patient in Study 1 and one in Study 3 required a blood transfusion due to excessive bleeding.

Pediatric Study results (≥13 and <18 years of age)

Of the 1,000 women enrolled in Study 3, 67 were less than 18 years of age. The number of participants is stratified by age below:

Table 10: Number of participants <18 years, by age

Age <18	n
13	1
14	6
15	16
16	20
17	24
Total	67

In that population, all women (100 %) had termination of pregnancy without the need for a surgical intervention. Women less than 18 years old tended to rate pain intensity higher and to report more frequently “feeling more pain than expected” than women 18 years and older.

Table 11 : Outcome of woman undergoing medical termination of pregnancy, by age (N=971)

Age	Efficacy % (n)
<18 years	100% (67)
≥18 years	97.1% (878)

Table 12: Reported pain and bleeding, by age (N=969)

	< 18 years	≥ 18 years
Reported pain	(n=67)	(n=887)
Mean pain score (SD) (range 1-7)	5.60 (1.3)	5.06 (1.7)
Pain perception, %(n)*	(n=66)	(n=896)
Less than expected	12.1 (8)	27.6 (247)
Same as expected	19.7 (13)	27.7 (248)
More than expected	68.2 (45)	44.8 (401)
Bleeding perception, %(n)*	(n=67)	(n=894)
Less than expected	14.9 (10)	32 (286)
Same as expected	50.7 (34)	41.3 (369)
More than expected	34.3 (23)	26.7 (239)

SD=standard deviation, *Excludes "Don't know" responses

Observational Studies

Authorised Prescriber Program Study

This retrospective observational study conducted in 15 clinics in Australia reported the outcome of 5,730 patients having termination of pregnancy of less than 63 days since last menstrual period with a regimen of 200 mg mifepristone followed 24-48 hours later by 800 mcg buccal misoprostol. 121 patients of less than 18 years of age were enrolled and one woman (0.8%) received a surgical intervention for retained products of conception. No other serious adverse events were reported in pediatric patients.

Australia Phase IV Study

This observational study conducted in women's health clinics in Australia reported the outcome of 10,822 patients having termination of pregnancy of 63 days since last menstrual period or less with a regimen of 200 mg mifepristone followed 24-48 hours later by 800 mcg buccal misoprostol. In the study, 138 women of less than 18 years of age were enrolled and 2.8% reported a method failure and required a surgical termination of pregnancy. Two patients reported an incomplete abortion and one patient a continuing pregnancy. All three required surgical termination of pregnancy. No serious haemorrhage or infection was reported in pediatric patients.

Table 13 : Number of participants <18 years in Australian Phase IV Study, by age

Age <18	n
13	0
14	2
15	16
16	32
17	86

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Single dose studies

Mifepristone

Mice, rats and dogs were administered single p.o. and i.p. doses of 1,000 mg/kg of mifepristone, resulting in severe toxicities (arched back, locomotor problems and abdominal distension) and one animal died. The drug dose used in these studies was about 300 fold greater (on a mg/kg basis) than would be administered to patients.

Misoprostol

Studies were performed in mice, rats and dogs. Oral LD50 values in mice and rats were 27-138 and 81-100 mg/kg, respectively, with corresponding values after i.p. dosing of 70-160 and 40-62 mg/kg. No deaths were reported in dogs up to 10 mg/kg, the maximum administered dose. The most prominent clinical signs were diarrhea and reduced motor activity in rodents and, in dogs, emesis, tremors, mydriasis and diarrhea. Most deaths occurred within 24 hours of dosing and surviving animals appeared normal within 3-4 days. The drug dose used in these studies was at least >750 fold greater (on an mg/kg basis) than would be administered to patients.

Long term studies

Mifepristone

Repeat dose toxicology studies were conducted in the rat and the monkey for 30 days and 6 months. A range of doses from 5 – 200 mg/kg/day were administered orally.

Monkeys administered 100 mg/kg/day had severe toxicity, where 3 were sacrificed moribund and the primary toxicological effects were vomiting, diarrhea, reduced appetite and body weight loss. Mid and high dose animals had reduced food consumption and loss of body weight. Serum ACTH levels were increased, cholesterol reduced, triglycerides had a transient rise and cortisol was increased. Both progesterone and estrogen levels were lower and LH levels were higher in females. Urinary excretion of potassium and chloride was reduced at all dose levels and sodium only at the high dose. In both sexes, kidney and adrenal weights were increased at all dose levels, liver weights were increased at the mid- and high-dose and pancreas reduced at the high-dose. Histopathology showed (i) non dose-related increased amounts and incidence of lipofucsin in liver, (ii) non dose-related increase in cortical scarring, cortical cysts and subcapsular foci of fibrosis in kidneys, (iii) increased eosinophilia of adrenal zona fasciculata in high-dose males and females and in one mid-dose male; high-dose females had an increased width of the zona reticularis, and (iv) increased incidence of brown pigment within the thyroid follicular epithelium in high-dose animals.

With regard to changes in reproductive organs in female monkeys, the following observations were made: (i) dilated ovarian follicles and an absence of corpora lutea, (ii) thinning of uterine endometrium; focal mucosal hyperplasia, squamous metaplasia and inflammatory cell infiltration (iii) non dose-related squamous metaplasia and inflammatory cell infiltration in the cervix, (iv) moderately keratinised vagina, (v) dilated lumen of fallopian tubes, (vi) slight increase in the degree of development of mammary glands.

Rats administered mid and high doses had reduced weight gain. Haematological measures showed reduced red cell parameters and reduced clotting time. Plasma glucose was dose-dependently reduced and serum protein and cholesterol increased. Urinalysis showed increased protein and increased urine

volume, presumably due to increased water intake. Histopathology showed (i) dose-related increase in centrilobular enlargement in livers, (ii) dose-related increase in hemosideresis in adrenals, (iii) dose-related increase in foci of basophilic/dilated kidney tubules containing colloid, glomerular hyalinisation/sclerosis, and interstitial fibrosis (iv) increased thyroid weight, increased height of the thyroid follicular epithelium; a thyroid follicular adenoma was observed in one high-dose female.

With regard to changes in reproductive organs in female rats, the following observations were made: (i) inhibition of oestrus cyclicity and reduction in corpora lutea, (ii) dose-related increase in ovarian cysts, (iii) reduction in endometrial stroma in all groups and dose-related dilatation of endometrial glands, (iv) striated squamous epithelium of the cervix/vagina, and (v) dose-related increase in distension of mammary acini and ducts.

The Cmax of single-dose oral mifepristone administration in rats and monkeys was compared to the Cmax in women administered 200 mg. Rats and monkeys were observed to have different mifepristone metabolism, as compared to humans, making it challenging to compare the doses used in animal studies to those proposed for human use.

Table 14: Comparative Cmax of single-dose mifepristone

	Dose (mg/kg)	C_{max} (ng/ml)	C_{max}:Dose
Rat	200	3,000	15
Monkey	90	160	1.7
Human	4	2,686	671.5

Misoprostol

Repeat dose studies were conducted in rats and dog for 5, 13 and 52 weeks and covered a dose range of 30 – 9000 mcg/kg/day via oral administration.

In rats, the major clinical signs were diarrhea, salivation, vaginal dilation and discharge, decreased body weight and increased food consumption. Principal clinical biochemistry changes were decreases in serum total protein and increases in serum iron, with any changes in other parameters remaining within normal limits and considered incidental. The decrease in protein levels may be a consequence of poor absorption of nutrients resulting from diarrhea. Stomach weights and stomach to body weight ratios were increased and hyperkeratosis of the aglandular part of the stomach and mucosal epithelial hyperplasia of the glandular part were confirmed by electron microscopy. It may be that misoprostol increased cell survival and decreased cell shedding. The changes were reversible upon cessation of treatment.

Pharmacokinetic exposure data for misoprostol was limited, making it challenging to compare the doses used in animal studies to those proposed for human use.

Carcinogenicity:

Mifepristone

Carcinogenicity studies were not conducted in animals.

Misoprostol

The carcinogenicity potential of misoprostol has been evaluated in both mice and rats. The study in mice was of 21 months duration and administered doses of 0, 160, 1600 and 16000 mcg/kg/day by oral gavage.

In the rat study, doses of 0, 24, 240 and 2400 mcg/kg/day were administered for 24 months by oral gavage. There was no indication of a carcinogenic effect in either species.

Genotoxicity:

Mifepristone

Mifepristone was tested for genotoxicity using both in vitro and in vivo studies. It showed no evidence of genotoxicity.

Misoprostol

Misoprostol was tested for genotoxic potential in a Ames test in five strains of *Salmonella typhimurium*, a mouse lymphoma TK+/- assay, a mitotic gene conversion in *Saccharomyces cerevisiae*, a sister chromatid exchange assay in CHO cells, a C3H/10T 1/2 cell transformation assay and an *in vivo* mouse micronucleus test. Misoprostol showed no evidence of genotoxicity.

Reproductive and Developmental Toxicology:

Mifepristone

Oral administration of mifepristone to rats disrupted the oestrus cycle at both dose levels, 0.3 and 1 mg/kg/day within 10 days of treatment, with a gradual restoration of the cycle over the 2-3 weeks after stopping dosing. There were no residual effects on reproductive performance, fertility or the wellbeing of offspring.

When administered to at a dose of 2.5 mg/kg/day for 24 days, starting 8 days before mating, with pregnancy status assessed on the day after final treatment, mifepristone did not affect the pregnancy rate, as compared to a concurrent control group. However, the mean number of normal implantation sites per pregnant rate was significantly reduced.

Mifepristone is embryotoxic and its administration to pregnant mice, rats and rabbits at doses lower than those proposed for human use (on a mg/kg basis) resulted in fetal loss. There were fetal anomalies reported in rabbits following mifepristone exposure of the dams during pregnancy: failure of closure of the cranium and haemorrhagic destruction of the upper part of the head or brain, no spinal column, no closure of the eyelids, exencephaly, interventricular communication in the heart, cleft palate, generalised eczema and celosomia. In monkeys embryos exposed to mifepristone showed compromised developmental potential. These anomalies may be a consequence of progesterone withdrawal, as progesterone is needed to maintain uterine accommodation during pregnancy, rather than direct teratogenic effect.

In a neonatal exposure study in rats, the administration of a subcutaneous dose of mifepristone up to 100 mg/kg on the first day after birth resulted in delays in the development of the righting reflex and the responses in the rotarod and water maze tests in pups. The onset of puberty was observed to be slightly premature in female rats neonatally exposed to mifepristone. However, reproductive function in males or females was normal.

In a separate study neonatal rats received 1 mg of mifepristone every second day from day 1 to day 15 or day 4 to day 18 of life. Female rats developed abnormalities of the oviduct and ovarian capsule and during adulthood anovulatory polyfollicular ovaries developed. Males showed retardation of testicular growth and delay of puberty. Sexual behaviour in adulthood was deficient in that ejaculations only rarely occurred; when they did occur, however, fertility was unimpaired. Adrenal gland development was also impacted but this recovered after the cessation of treatment whereas the effects on reproduction continued into adulthood.

Misoprostol

The effect of misoprostol on female cyclicity, mating and fertility was not studied.

In two fertility studies, female rats were administered misoprostol by oral gavage from 15 days premating to parturition and from 14 days premating to day 7 of gestation. The number of implantations was decreased at 1,600 and 10,000 mcg/kg/day and an increase in resorptions occurred at 1,000 and 10,000 mcg/kg/day. As a consequence, there were a decreased number of live foetuses or pups at 10,000 mcg/kg/day and a decreased number of foetuses at 1,600 mcg/kg/day. Foetal and pup survival and development were not affected.

In two teratology studies in rats pregnant dams were dosed on days 6 to 15 or 7 to 17 of gestation up to 10,000 mcg/kg/day via oral gavage; there was no evidence of embryotoxicity, foetotoxicity or teratogenicity. Two rabbit studies used doses up to 1,000 mcg/kg/day via oral gavage on days 6 to 18 of gestation and also showed no evidence of foetotoxicity or teratogenicity, although there was an increased number of resorptions at 1,000 mcg/kg/day in one study.

However, a more recent study in mice treated with single doses of 20 or 30 mg/kg of misoprostol on day 10 of pregnancy showed an increase in resorptions at 30 mg/kg and an increased occurrence of cleft palate as well as other skeletal abnormalities in surviving fetuses. The link between misoprostol exposure during pregnancy and congenital malformations might be attributed to disturbances in blood supply to the foetus.

A retrospective analysis of human data also determined there to be a link between misoprostol exposure during pregnancy and congenital malformation.

Special Toxicology:

Phototoxicity

Mifepristone

No evidence of phototoxicity was observed with mifepristone being tested up to a concentration of 8 mcg/mL in Balb/c 3T3 fibroblasts, the limit of solubility under the conditions of the assay.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrMIFEGYMISO
Mifepristone tablet / Misoprostol tablets

Read this carefully before you start taking **Mifegymiso** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Mifegymiso**.

Serious Warnings and Precautions

Follow-up appointment:

You must have a follow-up appointment with a health professional, 7 to 14 days after Step 1 (taking the mifepristone tablet from the green box). The health professional will check whether your pregnancy has completely ended. If the pregnancy continues, there is a possibility of birth defects. Your health professional will talk with you about your options.

Risk of infection and sepsis:

If you have abdominal pain or discomfort, or you are "feeling sick", including weakness, nausea, vomiting or diarrhea, with or without fever, more than 24 hours after taking misoprostol, you should contact your health professional without delay. Very rarely, this can cause death.

Risk of skin reactions:

Taking Mifegymiso may lead to serious skin reaction conditions such as toxic epidermal necrolysis and acute generalized exanthematous pustulosis. Stop using Mifegymiso and seek medical attention immediately if you notice any of the symptoms. See **Serious side effects and what to do about them** for more information on the symptoms. If you get a serious skin reaction you should not use Mifegymiso again in the future.

Prolonged heavy bleeding:

Contact a health professional right away if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours. Bleeding can be so heavy that it requires a surgical procedure. Some patients also require a blood transfusion.

Risks of birth defects:

Once you start Mifegymiso, you should complete both steps. Both Mifepristone and Misoprostol can cause birth defects if your pregnancy is continued.

If you do NOT want to get pregnant after the termination of your pregnancy:

You must start using birth control right away.

You can get pregnant right after the abortion:

If you want to have a baby, tell your health professional. To decrease the chance of birth defects, avoid getting pregnant again before your next period. This will protect the baby from any exposure to Mifegymiso. Use birth control during this one month waiting period.

What is Mifegymiso used for?

- Mifegymiso is used for ending your pregnancy. This is called an abortion. Mifegymiso is only used if your last period started 63 days ago or less.

How does Mifegymiso work?
Do NOT use Mifegymiso as birth control.

Mifegymiso is prescribed by health professionals. They must have knowledge of abortion. Before you take it, they must determine the age of your pregnancy.

Before you take Mifegymiso:

- You will get counselling. Your health professional will tell you about:
  - The chance of bleeding
  - The chance of infection
  - The chance of an incomplete abortion
  - How to access the treatment centre by telephone or local access
- You should give your informed consent to take Mifegymiso
- You might get an ultrasound scan
- You will get a printed copy of the Mifegymiso:
  - Patient Medication Information
  - Patient Information Card that was completed by the health professional.

Patient Information Card
Keep this card with you at all times while taking Mifegymiso until your health professional tells you that your abortion is complete.

When completed, the Patient Information Card contains the following information:

- When you should take the drugs for Step 1 and Step 2
- Your follow-up appointment date, and time
- Contact information in case you need to call your health professional or clinic
- Where to go if you have an emergency in the 14 days after you take Mifegymiso. Show this Card to the emergency health professional.

To end your pregnancy, you will need to take two drugs.

Step 1 (Green Box)
Mifepristone is taken first to block a hormone that is needed for your pregnancy to continue.

Step 2 (Orange Box)
Misoprostol is the second drug. It is taken 24-48 hours later. It causes the uterus to contract and relaxes the opening of the cervix.

Vaginal bleeding usually starts a few hours after taking the Misoprostol tablets.

Cramping and vaginal bleeding are normal with this treatment. Usually, this indicates that the treatment is working. Bleeding lasts for an average of 11 days. It is usual for bleeding to be heavier than

a normal period for 2 to 3 days. You may see blood clots and tissue. This is an expected part of ending the pregnancy.

What are the ingredients in Mifegymiso?

Medicinal ingredients:
Green box: Mifepristone
Orange box: Misoprostol

Non-medicinal ingredients:
Mifepristone (green box): colloidal silica anhydrous, magnesium stearate, maize starch, microcrystalline cellulose, povidone K30

Misoprostol (orange box): hydrogenated castor oil, hypromellose, microcrystalline cellulose, sodium starch glycolate

Mifegymiso comes in the following dosage forms:

Green box: 1 Mifepristone tablet, 200 mg for oral use

Orange box: 4 Misoprostol tablets, 200 mcg each (800 mcg total) for buccal use

Do not use Mifegymiso if:

- You are pregnant and wish to carry your pregnancy to term
- You do NOT have access to emergency medical care. You must be able to get medical help in the 14 days after you take the mifepristone tablet
- You have or suspect an ectopic pregnancy (This is when the egg is implanted outside the womb)
- You are using an intrauterine contraceptive device (IUD) in your uterus
- The duration of your pregnancy is uncertain
- You have any allergies to mifepristone, misoprostol or any of the other ingredients listed in this leaflet
- You have a chronic adrenal disease
- You take corticosteroids on a regular basis
- You have a bleeding problem
- You take a blood thinner (anticoagulant like coumadin)
- You have inherited porphyria. This is a blood disease that causes skin symptoms as a result of oversensitivity to sunlight
- You have uncontrolled asthma

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Mifegymiso. Talk about any health conditions or problems you may have, including if you:

- Have kidney problems
- Have liver problems
- Are underweight
- Have problems with your adrenal glands
- Have a heart or cardiovascular disease
- Have anemia (problems of red blood cells)
- Have asthma
- Have had seizures
- Are taking medications (corticosteroids) for the treatment of asthma
- Are diabetic
- Are a heavy smoker and over 35 years old

Other warnings you should know about:

If your blood group is negative (A^-, B^-, AB^-, O^-), your health professional will give you an additional medication prior to giving you Mifegymiso.

Mifegymiso does not work in 3 to 5 of cases out of 100. As pregnancy progresses the risk of this goes up. If this happens to you, you will need a surgical abortion.

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to Mifegymiso. Dizziness, fatigue, headache, and fainting can occur. These side effects slow down after Day 3. They are usually gone by Day 14. Plan to rest for 3 hours after taking the Misoprostol tablets (Step 2, Orange box).

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Mifegymiso:

- Drugs used in the treatment of fungal infection such as ketoconazole, itraconazole
- Antibacterial named erythromycin
- Antibiotic used in the treatment of tuberculosis named rifampin
- Certain anticonvulsants used to treat epilepsy, such as phenytoin, phenobarbital and carbamazepine
- Corticosteroids
- Herbal supplements containing St. John's Wort
- Grapefruit juice
- Some drugs used for general anaesthesia.

How to take Mifegymiso:

- Mifegymiso will be given to you by a healthcare professional in a healthcare setting.

Usual dose:

Take Mifegymiso as directed by your health professional.

Step 1:
(Green box)
Take the Mifepristone tablet

- Swallow tablet with a glass of water

24 to 48 hours after taking the Mifepristone tablet, you must do Step 2.

Step 2:
(Orange box)

- Place the 4 Misoprostol tablets (as a single 800 mcg buccal dose) in your mouth
- Keep the 4 tablets between your cheeks and gums for 30 minutes
- Then, swallow any fragments that are left with water

Plan to rest for 3 hours after taking the Misoprostol tablets.

Overdose:

If you think you, or a person you are caring for, have taken too much Mifegymiso, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

Take each step of **Mifegymiso** at the date and time written on the Patient Information Card.

Step 1 (Green box) Mifepristone tablet
Contact your health professional right away if you delay or if you did NOT take the Mifepristone tablet. Your health professional will tell you if it is still safe for you to take **Mifegymiso**.

Step 2 (Orange box) Misoprostol tablets
Contact your health professional immediately if you forget to take the Misoprostol tablets and it **is more than** 48 hours after you took the Mifepristone tablet (Step 1).

If it is less than 48 hours since you took Step 1 but after the time and date on your card, take the Misoprostol tablets (Step 2) right away.

If you have any question about when to take your medication, contact your health professional.

What are possible side effects from using Mifegymiso?

These are not all the possible side effects you may have when taking Mifegymiso. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- breast tenderness
- hot flushes, chills
- diarrhea
- dizziness, headache, fainting
- fatigue
- nausea

- vomiting

Patients who are less than 18 years old often get more vomiting and pain.

These side effects slow down after Day 3 and are usually gone by Day 14. Your health professional will tell you how to manage any pain or other side effects.

Mifegymiso can cause abnormal blood test results. Your health professional will decide when to perform tests and interpret the results.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Prolonged heavy bleeding **Severe hemorrhage:** you bleed enough to soak through two full-size sanitary pads per hour for two consecutive hours.			√ √
Fever			√
Endometritis (an infection in the lining of the uterus): Pain in the lower abdomen. Fever and abnormal vaginal discharge and bleeding.			√
UNCOMMON			
Hemorrhagic shock (shock from blood loss): Dizziness and confusion. Rapid breathing and heartbeat. Weakness, low blood pressure, less urine than normal Cool clammy skin, thirst and dry mouth.			√
Hypotension (low blood pressure): dizziness, fainting, lightheadedness	√		
Infection: 24 hours or more after Step 2, fever, chills and abdominal pain, cramps or tenderness that persist for 4 hours with or without nausea, vomiting, diarrhea, weakness, rapid heartbeat or feel unwell.			√
Skin rash: Red spots on your skin			√

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Acute generalised exanthematous pustulosis: target-like circular reddish patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes; sometimes with fever and flu-like symptoms			√
RARE			
Anaphylactic shock or Angioedema (serious allergic reaction): Itching, rash, hives. Swelling of the face, lips, tongue or throat. Difficulty swallowing or breathing.			√
Toxic shock syndrome (life-threatening infection): Fever, diarrhea, nausea, vomiting, muscle aches. Low blood pressure, headache, confusion and seizures. Rash or red spots that look like a sun burn. Redness of the eyes, mouth and throat.			√
Asthma or bronchospasm: Difficulty breathing and coughing. Whistling sound when you breathe. Chest tightness and mucus in your lungs.			√
Severe Skin Reaction: **Urticarial reaction**: Skin with red spots which burn, itch or sting. **Toxic epidermal necrolysis:** Severe skin peeling, especially in mouth and eyes **Erythema nodosum** (swelling of the fat cells under the skin): Tender red lumps usually on both shins.			√ √ √

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Do not use after any expiry date printed on the boxes, or if the boxes are damaged.
Keep out of reach and sight of children.

Storage of Mifegymiso
Store entire package between 15-25°C in its original box in order to protect from light.

Storage of mifepristone 200 mg tablet
When separated, mifepristone should be stored in the green box between 15-30°C, in order to protect from light.

Storage of misoprostol 200 mcg tablets
When separated, misoprostol should be stored in the orange box between 15-25°C.

If you want more information about Mifegymiso:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the importer and distributor in Canada website https://www.linepharma.ca, or by calling 1-877-230-4227.

This leaflet was prepared by Linepharma International Limited.

Last Revised: MAY. 02, 2023

Linepharma

PrMifegymiso

Patient Information Card

To be completed by your health professional.
Please keep it with you.

Date and time of treatment:

Step 1 (green box): .....

Step 2 (orange box): .....

If you have a serious symptom or side effect, get immediate medical help.
If you have an emergency, go to:

.....

.....

.....

[Add the emergency contact information above]
Show this Card to the emergency health professional.

PrMifegymiso

Patient Information Card

To be completed by your health professional.
Please keep it with you.

If you have a troublesome symptom or side effect that becomes bad enough to interfere with your daily activities, talk to your health professional.

Phone number and address of your health professional, clinic or treatment center:

.....

.....

.....

You must have a follow-up appointment 7 to 14 days after taking Mifegymiso.

Follow-up appointment date (MM/DD/YYYY) and time:

.....

.....

.....

Importer and distributor in Canada:
Linepharma International Inc.
Toronto, ON, M4T 1L9 - Canada
1 877-230-4227 - www.linepharma.ca

Document 6

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Clinical Evaluation Report – Type J
Prescription Medicines Authorisation Branch

Active substance: Mifepristone and misoprostol

Product name: MS-2 Step composite pack

Sponsor: s47 [redacted] on behalf of MS Health Pty Ltd [redacted]

Submission number: PM-2022-05475-1-5

eSubmission number: e004967

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989*, applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

Contents

List of abbreviations

Abbreviation	Meaning
ITT	Intention-to-treat
MLP	Mid-level healthcare provider
MToP	Medical termination of pregnancy
MVA	Manual vacuum aspiration
PI	Product Information
PP	Per protocol
SAE	Serious adverse event
WHO	World Health Organization

List of tables

1. Submission details

1.1. Identifying information

Submission number	PM-2022-05475-1-5
eSubmission number	e004967
eSubmission sequences covered in this report	0007, 0012
Sponsor	s47 [redacted] on behalf of MS Health Pty Ltd
Trade name	MS-2 Step composite pack
Active substance	Mifepristone and misoprostol

1.2. Submission type

This is a Category 1, Type J application (variation to the register entry resulting in a change of product information requiring evaluation of clinical, non-clinical or bioequivalence data) to update the PI for MS-2 Step composite pack.

Section 4.2 of the current PI advises MS-2 Step can only be prescribed by doctors with the appropriate qualifications and certified training. The Sponsor proposes to amend 'medical practitioner' in the boxed warning and 'doctors' in Section 4.2 of the PI to 'healthcare practitioners'.

1.3. Drug class and therapeutic indication

As per the MS-2 Step PI [1]:

Mifepristone belongs to the Pharmacotherapeutic group: Other sex hormone and modulator of the reproductive function/antiprogestogen, ATC code GO3XB01.

Misoprostol belongs to the Pharmacotherapeutic group: Other gynaecological medicines – prostaglandins, ATC code G02AD06.

Mifepristone is a synthetic steroid with an antiprogestational action as a result of competition with progesterone at the progesterone receptors. In women at doses of greater than or equal to 1 mg/kg, mifepristone antagonises the endometrial and myometrial effects of progesterone. During pregnancy it sensitises the myometrium to the contraction inducing action of prostaglandins. Misoprostol is a synthetic analogue of prostaglandin E1. At the recommended dosages, misoprostol induces contractions of the smooth muscle fibres in the myometrium and relaxation of the uterine cervix. In the event of an early termination of pregnancy, the combination of a prostaglandin analogue used in a sequential regimen after mifepristone leads to an increase in the success rate and accelerates the expulsion of the conceptus.

The approved indication is [1]:

MS-2 Step is indicated in females of childbearing age for the medical termination of an intrauterine pregnancy, up to 63 days of gestation.

It is recommended that the duration of pregnancy (i.e., up to 63 days gestation) be confirmed by ultrasound. In the event that an ultrasound is not possible, extra caution should be exercised.

Ultrasound is also useful to exclude ectopic pregnancy.

1.4. Dosage forms and strengths

The following dosage forms and strengths are currently registered:

MS-2 Step composite pack (MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet blister; GyMiso misoprostol 200 microgram tablet blister) AUST R 210574

No new dosage forms or strengths are proposed.

2. Background

2.1. Clinical rationale

The Sponsor's rationale was provided in the Cover letter (dated 22nd December 2022), summarised as follows:

Currently the MS-2 Step PI defines MS-2 Step can only be prescribed by doctors with the appropriate qualifications and certified training, with the subsequent post administration follow up to be conducted by a medical practitioner, preferably the prescriber. Therefore, access to early medical abortion (as indicated up to 63 days of gestation) is restricted to where a certified medical practitioner is located.

To ensure timely access to patients, and to ensure that the product is prescribed by the persons authorised by state and territory legislation, the application proposes to amend the black box warning from referencing 'medical practitioner' to 'healthcare practitioner', and for the reference to 'doctors' in section 4.2 to be amended to 'healthcare practitioners'.

2.2. Regulatory history

2.2.1. Australian regulatory history

The individual components of MS-2 Step, Mifepristone Linepharma (mifepristone 200 mg tablet) and GyMiso (misoprostol 200 microgram tablet) were registered in Australia on 29th August 2012 for medical termination of developing intrauterine pregnancy up to 49 days gestation as follows:

Mifepristone Linepharma (AUST R 175671):

Medical termination of a developing intra-uterine pregnancy. In sequential combination with a prostaglandin analogue up to 49 days of gestation; and preparation for the action of registered prostaglandin analogues that are indicated for the termination of pregnancy for medical reasons beyond the first trimester.

GyMiso (AUST R 188015):

GyMiso is indicated in females of childbearing age for the medical termination of a developing intrauterine pregnancy in sequential combination with a mifepristone 200 mg tablet, up to 49 days of gestation.

MS-2 Step composite pack containing Mifepristone Linepharma (mifepristone) 200 mg tablet and GyMiso (misoprostol) 200 microgram tablets was registered on 4th June 2014 (Submission PM-2013-01037-1-5). As part of this submission, the indication was extended to the medical termination of a developing intrauterine pregnancy from 49 days up to 63 days gestation.

Following registration of MS-2 Step composite pack, the Sponsor withdrew the GyMiso mono product from the market, and removed the indication for medical termination of pregnancy up to 49 days for the Mifepristone Linepharma mono product (Submission PM-2014-03311-1-5).

2.2.2. Related submissions

• The Sponsor submitted an updated AU-RMP (version 04) to the TGA on 1st December 2022 (eSubmission e004967, sequence 0006) for review by the Risk Management Section.

Evaluator comment*: The RMP was submitted to TGA prior to submission of the current application. The Evaluator notes the Sponsor proposes to remove the requirement for re-certification training for prescribers from the RMP. This is drawn to the attention of the Delegate. An updated RMP was submitted during the evaluation phase of the current submission (See Section 3 below).*

2.2.3. Overseas regulatory history

Module 1.11 was not provided in the dossier (i.e. no foreign regulatory information).

MS-2 Step combination pack is not registered in other countries/regions.

The combination product Mifegymiso (mifepristone 200 mg tablet and misoprostol 200 microgram tablet combination pack, Linepharma International Limited) is approved in Canada for a comparable indication to MS-2 Step composite pack [2]:

'*Mifegymiso (mifepristone tablet/misoprostol tablets) is indicated for:*

• medical termination of a developing intra-uterine pregnancy with a gestational age up to 63 days as measured from the first day of the Last Menstrual Period (LMP) in a presumed 28-day cycle.

Mifegymiso is not intended for routine use as a contraceptive.'

Mifepristone is registered in the USA, UK and various countries in Europe. In the USA, Mifeprex (mifepristone) is only available through the mifepristone risk evaluation and mitigation strategy (REMS) Program [3].

2.3. Guidance

The following TGA guidelines are considered relevant to the current submission:

• Form for providing product information https://www.tga.gov.au/form-providing-product-information

• Boxed warning guidance https://www.tga.gov.au/resources/resource/guidance/boxed-warning-guidance

3. Contents of the clinical dossier

The dossier was submitted in eCTD format. The submission contained the following clinical information:

- Module 1
  - Application letter, application form, draft Australian PI, draft Australian Consumer Medicine Information (CMI)
- Module 2

- Clinical Overview Addendum

- Module 5
  - Periodic Safety Update Reports covering the intervals 1st June 2016 – 31st May 2017, 1st June 2021 – 31st May 2022
  - Literature references

***Evaluator comment**: As noted in Section 2.2.2 above, an updated AU-RMP (version 04) was submitted separately to the TGA on 1st December 2022. In the Cover letter for the current submission (dated 22nd December 2022), the Sponsor states 'An updated RMP was submitted to the TGA for review on the 1st December 2022 (version 04). Following the completion of the evaluation of this Category 1 application, the version 04 of the RMP will be updated in accordance with the approved changes and is proposed to be submitted with the next safety update.'*

Following discussion with TGA, a separate updated RMP (v4.0, 17th February 2023) was submitted to TGA (on 20th February 2023) during the evaluation phase of the current submission and is under review by the Risk Management Section. The Evaluator notes in the Cover letter for this updated RMP the Sponsor proposes removal of the mandatory medical education program.

This evaluation is based on the data provided in Module 2.5 to support the proposed changes to the PI provided in Module 1.3 (e004967 (0007-) - Product Information - Annotated). The Delegate is advised the proposed change to the RMP regarding removal of the mandatory medical education program was not discussed in the Clinical Overview Addendum.

4. Proposed changes to the PI

The following comments relate to the proposed MS-2 Step PI (e004967 (0007-) - Product Information - Annotated) provided in Module 1.3. Existing text in black, proposed additional text in blue, text for deletion in red strikethrough.

Proposed MS-2 Step PI change
Boxed warning It is very important that all patients receiving these medications are followed up by a ~~medical~~ healthcare practitioner, preferably the prescriber, to ensure that the medication has been effective. Even if no adverse events have occurred all patients must receive follow-up 14 to 21 days after taking mifepristone. Read the Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE carefully.
4.2 Dose and method of administration MS-2 Step is indicated for medical termination of intrauterine pregnancy, up to 63 days of gestation. The method of administration is as follows: Mifepristone: 200 mg of mifepristone (1 tablet containing 200 mg) orally, followed 36 to 48 hours later by the administration of GyMiso®. GyMiso®: 800 micrograms of misoprostol (4 tablets, each tablet containing 200 micrograms) buccally, i.e: kept between the cheek and the gum for 30 minutes before any fragments being swallowed with water. When MS-2 Step fails to cause termination of intra-uterine pregnancy, the patient should return to the treating doctor for assessment and discussion of treatment options, which may include pregnancy termination by surgery.

No dosage adjustment of misoprostol or mifepristone is necessary with renal or hepatic insufficiency when administered at the recommended doses.

There are no data available on the effect of food intake on the absorption of mifepristone or misoprostol. MS-2 Step should be taken 2 hours before or 2 hours after a meal.

Refer also to 4.3 CONTRAINDICATIONS, and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

MS-2 Step should only be prescribed by healthcare practitioners ~~doctors~~ with the appropriate qualifications and certified training. Ectopic pregnancy should be excluded, an intrauterine device (IUD) (if present) must be removed, consent must be obtained and patients must have the ability to access 24-hour emergency care if and when required for incomplete abortion or bleeding.

4.1.1. Supporting evidence

Supportive evidence was provided in the Clinical Overview Addendum. The Clinical Expert states as MS-2 Step can only be prescribed by doctors with the appropriate qualifications and certified training, with the subsequent post administration follow up to be conducted by a medical practitioner (preferably the prescriber), access to early medical abortion is restricted to patients and locations where a certified medical practitioner is accessible. The availability of prescribers is particularly limited in regional and remote areas of Australia, based on data from the Sponsor's certification program (see Table 1).

The Clinical Expert stated further:

- Allowing mid-level healthcare practitioners such as nurses, midwives and nurse practitioners to prescribe MS-2 Step (and as defined by the current state and territory legislation) will improve the current access for women by increasing the number of certified prescribers and removing the need for women to travel long distances to access a certified prescriber and safe abortion services.

- MS Health proposes to continue providing the same (existing) standardised training for all potential prescribers (as detailed in the current approved Australian RMP) which will ensure a minimum baseline of education regardless of training background.

- Use of the term 'healthcare practitioner' will encompass any variability in the state and territory terminology therefore allowing the specific state and territory legislation to define the persons authorised to perform or assist with medical termination of pregnancy (MToP).

The proposed changes are also stated to align with WHO recommendations for provision of MToP. The following points are noted from the WHO Abortion Care Guideline 2022 [4]:

• Strengthening access to comprehensive abortion care within the health system is fundamental to meeting the Sustainable Development Goals (SDGs) relating to good health and well-being (SDG3) and gender equality (SDG5).

• Quality abortion care must be both accessible (timely, affordable, geographically reachable, and provided in a setting where skills and resources are appropriate to medical need) and acceptable (incorporating the preferences and values of individual service users and the cultures of their communities).

• Recommendations regarding health worker roles are appropriate for, and intended for, all resource settings (high, middle and low-resource settings).

• The recommendations all assume that health workers who are in a category that is recommended or suggested to perform specific tasks will have received the appropriate task-specific training and information prior to performing that task.

• Medical abortion includes information provision (including reasons to seek urgent care at any point during the process) and the following components or subtasks: assessing eligibility for

medical abortion (diagnosing and dating the pregnancy, ruling out medical contraindications), administering the abortion medicines with instructions on their appropriate use and managing the common side-effects, and assessing whether the abortion process has had a successful outcome and whether any further intervention is required.

Supportive evidence from the literature was provided:

4.1.1.1. Randomised controlled trials (RCTs)

(i) Kopp Kallner et al. (2014) [5]

Kopp Kallner *et al*. conducted a randomised, controlled, single-centre equivalence trial to assess the efficacy and safety of early MToP provided by doctors or nurse-midwives at an out-patient family planning clinic of the Karolinska University Hospital, Stockholm, Sweden. The study included women ≥ 18 years of age in good general health with no continuing medication for chronic disease, pregnancy of less than 63 days gestation according to LMP, and no contraindication to MToP.

There were 1180 eligible subjects randomised in 1:1 ratio to nurse-midwife arm (n = 597) or to the standard-care (doctor) arm (n = 583) using computer-generated randomisation allocation code. The nurse-midwife arm included 2 nurse-midwives experienced in MToP who received training in vaginal ultrasound of early pregnancy, and the doctor arm included 34 doctors with variable training and experience. Ultrasound was performed in all cases by the allocated provider. In the nurse-midwife group, subjects were examined, counselled, informed, and treated by a single nurse-midwife. In the doctor group, counselling and examination was provided by a doctor, and additional information and medication provided by a nurse-midwife as per clinical routine.

MToP was as per WHO protocol. All participants received mifepristone 200 mg in the clinic and administered 800 micrograms misoprostol vaginally in the clinic or at home 24 hours later. Subjects were advised to take prophylactic pain relief (paracetamol and diclofenac). Follow-up in all cases comprised urinary hCG performed by a nurse-midwife (not involved in the study) approximately 3 weeks later. If this was positive, serum hCG was performed and patients referred for ultrasound to assess for continuing pregnancy. Subjects who did not attend for follow-up were contacted on two attempts, and considered lost to follow up thereafter.

Efficacy was the primary outcome, defined as the successful completion of TOP without need for vacuum aspiration. Safety was a secondary outcome, defined as need for hospitalisation or blood transfusion. Efficacy and safety outcomes were assessed by self-administered patient questionnaires and electronic patient records (completed after initial examination and follow-up visit).

Baseline demographics were comparable between the 2 groups. The median age of subjects was 27 years and median duration of gestation 45 days (see Table 2). Overall, 1068 subjects received and completed the allocated treatment (n = 535 nurse-midwife group, n = 533 doctor group). There were 105 subjects who did not have MToP (n = 62 nurse-midwife, n = 43 doctor group), most commonly due to choosing surgical ToP and advanced gestational age. There were 3 subjects in each group with ectopic pregnancy. The proportion of subjects lost to follow up was comparable between arms (n = 54 [10.1%] nurse-midwife arm, n = 76 [14.3%] doctor group), and stated by the authors to be comparable with studies in TOP. A total of 938 subjects were included in the analyses (n = 481 nurse-midwife group, n = 457 doctor group).

Sample size calculations determined 400 subjects per group sufficient to demonstrate equivalence within a 5% margin with 80% power. Analyses were per-protocol.

Efficacy (i.e. complete TOP without need for surgical intervention) was attained for 99% and 97.4% subjects allocated to the nurse-midwife and doctor arms respectively; risk difference

1.6% with 95% CI within the margin of equivalence (0.2 - 3.0%). There were 5 subjects in the nurse-midwife arm and 12 in the doctor arm requiring surgery, most commonly due to incomplete ToP (n = 5 nurse-midwife group, n = 7 doctor group) and bleeding (unscheduled) (n = 3 doctor group); see Table 3. The authors stated there were no serious complications and no blood transfusions given.

There were 9% and 9.7% subjects in the nurse-midwife and doctor groups respectively with unscheduled visits. The proportion of subjects with complications (defined as need for causal treatment at an unscheduled visit up to 6 weeks after ToP) was comparable; 4.1% and 6.1% patients in the nurse-midwife and doctor groups respectively. The main between-group differences were pain (1.5% doctor group vs. 0.4% nurse-midwife group) and signs of infection (1.3% doctor group vs. 0.6% nurse-midwife group). See Table 4.

Second opinion consultation (doctor for nurse-midwives or second doctor for doctor group; all second opinions performed immediately by other doctors at the clinic to avoid delay to MToP) were reported for 26% (139/535) cases in the nurse midwife group and 4% (21/533) cases in the doctor group. The most common reasons for second opinion in the nurse-midwife group were ultrasound (59 cases) and prescription/second opinion for suspected bacterial vaginosis (54 cases). The authors stated the '*frequency of ultrasound consultations for nurse-midwives went down as the study progressed, indicating a learning curve*'.

Evaluator comment*: The inclusion of only healthy women in the study is not reflective of the general population and is a limitation of the study acknowledged by the authors.*

The reasons for surgery and complications are generally consistent with the known risks of MToP with mifepristone/misoprostol [1].

The proportion of cases requiring second opinion in each group is noted. However, in the Australian setting, patients would generally be referred to a radiology facility for ultrasound assessment. The authors stated nurse-midwives are not able to prescribe antibiotics for bacterial vaginosis in Sweden, which likely accounts for this between-group difference. Excluding these reasons, the main between-group difference was for 'medical reasons' (2.4% nurse-midwife group vs. 0.8% doctor group) for which no further information was provided (see Table 5).

(ii) Warriner et al. (2011) [6]

Warriner and colleagues reported a randomised, controlled, multicentre, equivalence trial in Nepal to assess whether early first trimester MToP provided by midlevel health care providers (MLP; nurses and nurse-midwives) was as safe and effective as MToP provided by doctors. The study was conducted in 5 rural district hospitals in Nepal from 15th April 2009 – 17th March 2010. The authors stated that at the time of the study, MToP service provision by nurses was limited to government facilities where a doctor was present, i.e. not independent of physician oversight. Clinical procedures for medical abortion followed the Nepalese medical abortion protocol.

Women ≥ 16 years of age with pregnancy ≤ 63 days gestation per date of LMP and as estimated by bimanual pelvic examination by the assigned healthcare provider, and residing ≤ 90 minutes from the study clinic with no contraindications to MToP were eligible to participate. Exclusion criteria included known or suspected ectopic pregnancy or undiagnosed adnexal mass, long-term corticosteroid therapy, chronic adrenal failure, inherited porphyria, haemorrhagic disorder or anticoagulant therapy, or an intrauterine device that could not be removed before administration of mifepristone.

Evaluator comment*: The exclusion criteria are generally consistent with contraindications to MS-2 Step as per the current PI [1]. The authors stated pregnancy tests and ultrasound are not routine for MToP in Nepal, although ultrasound machines were available for the study at the discretion of the*

health care provider. Use of ultrasound in the study to assess gestation was low; 0.4% MLP, 4.3% doctors.

The study included providers trained in manual vacuum aspiration (MVA); n = 11 MLP (8 staff nurses, 3 auxiliary nurse-midwives) and n = 14 doctors (6 obstetrician/gynaecologists, 3 GPs and 5 other doctors [with MBBS]). All providers received 3 day training in MToP and were certified.

Subjects were randomly assigned to MLP or doctor via a computer-generated randomisation scheme stratified by study centre. All subjects received mifepristone 200 mg orally on Day 1 and 800 microgram misoprostol tablets vaginally on Day 3 administered by the assigned provider. Subjects returned to the assigned provider for follow-up clinical assessment after 10-14 days.

The primary endpoint was complete abortion without MVA within 30 days of treatment. The secondary endpoint measured case-management decisions by recording case-management discussions and referrals between providers to assess the extent to which each group provided medical abortion services independently. Serious adverse events (SAEs; haemorrhage necessitating blood transfusion, conditions necessitating hospitalisation) were recorded and completeness of abortion and any complications identified via patient interview and clinical examination.

A sample size of 1086 women was determined to provide 80% power to demonstrate equivalence assuming a 5% margin of equivalence and 10% loss to follow-up. The primary analysis was ITT with a supplementary PP analysis on the primary endpoint conducted.

Overall, 1104 subjects were randomised, 1077 treated and 1032 included in analyses of the primary endpoint (n = 518 MLP group, n = 514 doctor group). There were 25 subjects excluded (n = 10 MLP group, n = 15 doctor group), mostly due to gestation > 9 weeks. One subject in each group had signs of ectopic or adnexal mass. Loss to follow up was low (4% both groups).

Baseline characteristics were comparable in the 2 provider groups. The mean (SD) duration of gestation by clinical examination was 6.8 (1.0) weeks and mean age of subjects 28.0 years. Complete abortion was reported for 97.3% subjects in the MLP group and 96.1% in the doctor group; risk difference within the predefined equivalence range (1.24% [95% CI: -0.53, 3.02]). PP analysis was consistent (see Table 6). The proportion of incomplete abortions was similar in both groups (n = 14 [2.7%] MLP group, n = 15 [2.9%] doctor group). All incomplete abortions and continuing pregnancies (n = 0 MLP group, n = 5 [1.0%] in doctor group) were terminated by MVA by the assigned provider. No SAEs were reported. The authors stated '*women reported typical side-effects such as nausea, vomiting, diarrhoea, abdominal pain, chills, and fever with no difference by type of provider*' although these data were not shown. In terms of the secondary endpoint, MLPs discussed < 2% cases with doctors and referred < 1% cases to doctors.

4.1.1.2. Observational studies

Jejeebhoy et al. (2012) [7]

These authors performed an observational cohort study at 5 clinics in urban areas in 2 states in India with limited access to health services, to assess whether medical abortions performed by nurses and ayurvedic physicians were as safe and effective as those done by allopathic physicians. The study was conducted from 2008 - 2010. At the time of the study, only gynaecologists and other certified allopathic physicians were able to provide abortions in India. To control for provider experience, providers with no experience in surgical or medical abortion, pelvic examination (other than academic training) or gestational age assessment were recruited; n = 10 nurses, n = 10 ayurvedic physician and n = 10 allopathic physician. All providers received medical abortion training (including classroom training, practice sessions, and training in the field with a minimum of 10 cases each of gestational age dating and assessment of completion of MToP). Assessment of subject eligibility and completed abortion

status was based on pelvic examination; ultrasonography was not used. The provider evaluations were verified by a certified abortion provider (verifier) who also prescribed the medication for MToP.

All 3 types of service providers were placed sequentially at each clinic until 35-40 medical abortions were completed, approximately 6 weeks. The study was not randomised, although subjects were not aware of which healthcare professional would provide services on the visit day.

Evaluator comment*: It is likely some subjects may have had follow-up with a different type of service provider if they presented during the latter part of a particular provider's placement. Overall, the number of subjects screened for eligibility and for abortion completeness was similar across the groups (n = 464 - 491 and n = 412 - 435 respectively). These assessments were also conducted by the verifier.*

Eligible subjects were those with pregnancy up to 8 weeks gestation (based on urine pregnancy test and pelvic examination) with no contraindications to MToP, haemoglobin ≥ 9 g/dL and residing within an hour of study site. Contraindications included suspected ectopic pregnancy, hypertension, cardiovascular disease and bronchial asthma. Subjects received mifepristone 200 mg orally on Day 1 and misoprostol 400 micrograms orally on Day 3, in line with government guidelines. Subjects returned for pelvic examination to assess for completeness of the abortion on Day 15, and Day 21 for those deemed to have an incomplete abortion.

Evaluator comment*: The study included pregnant women up to 8 weeks gestation which is more restrictive than the approved Australian population (up to 63 days gestational age). Further, the dose of misoprostol used is different (lower) than that used with MS-2 Step. No information was provided as to whether repeat doses of misoprostol were required.*

Sample size calculations estimated 380 subjects per provider arm would provide 80% power to establish equivalence between allopathic physicians and each of the other provider groups, assuming equivalence margin of 5.5% and 5% loss to follow-up. There were 1414 subjects screened and 1225 (87%) recruited. The reasons for screen failure were not stated. Loss to follow-up was small; 4 – 6% across groups.

Although this was not a randomised study, baseline demographic characteristics were generally consistent across the 3 groups. The mean age of subjects ranged from 26.6 – 27.1 years. Gestational age was not stated.

The key outcome measure was observed failure rate (proportion of subjects for whom complete information was available who had an ongoing pregnancy on Day 15, or an incomplete abortion on Day 15 or Day 21 if extended follow-up was advised). The observed failure rate was 4.6% in the nurse and allopathic physician group and 5.5% in the ayurvedic physician group with differences in failure rates (allopathic physicians vs. nurses and allopathic vs. ayurvedic physicians) within the predefined margin of statistical equivalence (Table 7). The proportion of subjects with incomplete abortion and ongoing pregnancy was comparable across groups (1.8 - 2.1% and 2.8 - 3.4% respectively). Convergence between assessments by the different healthcare providers and verifiers was high. All subjects with an ongoing pregnancy or incomplete abortion underwent MVA by the verifier. There were no serious complications and no subjects required blood transfusion or hospitalisation. Unscheduled visits (5%) or phone calls (4%) were stated to be related mostly to extent and duration of bleeding or uncertainty regarding procedure; these data were not shown.

4.1.1.3. Cochrane review – Barnard et al. (2015) [8]

A Cochrane Collaboration review by Barnard *et al.* assessed the safety and effectiveness of abortion procedures administered by MLPs compared to doctors. The review included RCTs,

prospective cohort or observational studies comparing safety and/or effectiveness of any first trimester abortion procedure by any type of MLP or doctors. Of the 8 studies meeting eligibility criteria, 5 studies assessed surgical abortions which are not considered relevant to the current submission. The 3 studies assessing medical abortion (2 RCTs, 1 cohort study); were those by Kopp Kallner *et al*., Warriner *et al*., and Jejeebhoy *et al.* discussed above [5, 6, 7].

Barnard and colleagues stated '*For medical abortion procedures the risk of failure was not different for mid-level providers or doctors (RR 0.81, 95% CI 0.48 to 1.36 from RCTs; RR 1.09, 95% CI 0.63 to 1.88 from observational studies). The quality of evidence of this outcome for the RCT analysis was considered to be high, although the quality of evidence of the observational studies was considered to be very low'.*

4.1.1.4. International experience

• The Clinical Expert stated MToP provision by MLPs such as nurses, midwives and nurse practitioners is already available and part of the standard of care in countries including Canada and the USA, with nurse practitioners in Canada able to prescribe mifepristone since 7th November 2017.

Evaluator comment*: The Health Canada Regulatory Decision Summary document to register Mifegymiso (29th July 2015, available in public domain [9]) states risk management activities included physician only dispensing and education and registration program for prescribers. In the Regulatory Decision Summary document (7th November 2017) to extend the indication for Mifegymiso from 49 to 63 days gestation, Health Canada stated 'the term "Doctors" was replaced by "health professionals" throughout the Mifegymiso product monograph as practice of medicine, including who can prescribe Mifegymiso, varies by province' [10].*

• Schummers *et al*. [11] noted mifepristone (in combination with misoprostol) was marketed in Canada in January 2017 with restrictions that were removed by the Canadian regulator in November 2017 such that mifepristone could be prescribed and dispensed as a normal prescription. The Clinical Expert stated '*Since 2017, there has not been an increase in the incidences of serious adverse events in Canada due to the change in prescriber indicating no increased risk to patients when MToP is provided by mid-level healthcare professionals*.'

The Evaluator notes Schummers and colleagues reviewed population-based administrative data from Ontario, Canada to assess abortion use, safety and effectiveness prior to availability of mifepristone (January 2012 – December 2016) and availability of mifepristone without restrictions (7th November 2017 – 15th March 2020). The dataset comprised linked records from practitioner visits, all hospital visits, and outpatient prescriptions for female Ontario residents aged 12 – 49 years who had received abortion services from 1st January 2012 - 15th March 2020.

Safety outcomes within 6 weeks after abortion included SAEs and complications of abortion. Effectiveness outcomes included incidence of subsequent uterine evacuation, ongoing intrauterine pregnancy and ectopic pregnancy diagnosed within 6 weeks of abortion. Although not the primary objective of the study, the data for first trimester medical abortions when mifepristone was available with restrictions (1st January 2017 – 6th November 2017) and when mifepristone was available without restrictions (7th November 2017 – 15th March 2020) are of most relevance to the current application to expand prescriber eligibility for MToP. These subgroup analysis results were included as supplementary tables (not provided with the reference in Module 5.4, however available in the public domain [12]); see Table 8 and Table 9.

Evaluator comment*: The short time period during which mifepristone was available with restrictions is noted and does limit interpretation of the results. Overall, SAEs and complications were low in both groups. For effectiveness outcomes, the proportion of women with ongoing pregnancy and ectopic pregnancy was similar whilst the proportion requiring subsequent uterine evacuation was lower in the mifepristone without restrictions group. The authors acknowledge early mifepristone uptake may*

be underestimated as mifepristone prescriptions dispensed after 10th August 2017 (following introduction of a universal subsidy) were universally captured whilst only mifepristone prescriptions among patients with income-based prescription subsidies and under 25 years of age were captured from January to 9th August 2017. Schummers et al. consider this limitation was mitigated by identification of medical abortions by other data. Whether this impacts the data presented for the mifepristone available with restrictions group, taking into consideration the short time period, is uncertain, and no firm conclusions can be drawn from these data.

The Clinical Expert stated '*as shown in the current Periodic Safety Report (PSUR; 1st June 2021-31st May 2022) there has been no increase or additional changes in the safety concerns monitored in Canada prior to the approval of the change of prescriber (*PSUR 1st June 2015 – 31st May 2016*) versus those that are currently monitored*'.

Evaluator comment*: The summary of safety concerns in these 2 documents is different (e004967 (0007-) - Periodic Safety Update Report 01 June 2016 to 31 May 2017 (#21) and e004967 (0007-) - Periodic Benefit Risk Evaluation Report 01 June 2021 to 31 May 2022 (#26)). The Clinical Expert did not elaborate on this point and it is not clear to the Evaluator the 'safety concerns' the Expert is referring to. The PBRER covering the period 01 June 2021 – 31st May 2022 has been submitted previously and reviewed by the TGA. Additional information was requested from the Sponsor following TGA review of the PSUR including provision of an updated RMP.*

• In the USA, trained advanced practice clinicians (including nurse practitioners, nurse-midwives and physician assistants) have been providing medical and, in some cases, early surgical abortion in 15 states since 2005 [13]. Schummers *et al*. [11] state mifepristone is approved for use in the USA with REMS restrictions (including mandatory prescriber certification, observed dosing, dispensing by the prescriber or medical facility with the exclusion of pharmacies, and submission of a prespecified patient consent form).

Evaluator comment*: From information available on the FDA website, the Mifepristone REMs Program was modified in December 2022 to remove the 'in-person' dispensing requirement and addition of certification of pharmacies. The Mifeprex product label (revised 01/2023) states Mifeprex is only available through the REMS program which includes prescriber certification, dispensing by, or under supervision of, the prescriber, or certified pharmacies [3].*

• Prescriber status for mifepristone in Europe or UK was not discussed in the Clinical Overview.

Berer (2009) [13] stated the following:

- In France and Great Britain, both medical and surgical abortions must be performed by a physician.

- In France, physicians confirm the pregnancy and conduct the follow-up visit but nurses are often responsible for all the other procedures involved in medical abortion.

- Regulations in Great Britain are already interpreted to allow nurses to administer medical abortion drugs, as long as the drugs are prescribed by a physician.

Evaluator comment*: The Evaluator notes this paper was published in 2009 and there may have been updates to medical abortion practices and prescriber eligibility in countries in Europe and the UK since then. The UK SPC for Mifepristone Linepharma [14] includes the following statement in Section 4.1, Therapeutic indications 'For termination of pregnancy, Mifepristone Linepharma 200mg tablet and prostaglandins can only be prescribed and administered in accordance with countries national laws and regulations.'*

In summary, the Clinical Expert concluded '*The proposed amendments to broaden the definition of prescriber do not pose a risk to patient safety. Evidence provided within this submission demonstrates there to be no detectable impact of MToP by appropriately trained healthcare*

professionals on patient outcomes; and that the provision of education for all prescribers will ensure a minimum baseline regardless of prescriber's background.'

4.1.2. Evaluator's assessment and recommendations

The main evidence provided to support the proposed change is from 3 studies, including data for approximately 1800 women receiving MToP up to 63 days gestation [5, 6] and approximately 1100 women receiving MToP up to 8 weeks gestation [7].

The Kopp Kallner *et al*. [5] study is considered most relevant to use in Australia. This study was conducted in a high-resource setting with ultrasound as part of the protocol, whereas the studies by Warriner *et al*. [6] and Jejeebhoy *et al*. [7] were conducted in low-resource settings. Neither of the latter 2 studies included ultrasound assessment per study protocol, nor was hCG testing utilised in the Warriner study. This does not generally align with the Australian MS-2 Step PI [1], which recommends confirmation of pregnancy duration by ultrasound in the indication, and lists 'pregnancy not confirmed by an ultrasound or biological test such as urine or serum HCG' as a contraindication. Furthermore, the study population and dose of misoprostol used in the Jejeebhoy *et al*. [7] study differs from approved use in Australia.

Although the Warriner *et al*. and Jejeebhoy *et al*. studies [6, 7] are less applicable to the Australian setting, overall there were no safety concerns with provision of MToP by MLPs identified in any of the 3 studies, with effectiveness outcomes comparable for MLPs and doctors. The risk of failure was comparable for MToP performed by MLPs and doctors in all studies and is a known risk described in the MS-2 Step PI [1]. There were no serious adverse events reported. The reasons for complications were provided by Kopp Kallner *et al*. [5] and noted to be consistent with the safety profile of MToP with mifepristone/misoprostol.

There was variability in provider experience across the 3 studies. Nurse-midwives experienced in MToP were recruited in the Kopp Kallner *et al*. [5] study with additional early pregnancy ultrasound training provided. All providers underwent MToP training in the Warriner *et al*. and Jejeebhoy *et al*. studies [6, 7]. The importance of education with regard to the MToP process was endorsed by the Clinical Expert who reiterated *'MS Health proposes to continue providing the same (existing) standardised training for all potential prescribers (as detailed in the current approved Australian RMP) and doing so will ensure a minimum baseline of education regardless of training background',* stating further *'The PI amendments proposed by MS Health simply enable individual jurisdictions to make decisions appropriate for their population'.*

Broadening the prescriber eligibility to include non-physician prescribers (in accordance with individual state and territory requirements) is consistent with established practice in Canada and the USA, noting the USA has REMS program requirements for all prescribers [3].

Overall, the Evaluator considers the evidence provided supports the proposed changes to the boxed warning of the MS-2 Step PI to amend '*medical practitioner*' to '*healthcare practitioner*' and to amend '*doctors with the appropriate qualifications and certified training'* in Section 4.2 to '*healthcare practitioners with the appropriate qualifications and certified training*' given the Sponsor proposes to maintain the existing standardised training for prescribers. However, the Evaluator was advised by the Risk Management Section the Sponsor proposes to remove the requirement for prescriber certification from the PI as part of the updated RMP provided to TGA (dated 17th February 2023). The proposed removal of prescriber certification from the PI does potentially bring into question the Sponsor's justification for the proposed changes to the PI as the Clinical Expert's assertion regarding a minimum baseline of education irrespective of training background would not hold if the requirement for prescriber certification is removed.

The proposed changes to the boxed warning and Section 4.2 give rise to inconsistencies in the PI which have not been addressed, and are drawn to the attention of the Delegate:

• Section 4.2 Dose and method of administration:

The Sponsor states in the Cover letter the application proposes to amend the reference to 'doctors' in Section 4.2 to 'healthcare practitioners'.

However Section 4.2 includes the text '*When MS-2 Step fails to cause termination of intra-uterine pregnancy, the patient should return to the treating doctor for assessment and discussion of treatment options, which may include pregnancy termination by surgery*.'

This text is not consistent with the proposed changes advising patients receiving these medications are followed up by a healthcare practitioner, preferably the prescriber.

• Section 4.4 Special warnings and precautions for use:

Section 4.4 includes information regarding particular co-morbidities as follows:

Take special care in case of suspected acute adrenal failure. In case of suspected acute adrenal failure, dexamethasone administration is recommended (please refer to the dexamethasone Product Information).

Due to the antiglucocorticoid activity of mifepristone, the efficacy of long-term corticosteroid therapy, including inhaled corticosteroids in asthmatic patients, may be decreased during the 3 to 4 days following intake of mifepristone. Therapy should be adjusted.

Patients with these medical comorbidities may require additional medical management such as adjustment of inhaled corticosteroid (ICS) therapy for asthma patients for example, that may be outside the scope of practice of non-physician healthcare providers. The Sponsor has not specifically addressed how patients with relevant medical comorbidities as described in the PI will be managed by non-physician healthcare providers.

• Section 4.4 Special warnings and precautions for use and Section 4.8 Adverse effects (undesirable effects):

Section 4.4 includes text regarding cases of serious bacterial infection, including very rare cases of fatal septic shock, with statements in the 'Infection' subsection specifically referring to 'doctors' as follows:

- *'Treating doctors evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event.'*

This text is not consistent with the proposed changes advising patients receiving these medications are followed up by a healthcare practitioner, preferably the prescriber. It would seem appropriate all healthcare providers would need to be aware of this risk.

- *'These symptoms, even without a fever, may indicate Clostridium sordellii infection. Strong consideration should be given to obtaining a complete blood count in these patients. Significant leukocytosis with a marked left shift and haemo-concentration may be indicative of sepsis. Doctors should consider immediately initiating treatment with antibiotics that includes coverage of anaerobic bacteria such as Clostridium sordellii.'*

This text is also included in Section 4.8 of the PI.

These statements refer to clinical management of a potentially serious infection/possible sepsis including initiation of appropriate antibiotic therapy. As aforementioned, it is not clear whether this is within the scope of practice of non-physician healthcare providers.

• Section 4.6 Fertility, pregnancy and lactation:

Section 4.6 includes the following text*:*

'To avoid the potential exposure of a subsequent pregnancy to MS-2 Step it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after administration of MS-2 Step.'

This is considered important safety information. It is not clear whether prescription of reliable contraceptive methods is within the scope of practice for all healthcare providers for whom expanded prescriber eligibility is proposed (acknowledging different state/territory legislation), and therefore if some patients may need to be referred to a different healthcare provider. Of note to the Delegate, 'Return to fertility' is included in the 'Serious warnings and precautions' box in the Canadian Mifegymiso product monograph [2].

These outstanding issues may require appropriate risk minimisation strategies such as updates to the educational materials.

5. Other issues

As discussed in Section 3, the Sponsor provided an updated RMP (v4.0, 17th February 2023) during the evaluation phase of the current submission. The RMP Evaluator advised 2 recommendations for Delegate/Clinical evaluator consideration:

(i) The Sponsor proposes to remove the requirement for prescriber certification from the PI. The RMP Evaluator recommended the Delegate/Clinical evaluator consider the proposed PI change from the clinical perspective, and whether advisory committee advice is needed.

Evaluator comment*: This Type J application proposes to expand prescriber eligibility for MS-2 Step. Removal of prescriber certification was not proposed in the PI submitted with the application, and not discussed in the Clinical Overview Addendum. On the contrary, to support the expansion of prescriber eligibility, the Clinical Expert stated 'MS Health proposes to continue providing the same (existing) standardised training for all potential prescribers (as detailed in the current approved Australian RMP) and doing so will ensure a minimum baseline of education regardless of training background …. The PI amendments proposed by MS Health simply enable individual jurisdictions to make decisions appropriate for their population'. This statement is not considered consistent with the proposed change to remove prescriber certification.*

Whether advisory committee advice is needed regarding the proposed change is for the consideration of the Delegate.

(ii) The Sponsor proposes to remove the requirement for a Sponsor provided 24-hour phone service. The RMP Evaluator recommended the Delegate/Clinical evaluator consider the proposed PI change from the clinical perspective, in particular, whether and how much value the 24-hour phone service adds to patient safety outcomes.

Evaluator comment: *The Sponsor has not provided any data in the current submission regarding use of the 24-hour phone service in Australia nor was removal of this statement from Section 4.4 of the PI discussed in the Clinical Overview Addendum. No clinical comment regarding this proposed change is therefore able to be provided.*

6. First round recommendation regarding authorisation

At this stage, approval of the variation to the register entry and Australian PI for MS-2 Step composite pack (mifepristone/misoprostol) is not able to be recommended for the following reasons:

- The Evaluator considers the data provided in the submission supports the proposed changes to the boxed warning to amend '*medical practitioner'* to '*healthcare practitioner'* and to amend '*doctors with the appropriate qualifications and certified training'* in Section 4.2 to '*healthcare practitioners with the appropriate qualifications and certified training*' (in accordance with individual state and territory requirements) on the basis the existing standardised training for

all potential prescribers is maintained as stated by the Clinical Expert. However, the Sponsor's proposal to remove the mandatory education program as proposed in an updated RMP subsequently submitted to the TGA is inconsistent with the Clinical Expert's assertion that a minimum baseline level of education will be provided for all prescribers, and does not support the justification for the prescriber eligibility changes.

7. Clinical questions

1. The RMP (dated 17th February 2023) provided to the TGA separate from the Type J dossier proposes removal of the requirement for prescriber certification. Please state how this proposed amendment aligns with the justification provided in the Clinical Overview Addendum to support the proposed expansion of prescriber eligibility - '*MS Health proposes to continue providing the same (existing) standardised training for all potential prescribers (as detailed in the current approved Australian RMP) and doing so will ensure a minimum baseline of education regardless of training background'.*

2. Please confirm whether the standardised training program will remain in place for all prescribers of MS-2 Step in Australia.

If not, please state how the risk with the proposed expansion of prescriber eligibility from medical professional to healthcare professional will be minimised.

8. Review of Sponsor's response

The Sponsor stated the evaluation report was reviewed for errors of fact or omissions and no corrections are required.

As part of the Section 31 response the Sponsor provided an updated PI (e004967 (0012-) - Product Information - Annotated) which includes additional proposed changes to Section 4.2 to remove '*and certified training'* as follows:

MS-2 Step should only be prescribed by healthcare practitioners~~doctors~~ with the appropriate qualifications ~~and certified training~~. Ectopic pregnancy should be excluded, an intrauterine device (IUD) (if present) must be removed, consent must be obtained and patients must have the ability to access 24-hour emergency care if and when required for incomplete abortion or bleeding.

The Sponsor response to the Clinical Questions (e004967 (0012-) - Response - 2023-04 Response to S31 Request, MS3) is copied below:

Question 1: The RMP (dated 17th February 2023) provided to the TGA separate from the Type J dossier proposes removal of the requirement for prescriber certification. Please state how this proposed amendment aligns with the justification provided in the Clinical Overview Addendum to support the proposed expansion of prescriber eligibility - '*MS Health proposes to continue providing the same (existing) standardised training for all potential prescribers (as detailed in the current approved Australian RMP) and doing so will ensure a minimum baseline of education regardless of training background'.*

Sponsor response: The Sponsor confirms that the existing standardised training (the Medical Education Program) will still be available for all healthcare practitioners that prescribe MS-2 Step via the existing online website (www.ms2step.com.au). The change proposed in the most recent submitted update to the RMP was to remove the mandatory aspect of the training and

the subsequent certification. As detailed in Question 2 below, it is the prescriber's obligation to acquire the knowledge and skill to prescribe a drug safely (which is a fundamental aspect of their practice), regardless of whether the RMP includes mandatory certification of prescribers. In the decade since the registration of MS-2 Step, the Sponsor has seen a number of education and training resources developed to support prescribers beyond that offered by the Medical Education Program included in the initial registration of the product. Examples include:

- Women's Health Victoria (https://whvtraining.com.au/product/early_medical_abortion/),

- Family Planning NSW (https://www.fpnsw.org.au/medical-abortion-online),

- the AusCAPPS network, an online community of practice network to support providers of early medical abortion (https://medcast.com.au/communities/auscapps)

- the compulsory module for RANZCOG trainees

- electronic Therapeutic Guidelines.

These resources are all available for clinicians who have an interest and wish to understand more about this area of medicine. The Sponsor notes that these alternate training resources are not subject to TGA oversight via incorporation into formal documentation such as an RMP. The need for the current approved restriction criteria (i.e. mandatory certification and training), while prudent and likely necessary at the time of first registration, is diminished in view of such extensive experience and availability of training.

The Sponsor would also request the assessor consider MS-2 Step in comparison with other products on the ARTG (with greater risk profiles), but which don't have the same restrictions or mandatory programs in place before the product can be prescribed. The expectation for these other products being that a prescriber would be professionally competent before prescribing any product. The Sponsor is simply asking the same standard to be applied to MS-2 Step.

Therefore, to reiterate the above, the Sponsor does not plan to remove the Medical Education Program, they only propose to remove this from being mandatory and subsequently not part of the RMP.

Question 2: Please confirm whether the standardised training program will remain in place for all prescribers of MS-2 Step in Australia.

If not, please state how the risk with the proposed expansion of prescriber eligibility from medical professional to healthcare professional will be minimised.

Sponsor response: As above, the Sponsor proposes to remove the mandatory component and associated certification of the Medical Education Program (currently included as part of the approved RMP and PI for MS-2 Step).

As detailed in the recently submitted draft RMP, the Medical Education Program will still be available to all treating healthcare practitioners. The sponsor is committed to continuing to improve patient access to the product by ensuring that training is available for prescribers and dispensers.

In accordance with the Australian Health Practitioner Regulation Agency (AHPRA) position, when a practitioner's practice is believed to be, or may be, unsatisfactory:

"Unsatisfactory professional performance, of a registered health practitioner, means the knowledge, skill or judgment possessed, or care exercised by, the practitioner in the practice of the health profession in which the practitioner is registered is below the standard reasonably expected of a health practitioner of an equivalent level of training or experience [[1]]."

Therefore, the prescriber's obligation to acquire the knowledge and skill to prescribe a drug safely is a fundamental aspect of their practice, regardless of whether the prescriber is a medical professional or healthcare professional. This is the case for most (if not all) other medicines where a prescriber is expected to understand when the medication can and cannot be prescribed; any testing, monitoring or other activity that must occur before administration; obtaining informed consent; and providing follow-up care as appropriate.

Therefore, the Sponsor does not believe that the removal of the mandatory certification (by completion of the Medical Education program) will result in any additional risk when the prescriber eligibility is changed from a medical professional to a healthcare professional as the Medical Education Program will continue to be available online via the existing website (www.ms2step.com.au), along with other education and training resources that are available over and above the Sponsor specific training.

Evaluator comment: The Sponsor's responses are noted. The justification provided by the Clinical Expert in the Clinical Overview Addendum to expand prescriber eligibility to include non-physician prescribers (in accordance with individual state and territory requirements) included assurance the existing standardised training for all potential prescribers as per current approved Australian RMP (i.e. mandatory practitioner training and certification) would be maintained, and was supported by data provided in the dossier. As noted in this report, all providers underwent MToP training in the Warriner *et al*. and Jejeebhoy *et al*. studies (including certification in the Warriner *et al*. study) [6, 7], and the Kopp Kallner study [5] recruited nurse-midwives experienced in MToP who received additional ultrasound training. The proposed removal of '*and certified training*' from the proposed PI provided with the Section 31 response does not align with the Clinical Expert's assertion that '*a minimum baseline of education regardless of training background will continue to be provided*' and data included in the submission to support the proposed expansion of prescriber eligibility.

9. Second round recommendation regarding authorisation

A recommendation regarding authorisation of the Type J application for MS-2 Step composite pack is not able to be provided.

As stated at Round 1, the data provided in the submission support the proposed changes to the boxed warning to amend '*medical practitioner'* to '*healthcare practitioner'* and to amend '*doctors with the appropriate qualifications and certified training'* in Section 4.2 to '*healthcare practitioners with the appropriate qualifications and certified training*' (in accordance with individual state and territory requirements) on the basis the existing standardised training for all potential prescribers is maintained.

However, the Sponsor also proposes to remove '*and certified training'* from the PI provided with the Section 31 response. The proposed changes to the PI include expansion of prescriber eligibility more broadly with proposed changes to current risk management measures to remove mandatory certified training for prescribers. There is uncertainty regarding the risk of expanding prescriber eligibility and removing the requirement for certified training. ACM advice is recommended.

The Delegate's attention is drawn to inconsistencies noted in Sections 4.2, 4.4, 4.6 and 4.8 of the MS-2 Step composite pack PI with the proposed expansion of prescriber eligibility as discussed in Section 4.1.2 of this report. These are considered outstanding issues to be addressed should the application be approved.

10. References

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2. Canadian Mifegymiso Product Monograph (date of revision 17th June 2022). Provided in Module 5.4 (e004967 (0007-) - Canada SmPC)

3. US Mifeprex Product Label. Revised 01/2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020687Orig1s025Lbl.pdf

4. WHO Abortion Care Guideline 2022. Geneva: World Health Organization; 2022. Provided in Module 5.4 (e004967 (0007-) - WHO - Abort Care guidelines - 2022)

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6. Warriner IK, Wang D, Huong NTM, Thapa K, Tamang A, Shah I *et al*. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomised controlled equivalence trial in Nepal. *Lancet*. 2011;377:1155-1161. Provided in Module 5.4 (e004967 (0007-) - Warriner 2011)

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9. Regulatory Decision Summary – Mifegymiso - Health Canada. https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detail.php?linkID=RDS00032

10. Regulatory Decision Summary – Mifegymiso - Health Canada. https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detail.php?linkID=RDS00294

11. Schummers L, Darling EK, Dunn S, McGrail K, Gayowsky A, Law MR *et al*. Abortion safety and use with normally prescribed mifepristone in Canada. *N Engl J Med*. 2022;386:57-67. Provided in Module 5.4 (e004967 (0007-) - Schummers 2022)

12. Schummers L, Darling EK, Dunn S, McGrail K, Gayowsky A, Law MR *et al*. Abortion safety and use with normally prescribed mifepristone in Canada. *N Engl J Med*. 2022;386:57-67. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7489974/

13. Berer M. Provision of abortion by mid-level providers: international policy, practice and perspectives. *Bull World Health Organ*. 2009;87:58-63. Provided in module 5.4 (e004967 (0007-) - Berer 2009)

14. UK SPC Mifepristone Linepharma 200 mg tablet (revised 27/10/22). https://mhraproducts4853.blob.core.windows.net/docs/72e81b0722b04c4d065babba78a7be4e0dbe89fb

11. Supporting information, tables and figures

11.1. Study synopses

Not applicable.

11.2. Other supporting tables and figures

Table 1: Prescribers: number of women of childbearing age per prescriber by region

	ACT	NSW	NT	QLD	SA	TAS	VIC	WA
Metro	2933	2246	-	2173	2681	-	1738	3132
Regional	13	1656	492	1592	2795	1068	1083	1666
Remote	-	2825	612	644	1685	2106	0	961

Note: a zero value indicates there are locations in that state or territory with that classification but no prescribers or dispensers are registered. A dash signifies there are no locations in that state or territory that fall under that classification. Classifications align with definitions provided by the Australian Bureau of Statistics (ABS).

Source: MS Health – July 2022 Update, Dispenser and prescriber program, Module 5.4 (e004967 (0007-) - MS Health 2022 - Update)

Table 2: Demographic characteristics of women

	Allocated to nurse-midwife *n* = 535 Median (range)	Allocated to doctor *n* = 533 Median (range)
Age	27 (18–47)	27 (18–46)
Gestational age at ultrasound (days)	45 (30–63)	45 (28–63)
Gravidity	2 (0–13)	2 (0–14)
Parity	0 (0–5)	0 (0–6)
Miscarriage	0 (0–4)	0 (0–5)
TOP, surgical	0 (0–3)	0 (0–5)
TOP, medical	0 (0–4)	0 (0–5)
Vaginal deliveries	0 (0–5)	0 (0–6)
Caesarian section	0 (0–3)	0 (0–3)

There were no statistically significant differences between the groups.

Source: Table 1, Kopp Kallner et al. [5]

Table 3: Reasons for surgery

Reason for surgery	Allocated to nurse midwife (N=5)	Allocated to physician (N=12)	Total of women
Incomplete TOP	5	7	12
Bleeding (unscheduled)	0	3	3
Prolonged bleeding	0	1	1
Pain	0	1	1
Total	5	12	17

None of the differences reached statistical significance

Source: Table S2, Kopp Kallner et al. [5]

Table 4: Reason for complication (defined as an unscheduled visit for symptoms that led to further treatment)

Reason for the unscheduled visit	Allocated To nurse midwife (%) (n=493, 41 missing)	Allocated to physician (%) (n=472, 61 missing)	Total (%) (n=965, 102 missing)
Bleeding	2 (0.4)	4 (0.8)	6 (0.6)
Bleeding due to incomplete TOP	8 (1.6)	5 (1.1)	13 (1.3)
Symptoms of continuing pregnancy	0 (0)	1 (0.2)	1 (0.1)
Pain	2 (0.4)	7 (1.5)	9 (0.9)
Positive u-hCG[1]	4 (0.8)	2 (0.4)	6 (0.6)
Prolonged bleeding	0 (0)	2 (0.4)	2 (0.2)
Signs of infection	3 (0.6)	6 (1.3)	9 (0.9)
Unknown	1 (0.2)	2 (0.4)	3 (0.3)
Total	20 (4.1)	29 (6.1)	49 (5.1)

None of the differences reached statistical significance (p>0.05).U-hcg= urinary human chorionic gonadotropin with cut off 500 IE/ml (specified in the text)

Source: Table S3, Kopp Kallner et al. [5]

Table 5: Reason for second opinion consultation

Reason for consultation	Allocated to nurse-midwife *n* (%)	Allocated to doctor *n* (%)	Total *n* (%)
Multiple pregnancy	7 (1.3)	1 (0.2)	8 (0.7)
High serum hCG*	0 (0)	1 (0.2)	1 (0.9)
Information	3 (0.6)	1 (0.2)	4 (0.4)
Medical reasons	13 (2.4)	4 (0.8)	17 (1.6)
Ultrasound	59 (11)	8 (1.5)	67 (6.3)
Unknown	3 (0.6)	4 (0.8)	7 (0.7)
Prescription/second opinion for suspected bacterial vaginosis	54 (10)	4 (0.8)	58 (5.4)
Total	535	533	1068

*hCG, human chorionic gonadotropin.

Source: Table 3, Kopp Kallner et al. [5]

Table 6: Outcomes of medical abortion by type of provider

	MLP	Doctors	Risk difference for the primary endpoint* (95% CI)	Risk difference for the primary endpoint-adjusted analysis† (95% CI)
ITT analysis				
Number of women	518	514	..	..
Complete abortion	504 (97·3%)	494 (96·1%)	1·24% (–0·53% to 3·02%)	1·49% (–0·17% to 3·14%)
Incomplete abortion	14 (2·7%)	15 (2·9%)	..	..
Continuing pregnancy	0	5 (1·0%)	..	..
PP analysis				
Number of women	504	472	..	..
Complete abortion	490 (97·2%)	455 (96·4%)	0·89% (–1·11% to 2·88%)	1·12% (–0·70% to 2·93%)
Incomplete abortion	14 (2·8%)	12 (2·5%)	..	..
Continuing pregnancy	0	5 (1·1%)	..	..

MLP=midlevel health-care providers. ITT=intention to treat. PP=per protocol. *Estimated from a generalised estimating equation model with treatment as the fixed effect and service provider as a random effect. †Adjusted for woman's age and duration of gestation.

Source: Table 4, Warriner et al. [6]

Table 7: Medication abortion failure rates, by provider type, and differences in failure rates between provider types (and 95% CI)

Indicator	Provider type			Difference	
	Ayurvedic physicians (N=382)	Nurses (N=393)	Allopathic physicians (N=389)	Ayurvedic vs. allopathic	Nurses vs. allopathic
Observed failure rate	5.5	4.6	4.6	0.9 (–2.2 to 4.0)	–0.1 (–3.0 to 2.9)
Ongoing pregnancy	2.1	1.8	1.8	0.3 (–1.7 to 2.3)	0.0 (–1.9 to 1.8)
Incomplete abortion	3.4	2.8	2.8	0.6 (–1.9 to 3.0)	0.0 (–2.4 to 2.3)

Note: Equivalence is indicated when the 95% confidence interval for the difference in failure rates between the allopathic physician group and each of the other two groups (ayurvedic physicians and nurses) lie within the predetermined margin of equivalence (±5.5%).

Source: Table 3, Jejeebhoy et al. [7]

Table 8: Subgroup Analysis: First Trimester Medication Abortion - Safety and Effectiveness

Abortion safety and effectiveness outcomes according to mifepristone regulatory period among first trimester medication abortions only in Ontario, Canada: January 2012 – December 2016 vs. November 7 2017 - March 15 2020

Policy period	Pre-mifepristone Jan 2012- Dec 2016	Mifepristone with restrictions Jan – Nov 6 2017	Mifepristone as a normal prescription Nov 7 2017 – Mar 2020
First trimester medication abortions per period	2,956	2,671	25,754
	n (%)	n (%)	n (%)
Abortion safety outcomes			
Severe adverse events*	0 (0.00)	0 (0.00)	<6**** (n/a)
Abortion complications**	15 (0.51)	24 (0.90)	196 (0.76)
Abortion effectiveness outcomes			
Subsequent uterine evacuation***	344 (11.6)	239 (8.9)	1,160 (4.5)
Intrauterine pregnancy continuing to subsequent delivery	0 (0.00)	7 (0.26)	34 (0.13)
Ectopic pregnancy detected post-abortion	19 (0.64)	13 (0.49)	89 (0.35)

* Severe adverse event includes blood transfusion, abdominal surgery (laparotomy, laparoscopy, hysterectomy), ICU admission, or sepsis, all concurrent with an abortion complication. See detailed definition in Supplemental Table 1.
** Abortion complications include incomplete or complete abortion complicated by infection, hemorrhage, embolism, damage to pelvic organs, venous complications, or other complications after an induced abortion. See detailed definition in Supplemental Table 1.
***Subsequent uterine evacuation includes aspiration, re-aspiration, or subsequent abortion procedure in the same pregnancy.
**** Cells with fewer than 6 events cannot be reported due to privacy and confidentiality requirements of our data steward.

Source: Table S5, Schummers et al. [9]

Table 9: Subgroup Analysis: First Trimester Medication Abortion - Severe Adverse Event and Complication Components

Incidence of components of severe adverse event and abortion complication outcomes according to mifepristone practice restriction policy periods among first trimester medication abortions only in Ontario, Canada: January 2012 – December 2016 vs. November 7 2017 - March 15 2020

Policy period	Pre-mifepristone Jan 2012- Dec 2016	Mifepristone with restrictions Jan – Nov 6 2017	Mifepristone without restrictions Nov 7 2017 – Mar 2020
	n (%)	n (%)	n (%)
Severe adverse event components			
Blood transfusion	0 (0.00)	0 (0.00)	0.03
Abdominal surgery	0.00	<6*** (n/a)	0.06
ICU admission	0.00	0.00	<6*** (n/a)
Sepsis	0.00	0.00	<6*** (n/a)
Abortion complication components			
Infection	<6***	<6*** (n/a)	0.08
Hemorrhage	0.37	0.60	0.49
Shock	0.00	0.00	0.00
Renal failure	0.00	0.00	0.00
Damage to pelvic organs	0.00	<6***	0.00
Other	<6***	<6***	0.21

*** Cells with fewer than 6 events cannot be reported due to privacy and confidentiality requirements of our data steward.

Source: Table S6, Schummers et al. [9]

Therapeutic Goods Administration

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Australian Government
Department of Health
Therapeutic Goods Administration

Risk Management Plan Evaluation Report

Mifepristone/ Misoprostol (MS-2-Step)

Submission No: PM-2022-05475-1-5

Sponsor: MS Health Pty Ltd

Updated RMP received: 01 December 2022
Initial Report: 13 December 2022
Sponsor's Response received: 13 January 2023
Succession 2 Report: 20 February 2023
Succession 3 Report (round 1 for PM-2022-05475-1-5): 27 February 2023
Round 2 Report: 20 April 2023

TGA Health Safety Regulation

RISK MANAGEMENT PLAN EVALUATION REPORT

Submission type: PI update (corresponding to RMP updates)

Sponsor: MS Health Pty Ltd
Generic name: **Mifepristone/ Misoprostol**
Trade name: **MS-2-STEP**

Submission No; eSubmission ID: PM-2022-05475-1-5; e004967
RMP file No: 2013/020378
TRIM reference: D22-6199891

AU-RMP: *(EU-RMP not available)*
Initial - Version 0.4; dated 24 November 2022; DLP 31 May 2022
e004967 (0006-) - Risk management plan - Clean
D22-6187939

Succession 2 - AU-RMP version 4.0 (dated 13 January 2023, DLP 31 May 2022)
D23-5035315

Succession 3/Round 1 - AU-RMP version 4.0 (dated 17 February 2023, DLP 31 May 2022)
D23-5140670

Round 2 – AU-RMP version 4.1 (dated 5 April 2023, DLP 31 May 2022)

Last evaluated AU-RMP: Version 03; dated 13 November 2014; DLP 28 April 2013
R14/1181088

Date finalised:
13 December 2022 [Initial]
20 February 2023 [Succession 2]
27 February 2023 [Succession 3, Round 1 for PM-2022-05475-1-5]
20 April 2023 [Round 2]

Referral to ACM: TBC

Reason(s) for update:
New safety concern added
Removed safety concern
Pharmacovigilance milestone met
Ceased risk minimisation activity
Other:

RMP compliance monitoring: No

SUMMARY

- On 1 December 2022, MS Health Pty Ltd submitted updated AU-RMP version 0.4 (dated 24 November 2022; DLP 31 May 2022) for MS-2 Step. The EU-RMP is not available. A revised AU-RMP version 4.0 (dated 13 January 2023; DLP 31 May 2022) was provided with the sponsor's response to RMP evaluator's recommendations dated 13 January 2023. On 20 February 2023, the sponsor submitted further changes in AU-RMP version 4.0 (dated 17 February 2023; DLP 31 May 2022) which has been linked to the Category 1, Type J application (PM-2022-05475-1-5). At Round 2, the sponsor submitted updated AU-RMP version 4.1 (dated 5 April 2023; DLP 31 May 2022) with their S31 response dated 6 April 2023.
- MS-2 Step is approved for the medical termination of an intrauterine pregnancy, up to 63 days of gestation, in females of childbearing age.
- The most recently evaluated and approved AU-RMP was version 03 (dated 13 November 2014; DLP 28 April 2013) (R14/1181088).
- The reason for this updated RMP is changes to the summary of safety concerns (SoSC) and changes to the risk minimisation plan. The key changes proposed for risk minimisation activities are as follows:
    - To remove the requirement for pharmacists to be registered to be able to dispense the product.
    - To remove the requirement for prescriber recertification.
    - To remove the need for prescribers to complete mandatory training and receive certification to be able to prescribe the product.
    - To remove the requirement for a Sponsor provided 24 hours aftercare service
- As the TGA has previously evaluated RMPs for this product, the focus of this review is on the differences between the AU-RMP versions and revisions to the additional risk minimisation materials.
- The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below:

Summary of safety concerns		**Pharmacovigilance**		**Risk Minimisation**	
		Routine	Additional	Routine	Additional
Important identified risks	Infection, toxic shock syndrome	✓	–	✓	✓1,2
	Method failure	✓	–	✓	✓1,2
	Cardiac disorders	✓	–	✓	✓2
Important potential risks	Inadvertent pregnancy exposure and risk of incomplete abortion with severe bleeding	✓	–	✓	✓2
	Inadvertent pregnancy exposure (risk of malformations)	✓	–	✓	✓2
	Potential interaction with CYP3A4 inhibitors or inducers	✓	–	✓	–
	Potential interaction with products interacting with the glucocorticoid receptor	✓	–	✓	–
	Induced bronchial asthma	✓	–	✓	–
	Effects in lactating women	✓	–	✓	–
	Effects in women with impaired liver function	✓	–	✓	–
	Effects in women with impaired renal function	✓	–	✓	–
	Effects in women with malnutrition	✓	–	✓	–

	Incorrect determination of gestational age	✓	–	✓	–
	Potential for missed ectopic pregnancy	✓	–	✓	✓[2]
	Potential for postnatal developmental delay	✓	–	✓	–
	Potential for off-label use beyond the first trimester	✓	–	✓	–
Missing information	Inherited porphyria	✓	–	–	–
	Theoretical interaction with NSAIDs	✓	–	–	–
	Potential interaction with products interacting with the progesterone receptor	✓	–	–	–
	Use in adolescents	✓	–	–	–
Pharmacological class effect	Risks related to the use of prostaglandin	✓	–	✓	✓[2]

[1] Black box warning
[2] Patient Information and Consent Agreement form

- The sponsor has updated the summary of safety concerns in line with recommendations by the RMP evaluator as well as to reflect up-to-date safety information for MS-2 Step. At Round 2, the sponsor has proposed to remove potential risk 'Potential for loss to follow-up' and this is acceptable from an RMP perspective. However, the sponsor has also removed potential risk 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up', which is not supported as there are additional considerations to this risk with regards to access to further advice or treatment if follow-up does not occur.

- The completed post marketing surveillance study has been removed from the pharmacovigilance plan. Routine pharmacovigilance is proposed for all safety concerns. There is one additional pharmacovigilance activity – an ongoing Canadian post-market surveillance study on the effectiveness and safety of combination mifepristone/misoprostol for medical abortion under 63 days gestation. Further changes to the pharmacovigilance plan in the AU-RMP is recommended.

- The sponsor proposes to remove from the risk minimisation plan the requirements for prescriber certification, pharmacist registration and a Sponsor-provided 24 hours aftercare service. Additional risk minimisation activities will consist of a black box warning, inclusion of CMI and instruction insert in pack, and Patient Information and Consent Agreement form. The sponsor will continue to make educational materials available as support to prescribers and dispensers. The proposed risk minimisation plan aligns with that in Canada and the UK. The RMP evaluator has noted the post-market experience with MS-2 Step, its well-established safety profile, and existing safety frameworks in place. The RMP evaluator has also noted the importance of timely access of this medicine in terms of patient-safety and the need to remove requirements that hinder patient access to reproductive services. The proposed changes to the risk minimisation plan are acceptable from an RMP perspective. Further changes to the risk minimisation plan are recommended. The sponsor is also requested to include a copy of the Educational Program materials and Patient Information and Consent Agreement form in the appendix of the AU-RMP.

TABLE OF CONTENTS

1. OUTCOME OF THE EVALUATION

1.1. RECOMMENDATIONS TO THE SPONSOR – ROUND 2

The updated AU-RMP (version 4.1, dated 5 April 2023, DLP 31 May 2022) has been considered.

The recommendations made in the initial evaluation and Round 1 evaluation, along with consideration of the sponsor response, are located in Section 6.1 and 6.2 respectively.

There are 2 outstanding recommendations after Round 2 evaluation:

Outstanding Recommendation 13: The ongoing Canadian post-market surveillance study should also be added to the tables in Section III.3 (Table 10) and V.3 (Summary of risk minimization measures) as appropriate. Refer to the Canadian RMP to identify the safety concerns that will be addressed by this additional pharmacovigilance activity.

It is acknowledged that the sponsor commits to submitting a revised RMP that considers completed study outcomes to the TGA when available. The sponsor should submit key findings from the study as an accompanying document. The full study report is only required upon TGA's request.

Outstanding Recommendation 14: The potential risk 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up' should remain in the SOSC as there are additional considerations to this risk with regards to access to further advice or treatment if follow-up does not occur.

Further, it is noted that this safety concern is not discussed in the PSUR, which uses the Canadian RMP as the reference document. It is requested that the sponsor provide an assessment of this safety concern with the PSUR submission expected August 2023. This assessment may serve to support the removal of this safety concern (can be submitted as an RMP update).

There are 2 new recommendations after Round 2 evaluation:

Recommendation 21. The annotated AU-RMP version 4.1 (dated 5 April 2023) tracks all changes since the approved version 03 (dated 13 November 2014) i.e. marks changes from version 0.4 to the two subsequent versions 4.0 to version 4.1. To avoid confusion and for ease of evaluation, annotated documents should only track the changes made since the last submitted version.

Recommendation 22. The sponsor should make the following changes to the risk minimisation plan:

- Include potential risk 'incorrect determination of gestational age' in Section V.3 Summary of risk minimization measures (table; page 38) in the AU-RMP
- Add potential risk 'Potential for off-label use beyond the first trimester' to Table 11 in Section V.1 of the AU-RMP
- Append the Educational Program materials and Patient Information and Consent Agreement form to the AU-RMP

- In Section V.2 Additional Risk Minimisation Measures
    - Under 'Inclusion of Instruction Insert in Composite Pack Carton', remove text relating to the mandatory training program and certification for prescribers:

      "These arrangements are set up and are accessible via the Sponsor's secure healthcare professional website www.ms2step.com.au, or by calling the company directly. The Sponsor may change the restrictions on supply if in the future an effective control mechanism on prescriber access becomes possible via the PBS."

    - Under 'Prescriber Training', specify availability via the website www.ms2step.com.au

1.2. WORDING FOR CONDITIONS OF REGISTRATION

Wording for conditions of registration will be provided once the outstanding RMP issues are addressed to the satisfaction of the TGA.

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> *The MS-2 STEP Australian Risk Management Plan (AU-RMP) (version 4.1, dated 5 April 2023, data lock point 31 May 2022), included with submission PM-2022-05475-1-5, to be revised to the satisfaction of the TGA, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*

1.3. ADVICE TO THE DELEGATE

Recommendations 19 and 20 from Round 1 are for the TGA delegate/clinical evaluator:

Recommendation 19. This is a recommendation for the TGA delegate/clinical evaluator. The requirement for prescriber certification is included in the approved PI. The sponsor has advised that it will remove this requirement and submit the updated PI following the completion of round 1 evaluation. From the RMP perspective, assessing prescriber competencies is more related to clinical practice than to product risk management. Therefore, the removal of prescriber certification from the RMP is acceptable. It is recommended that the delegate/clinical evaluator considers the proposed PI change from the clinical perspective, and whether advisory committee advice is needed.

Recommendation 20. This is a recommendation for the TGA delegate/clinical evaluator. The provision of 24-hour phone service for patients is included in the approved PI. The sponsor has advised that it will remove this service and submit updated PI following the completion of round 1 evaluation. It is noted that the PI also advises that 'patients must have the ability to access 24-hour emergency care'. This would ensure timely access to urgent medical attention and intervention. Therefore, the removal of 24-hour phone service is acceptable

from the RMP perspective. It is recommended that the delegate/clinical evaluator considers the proposed PI change from the clinical perspective, in particular, whether and how much value the 24-hour phone service adds to patient safety outcomes.

The sponsor has provided a response to these (see in Section 6.2).

2. BACKGROUND

- On 1 December 2022, MS Health Pty Ltd submitted updated AU-RMP version 0.4 (dated 24 November 2022; DLP 31 May 2022) for MS-2 Step. The EU-RMP is not available. The sponsor provided revised Education Program material (included as Appendix 1) with this submission. A revised AU-RMP version 4.0 (dated 13 January 2023; DLP 31 May 2022) was provided with the sponsor's response to RMP evaluator's recommendations dated 13 January 2023. On 20 February 2023, the sponsor submitted further changes in AU-RMP version 4.0 (dated 17 February 2023; DLP 31 May 2022) which has been linked to the Category 1, Type J application (PM-2022-05475-1-5). At Round 2, the sponsor submitted updated AU-RMP version 4.1 (dated 5 April 2023; DLP 31 May 2022) with their S31 response dated 6 April 2023.
- Note: Succession 2 was completed internally however the sponsor submitted the new AU-RMP version 4.0 (dated 17 February 2023; DLP 31 May 2022) before outcomes/recommendations were sent to sponsor. Therefore, these were incorporated into Succession 3 report.
- MS-2 Step is approved for the medical termination of an intrauterine pregnancy, up to 63 days of gestation, in females of childbearing age.
- The most recently evaluated and approved AU-RMP was version 03 (dated 13 November 2014; DLP 28 April 2013) (R14/1181088).
- The reason for this updated RMP is changes to the summary of safety concerns (SoSC) and changes to the risk minimisation plan. The key changes proposed are as follows:
    - To remove the requirement for pharmacists to be registered to be able to dispense the product.
    - To remove the requirement for prescriber recertification.
    - To remove the requirement for prescribers to complete mandatory training and receive certification to be able to prescribe the product.
    - To remove the requirement for a Sponsor provided 24 hours aftercare service
- This RMP update is linked to the Category 1, Type J application (PM-2022-05475-1-5) that is currently under evaluation due to accompanying changes warranted to the Australian Product Information to support the proposed changes to the risk minimisation plan.
- As the TGA has previously evaluated RMPs for this product, the focus of this review is on the differences between the AU-RMP versions and revisions to the additional risk minimisation materials.

3. CHANGES TO THE SUMMARY OF SAFETY CONCERNS AND PHARMACOVIGILANCE/RISK MINIMISATION ACTIVITIES

At Round 2, the changes to safety concerns and/or activities proposed since the previous RMP evaluation of AU-RMP Version 03 (dated 13 November 2014; DLP 28 April 2013) are presented in the table below (~~Strikethrough~~ text indicates risks that have been removed and **bold** text indicates new/changed risks):

Summary of safety concerns		**Pharmacovigilance**		**Risk Minimisation**	
		Routine	Additional	Routine	Additional
Important identified risks	~~Bleeding~~	~~✓~~	~~1~~	~~✓~~	~~✓2,3,4,5,6~~
	Infection, toxic shock syndrome	✓	1	✓	✓2,3,~~4,5,6~~
	Method failure	✓	1	✓	✓2,3,~~4,5,6~~

	~~Uterine contractions / cramping~~	~~✓~~	~~–[1]~~	~~✓~~	~~✓[3,5,6]~~
	~~Uterine infection (endometritis, pelvic inflammatory disease)~~	~~✓~~	~~–[1]~~	~~✓~~	~~✓[3,5,6]~~
	~~Nausea, vomiting~~	~~✓~~	~~–[1]~~	~~✓~~	~~✓[3,5,6]~~
	~~Diarrhoea~~	~~✓~~	~~–[1]~~	~~✓~~	~~✓[3,5,6]~~
	~~Hypotension~~	~~✓~~	~~–[1]~~	~~✓~~	~~✓[3,5,6]~~
	~~Skin rashes, urticarial~~	~~✓~~	~~–[1]~~	~~✓~~	~~✓[3,5,6]~~
	Cardiac disorders	✓	–[1]	✓	✓[3,~~5,6~~]
Important potential risks	Inadvertent pregnancy exposure and risk of incomplete abortion with severe bleeding	✓	–	✓	✓[3,~~5,6~~]
	Inadvertent pregnancy exposure (risk of malformations)	✓	–	✓	✓[3,~~5,6~~]
	Potential interaction with CYP3A4 inhibitors or inducers	✓	–	✓	~~✓[6]~~
	Potential interaction with products interacting with the glucocorticoid receptor	✓	–	✓	~~✓[6]~~
	~~Severe asthma uncontrolled by treatment~~ **Induced bronchial asthma**	✓	–	✓	~~✓[6]~~
	Effects in lactating women	✓	–	✓	~~✓[6]~~
	Effects in women with impaired liver function	✓	–	✓	~~✓[6]~~
	Effects in women with impaired renal function	✓	–	✓	~~✓[6]~~
	Effects in women with malnutrition	✓	–	✓	~~✓[6]~~
	Incorrect determination of gestational age	✓	–	✓	~~✓[6]~~
	Potential for missed ectopic pregnancy	✓	–	✓	✓[3,~~5,6~~]
	Potential for postnatal developmental delay	✓	–	✓	–
	Potential for off-label use beyond the first trimester	✓	–	✓	~~✓[6]~~
	~~Potential for loss to follow-up~~	~~✓~~	~~–~~	~~✓~~	~~–~~
	~~Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up~~	~~✓~~	~~–~~	~~✓~~	~~✓[6]~~
Missing information	Inherited porphyria	✓	–	–	–
	Theoretical interaction with NSAIDs	✓	–	–	–
	Potential interaction with products interacting with the progesterone receptor	✓	–	–	–
	Use in adolescents	✓	–	–	–
Pharmacological class effect	Risks related to the use of prostaglandin	✓	–	✓	✓[3,~~5,6~~]

[1] ~~Post-marketing surveillance study~~ (completed)
[2] Black box warning
[3] Patient Information and Consent Agreement form
[4] ~~Optional SMS follow-up text message~~
[5] ~~24-hour nurse after-care call service~~
[6] ~~Physician education~~

A clean SOSC table is provided below:

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Infection, toxic shock syndrome	✓	–	✓	✓[1,2]
	Method failure	✓	–	✓	✓[1,2]
	Cardiac disorders	✓	–	✓	✓[2]
Important potential risks	Inadvertent pregnancy exposure and risk of incomplete abortion with severe bleeding	✓	–	✓	✓[2]
	Inadvertent pregnancy exposure (risk of malformations)	✓	–	✓	✓[2]
	Potential interaction with CYP3A4 inhibitors or inducers	✓	–	✓	–
	Potential interaction with products interacting with the glucocorticoid receptor	✓	–	✓	–
	Induced bronchial asthma	✓	–	✓	–
	Effects in lactating women	✓	–	✓	–
	Effects in women with impaired liver function	✓	–	✓	–
	Effects in women with impaired renal function	✓	–	✓	–
	Effects in women with malnutrition	✓	–	✓	–
	Incorrect determination of gestational age	✓	–	✓	–
	Potential for missed ectopic pregnancy	✓	–	✓	✓[2]
	Potential for postnatal developmental delay	✓	–	✓	–
	Potential for off-label use beyond the first trimester	✓	–	✓	–
Missing information	Inherited porphyria	✓	–	–	–
	Theoretical interaction with NSAIDs	✓	–	–	–
	Potential interaction with products interacting with the progesterone receptor	✓	–	–	–
	Use in adolescents	✓	–	–	–
Pharmacological class effect	Risks related to the use of prostaglandin	✓	–	✓	✓[2]

[1] Black box warning
[2] Patient Information and Consent Agreement

3.1. SUMMARY OF CHANGES TO THE SOSC – INITIAL EVALUATION

In the AU-RMP version 0.4 (dated 24 November 2022; DLP 31 May 2022) for MS-2 Step, the following new safety concerns have been added to the SoSC to align with the Canadian RMP (e004967 (0009-) - Attachment 1 - Canadian RMP) and the PI:

- important identified risk - cardiac disorders
- important potential risk - incorrect determination of gestational age

3.2. RMP EVALUATOR COMMENTS/ RECOMMENDATIONS ON THE SOSC – INITIAL EVALUATION

The Canadian RMP (dated 27 August 2020) was used as the reference RMP in the sponsor's Periodic Benefit-Risk Evaluation Report (PBRER) for mifepristone and misoprostol combipack

presentations, covering 01 June 2021 to 31 May 2022 (D22-6031778). The SoSC in the current Canadian RMP:

Identified risk:	Method failure Infection Toxic shock syndrome Cardiac disorders
Potential risk:	Inadvertent risk of pregnancy Induced bronchial asthma Incorrect determination of gestational age Complication arising from the use in undiagnosed ectopic pregnancy
Missing information:	Pregnant and lactating subjects Paediatric patients Geriatric patients Patients with Renal, Hepatic or Cardiac Impairment Off Label use

There are significant differences between the Canadian and Australian RMP.

The PBRER has been reviewed by the TGA: D22-6065496 The PBRER reviewer has requested that the RMP evaluator address the following:

> *The following risks from the current RMP do not appear to be in the 'summary of safety concerns' in the RMP version 0.3:*
>
> - *Identified risks: cardiac disorders*
> - *Potential risks: induced bronchial asthma (in contrast with severe asthma uncontrolled by treatment), incorrect determination of gestational age, complication arising from the use in undiagnosed ectopic pregnancy.*
> - *Missing information: patients (sic) with renal, hepatic or cardiac impairment.*
>
> *It is also noted that pregnant subjects have been included as missing information. This missing information covers the entire indication for which clinical trial and post-market experience should have provided sufficient evidence. This should be addressed by the RMP evaluator when the RMP document is submitted.*

In the AU-RMP version 0.4 (dated 24 November 2022; DLP 31 May 2022) for MS-2 Step, the below differences with the Canadian RMP (dated 27 August 2020) remain:

- Potential risks: induced bronchial asthma (in contrast with severe asthma uncontrolled by treatment), complication arising from the use in undiagnosed ectopic pregnancy.
- Missing information: patients with renal, hepatic or cardiac impairment.

Potential risk of 'complication arising from the use in undiagnosed ectopic pregnancy' is considered to be captured by 'Potential for missed ectopic pregnancy' included in the AU-RMP. This is satisfactory.

Missing information of 'patients with renal, hepatic or cardiac impairment' is in part captured by potential risks 'Effects in women with impaired liver function' and 'Effects in women with impaired renal function'. Given the classification of cardiac disorders as an important identified

risk, and associated warnings in the PI to use with caution in women with risk factors for cardiovascular disease or established cardiovascular disease, this is satisfactory.

Use in pregnant subjects is not listed in the AU-RMP as missing information. This is satisfactory.

The sponsor should be asked to provide reasons on the difference in potential risk of 'induced bronchial asthma' vs 'severe asthma uncontrolled by treatment'.

The sponsor should also be reminded to routinely review the safety concerns in the AU-RMP to ensure it reflects up-to-date safety information. Taking into account the product's reasonable marketing experience (as single ingredient and as combination pack), as well as the fact no additional pharmacovigilance activity is planned to further characterise the risks, the sponsor should evaluate whether any safety concerns can be removed. Further, in the absence of an EU-RMP, any changes to international RMPs should be assessed to determine whether similar updates are warranted in Australia.

The sponsor is requested to provide a description of the process for maintenance of the AU-RMP (e.g. standard operating procedure document).

3.3. Summary of key changes to Safety Specification - Succession 2 & 3 (Round 1)

Changes from AU RMP version 03 to version 4.0	RMP evaluator comment
Removed the following important identified risks: • Bleeding • Contractions / cramping • Uterine infection • Nausea and vomiting • Diarrhoea • Hypotension • Skin rashes / urticaria	This aligns with the Canadian RMP.
Important potential risk "Severe asthma uncontrolled by treatment" changed to "Induced bronchial asthma"	This aligns with the Canadian RMP.

There were no further changes to the safety specification between AU-RMP version 4.0 (dated 13 January 2023; DLP 31 May 2022) and AU-RMP version 4.0 (dated 17 February 2023; DLP 31 May 2022).

The sponsor has noted that AU-RMP also has further potential risks that are not included in the Canadian RMP, or risks that are presented slightly differently.

3.4. RMP Evaluator comments/ recommendations on the SoSC – Succession 2 & 3 (Round 1)

The summary of safety concerns is considered acceptable from an RMP perspective.

It is acknowledged that the sponsor has committed to ensuring that any future changes that are made to Canadian RMP will be assessed to determine whether the same updates are also warranted in Australia.

The updated RMP version 4.0 (dated 17 February 2023) submitted by the sponsor has the same version number with a different date from version 4.0 (dated 13 January 2023). To avoid confusion, for future submissions, the sponsor should update the version number and date for each revision.

3.5. Summary of key changes to Safety Specification – Round 2

Changes from AU RMP version 4.0 to 4.1	RMP evaluator comment
Removed important potential risks 'Potential for loss to follow-up'	This aligns with the Canadian RMP. Given there are no additional pharmacovigilance activities and additional risk minimisation activities to specifically address these safety concerns, and the importance of follow-up is well described in the PI and CMI, this is acceptable.
Removed important potential risks 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up'	This should remain in the SOSC as there are additional considerations to this risk with regards to access to further advice or treatment if follow-up does not occur.

3.6. RMP Evaluator comments/ recommendations on the SoSC – Round 2

The potential risk 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up' should remain in the SOSC as there are additional considerations to this risk with regards to access to further advice or treatment if follow-up does not occur.

Further, it is noted that this safety concern is not discussed in the PSUR, which uses the Canadian RMP as the reference document. It is requested that the sponsor provide an assessment of this safety concern with the PSUR submission expected August 2023. This assessment may serve to support the removal of this safety concern (can be submitted as an RMP update).

4. PHARMACOVIGILANCE PLAN

4.1. Summary of changes to the pharmacovigilance plan – Initial evaluation

The post marketing surveillance study of use of mifepristone/mifepristol for early medical abortion within MSIA clinics is now completed. Section III.2 and Section SIII has been updated to capture this.

4.2. RMP Evaluator comments/ recommendations on pharmacovigilance plan – Initial evaluation

Information regarding the study should be removed from the pharmacovigilance plan in the RMP since final study report/results have been submitted to the TGA for assessment. The study should also be deleted as an additional pharmacovigilance activity in Section V.3 in AU-RMP.

4.3. SUMMARY OF CHANGES TO THE PHARMACOVIGILANCE PLAN – SUCCESSION 2 & 3 (ROUND 1)

The completed study has been removed from the pharmacovigilance plan in the updated AU RMP, as requested.

There were no changes to pharmacovigilance plan submitted in Succession 3.

4.4. RMP EVALUATOR COMMENTS/ RECOMMENDATIONS ON PHARMACOVIGILANCE PLAN – SUCCESSION 2 & 3 (ROUND 1)

There are no additional pharmacovigilance activities in the AU RMP. It is noted that the Canadian RMP includes a planned Canadian-specific post-market study:

Safety Concern	Additional activity	Proposed actions/ outcomes	Planned submission date
		Planned studies	
Method failure, Infection, toxic shock syndrome, cardiac disorders, Inadvertent risk of pregnancy, induced bronchial asthma, incorrect determination of gestational age, Potential for missed ectopic pregnancy	**Canadian Phase IV study**	**A Phase IV Multi-Centre Prospective Study on the Safety of Combination Mifepristone/Misoprostol for Medical Abortion Under 63 Days Gestation Among Canadian Women** **Primary objective: To determine rate of surgical aspiration, for any reason, within 21 days following medical abortion with combination mifepristone/misoprostol**	**TBD**

The findings from the above study are applicable to Australia and should be included in the AU-RMP. The sponsor should include planned submission dates of study reports.

When available a revised RMP which considers the completed study outcomes should be submitted to the TGA for review.

4.5. SUMMARY OF CHANGES TO THE PHARMACOVIGILANCE PLAN – ROUND 2

The sponsor has included information on the ongoing Canadian Phase IV study in Section III.2 of the AU-RMP, as requested.

4.6. RMP EVALUATOR COMMENTS/ RECOMMENDATIONS ON PHARMACOVIGILANCE PLAN – ROUND 2

The ongoing Canadian post-market surveillance study should also be added to the tables in Section III.3 (Table 10) and V.3 (Summary of risk minimization measures) as appropriate. Refer to the Canadian RMP to identify the safety concerns that will be addressed by this additional pharmacovigilance activity.

It is acknowledged that the sponsor commits to submitting a revised RMP that considers completed study outcomes to the TGA when available. The sponsor should submit key findings from the study as an accompanying document. The full study report is only required upon TGA's request.

The annotated AU-RMP version 4.1 (dated 5 April 2023) tracks all changes since the approved version 03 (dated 13 November 2014) i.e. marks changes from version 0.4 to the two subsequent versions 4.0 to version 4.1. To avoid confusion and for ease of evaluation, annotated documents should only track the changes made since the last submitted version.

5. RISK MINIMISATION PLAN

5.1. SUMMARY OF CHANGES TO THE RISK MINIMISATION PLAN – INITIAL EVALUATION

The sponsor proposes to remove from the risk minimisation plan:

- the requirement for pharmacist registration to dispense the product
- the requirement for re-certification training for prescribers.

5.2. RMP EVALUATOR COMMENTS/ RECOMMENDATIONS ON THE RISK MINIMISATION PLAN – INITIAL EVALUATION

Detailed evidence/justification to support these proposals have not been provided. The sponsor should provide discussion on:

- additional risk minimisation activities in other countries where MS-2 Step is available compared to Australia
- any safety concerns on the removal of pharmacist registration and prescriber re-certification
- number/percentage of pharmacies registered to dispense MS-2 Step in Australia
- any reports on evaluation of effectiveness of additional risk minimisation activities

Given the reasonable worldwide marketing experience with mifepristone and mifepristol (IBD 28 June 1984 for misoprostol, 29 December 2010 for mifepristone, and MS-2 Step first registered in Australia 04 June 2014), the safety profile is considered well established. Clinical practice and understanding, along with the other additional risk minimisation activities in place, are likely adequate to manage the risks. It is acknowledged that the timeliness of access is essential and corresponds to effectiveness of the product. Final decision on the proposed changes to the risk minimisation plan will be made after review of the sponsor's response.

The sponsor has proposed that 'once registered and certified no re-registration or re-certification is required' for prescribers. It is assumed that this re-certification refers to the periodic renewal of the certificate for the purpose of knowledge maintenance. The sponsor should provide clarification in the RMP on whether and how it plans to inform prescribers of the updated safety information when new evidence becomes available.

The sponsor has stated under 'Restricted Access to MS-2-Step' that the program is to ensure that 'distribution of MS-2-Step is controlled and monitored. With the proposed removal of pharmacist registration, the sponsor should clarify how this is achieved. The sponsor should

note, according to the EMA GVP Module XVI, controlled distribution and controlled access programs are different measures that serve different purposes[1].

Further, the sponsor should amend Section V.3 Summary (table) of risk minimisation measures as follows:

- Completed post-marketing surveillance study is still listed as an additional pharmacovigilance activity – this should be removed from the table
- 'Special attention in PSURs' was listed as an additional pharmacovigilance activity – this is considered part of routine pharmacovigilance.
- 'Physician education' is not described as an additional risk minimisation activity for potential risks: Potential interaction with CYP3A4 inhibitors or inducers, Potential interaction with products interacting with the glucocorticoid receptor, Severe asthma uncontrolled by treatment, Incorrect determination of gestational age – this should be revised accordingly
- 'Potential for loss to follow up' is not included – this should be added for completeness

5.3. SUMMARY OF CHANGES TO THE RISK MINIMISATION PLAN – SUCCESSION 2 & 3

The sponsor has submitted additional changes to the risk minimisation plan in AU-RMP version 4.0 (dated 17 February 2023; DLP 31 May 2022). In summary, the following changes to the risk minimisation plan are proposed (new in **bold**):

- To remove the requirement for pharmacists to be registered to be able to dispense the product.
- To remove the requirement for prescriber recertification.
- **To remove the requirement for prescribers to complete mandatory training and receive certification to be able to prescribe the product.**
- **To remove the requirement for a Sponsor provided 24 hours aftercare service**

As the requirement for prescriber certification and 24-hour phone service are included in the PI, the sponsor has advised that it will remove these and submit the updated PI following the completion of round 1 evaluation[2].

The sponsor states that this would align the MS-2 Step RMP with the expectations of RMPs of the majority of medicines registered with the TGA, and with expectations around prescriber competency for a medicine that has been in-market for many years with hundreds of thousands Australian women having been prescribed MS-2 Step since it was first registered over 8 years ago.

The information in the AU-RMP regarding restricted distribution has been deleted with the proposed removal of mandatory training program and certification for prescribers.

[1]EMA Guideline on good pharmacovigilance practices Module XVI, dated 28 March 2017, EMA/204715/2012 Rev 2, https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-xvi-risk-minimisation-measures-selection-tools_en-3.pdf
[2] e004967 (0009-) - Cover Letter - 2023-02 Cat 1, Type J, RMP

5.4. RMP EVALUATOR COMMENTS/ RECOMMENDATIONS ON THE RISK MINIMISATION PLAN – SUCCESSION 2 & 3 (ROUND 1)

The Sponsor has amended Section V.3 Summary of risk minimisation measures (table) in accordance with the above requested changes. However, further changes are required:

- Identified risk 'Cardiac disorders' is missing and needs to be added
- Potential risks 'Incorrect determination of gestational age' and 'Potential for loss to follow-up' are missing and need to be added

Additionally, the sponsor should make the below changes to Table 11 in Section V.1:

- Remove 'physician education' as a routine risk minimisation measure as this is considered additional risk minimisation
- Potential risks 'Potential for off-label use beyond the first trimester' and 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up' are missing and need to be added

Misoprostol was first approved in Australia on 7 July 1993, mifepristone on 29 August 2012 and MS-2 Step was registered on 4 June 2014. Given the post-market experience with MS-2 Step in Australia and worldwide, the product's safety profile is well-established. Safety concerns in the SOSC have been removed with this AU-RMP update, which still includes additional potential risks to the Canadian RMP.

Furthermore, it is reasonable to expect that prescribers and dispensers have a level of clinical knowledge of MS-2 Step, or be able to refer to resources available (e.g. the PI) to ensure safe and effective use as like any other medicine. The sponsor will also continue to make the MS-2 Step training materials available to both prescribers and dispensers so that skill levels can be maintained. The patient information and consent form should continue to be implemented.

The sponsor has informed that based on the latest available data in 2020, less than 20% of pharmacists are registered in Australia to dispense MS-2 Step (see Section 6.1, Recommendation 6). As indicated, this presents a patient-safety risk of delayed access to medication, particularly in regional and rural areas as well as for patients whose gestation is approaching the upper limit of MS-2 Step's registered indication.

It is noted that in Australia, there is a government funded service available - healthdirect hotline – which provides 24-hour/7-day health advice from a registered nurse. Moreover, distribution of MS-2 Step will be tracked via general pathways of PBS Authority prescription and PBS dispensing and safety concerns will continue to be monitored by the sponsor under routine pharmacovigilance and reported as necessary as specified in Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements. The sponsor may also be requested to provide a PSUR to the TGA at any time. The sponsor has been requested to provide the next 12-month PBRER/PSUR covering 01 June 2022 to 31 May 2023 to the TGA when available, expected August 2023.

The sponsor has pointed out that internationally, in Canada, since 2017 registration of health professionals with Celopharma is no longer required in order to prescribe or dispense

Mifeqymiso[3]. The sponsor states no adverse safety signals or additional risk minimisation activities identified in Canada with this change to a broader access regimen. It was noted in the Canadian Monograph for Mifeqymiso[4], it is stated that "*Mifegymiso should be prescribed by health professionals with adequate knowledge of medical abortion and/**or** who have completed a Mifegymiso education program*".

The RMP evaluator has noted the need to remove requirements that hinder patient access to reproductive services. The evaluator has also noted different risk mitigation strategies employed by different comparable overseas regulators.

In the UK, MHRA has advised the TGA that there are no certification requirements in the SmPC or RMP for mifepristone/misoprostol for medical abortion for prescribers or dispensers. Furthermore, in December 2018, misoprostol tablets could be administered at home in England after taking the mifepristone tablet in a clinic. In March 2020, temporary approval of home use was granted for both components for some abortions (up to 9 weeks and 6 days) without the need to first attend a clinic to ensure continued access during the pandemic lockdowns. Scotland and Wales implemented temporary measures for early medical abortion, along the same lines as England. This provision was made permanent in England and Wales in 2022 and remains in place (but under review) in Scotland.

The US FDA has reviewed and finalised the Risk Evaluation and Mitigation Strategies (REMS) for mifepristone on 3 January 2023. The REMS lists 'requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program' as a goal of the REMS[5].

The RMP evaluator has noted that the advice on 24-hour phone service is also provided in the Australian Consumer Medicine Information (CMI). The sponsor should submit the updated CMI to ensure consistent information in the RMP, PI, and CMI.

The requirement for prescriber certification is included in the Australian Product Information (PI). The sponsor has advised that it will remove this requirement and submit the updated PI following the completion of round 1 evaluation. From the RMP perspective, assessing prescriber competencies is more related to clinical practice than to product risk management. Therefore, the removal of prescriber certification from the RMP is acceptable. It is recommended that the delegate/clinical evaluator considers the proposed PI change from the clinical perspective, and whether advisory committee advice is needed.

The provision of 24-hour phone service for patients is included in the PI. The sponsor has advised that it will remove this service and submit updated PI following the completion of round 1 evaluation. It is noted that the PI also advises that 'patients must have the ability to access 24-hour emergency care'. This would ensure timely access to urgent medical attention and intervention. Therefore, the removal of 24-hour phone service is acceptable from the RMP perspective. It is recommended that the delegate/clinical evaluator considers the proposed PI

[3] MIFEGYMISO (mifepristone and misoprostol tablets) - Updates to Product Monograph and Risk Management Plan, accessed 23 February 2023, MIFEGYMISO (mifepristone and misoprostol tablets) - Updates to Product Monograph and Risk Management Plan - Canada.ca
[4] MIFEGYMISO (mifepristone and misoprostol tablets) Canadian Product Monograph, accessed 23 February 2023, 00050659.PDF (hres.ca)
[5] US FDA approved REMS for mifepristone, accessed on 24 February 2023, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390

change from the clinical perspective, in particular, whether and how much value the 24-hour phone service adds to patient safety outcomes.

5.5. RMP EVALUATOR COMMENTS/ RECOMMENDATIONS ON THE RISK MINIMISATION PLAN – ROUND 2

At Round 2, the sponsor confirms that the existing standardised training (the Medical Education Program) will still be available for all healthcare practitioners and prescribers and dispensers will be made aware on how to access them via the existing online website (www.ms2step.com.au).

The proposed changes to the risk minimisation plan to remove pharmacist registration, prescriber certification and the Sponsor provided 24 hours aftercare service are considered acceptable from an RMP perspective for the reasons discussed above. The PI and CMI have been updated to reflect the proposed changes to the risk minimisation plan.

As requested at Round 1, the Patient Information and Consent Agreement form and the Educational program materials should be appended to the AU-RMP. The Educational program is still part of the RMP, and the sponsor should provide the educational materials - see TGA RMP guidance Section 5.3. From RMP perspective, the educational materials continue to be provided to prescribers and it is our expectation that prescribers will undergo the training. The sponsor needs to include educational materials in track changed version to show any update since the last time RMP was evaluated.

The sponsor is requested to make further changes to the risk minimisation plan, as follows:

- Include potential risk 'incorrect determination of gestational age' in Section V.3 Summary of risk minimization measures (table; page 38) in the AU-RMP
- Add potential risk 'Potential for off-label use beyond the first trimester' to Table 11 in Section V.1 of the AU-RMP
- Append the educational materials and the Patient Information and Consent Agreement form to the AU-RMP
- In Section V.2 Additional Risk Minimisation Measures
    - Under 'Inclusion of Instruction Insert in Composite Pack Carton', remove text relating to the mandatory training program and certification for prescribers:

      "These arrangements are set up and are accessible via the Sponsor's secure healthcare professional website www.ms2step.com.au, or by calling the company directly. The Sponsor may change the restrictions on supply if in the future an effective control mechanism on prescriber access becomes possible via the PBS."

    - Under 'Prescriber Training', specify availability via the website www.ms2step.com.au

5.6. RMP EVALUATOR COMMENTS/ RECOMMENDATIONS OF ADDITIONAL RISK MINIMISATION ACTIVITIES

Additional risk minimisation activities consist of a black box warning, inclusion of CMI and instruction insert in pack, Patient Information and Consent Agreement, and prescriber educational materials (as supportive resources; non-mandatory training).

This is considered sufficient based on the above discussion.

5.7. PRODUCT LABELLING

5.7.1. Product Information

The sponsor should confirm whether the new data from the completed post-market surveillance study study added to Section SIII (Clinical trial exposure) of the AU-RMP version 0.4 (and Section 3.6 of Annex 1.1) will be added to the Australian PI:

> *In an observational cohort study of 15 008 women attending one of 16 Marie Stopes International clinics in Australia for MTOP (gestational age ≤ 63 days) between 1 March 2013 and 30 September 2015, patients were **administered** 200 mg mifepristone orally in-clinic, followed 24- 48 hours later by 800 micrograms of misoprostol buccally, self-administered at home. Method success was defined as complete abortion not requiring surgical intervention. Follow up information was available for 13,078 (87.2%) of the total cohort. Medical abortion was successful in 95.16% (12,445/13,078) of women with follow-up. Higher patient and gestational ages were associated (P < 0.001) with a slight increase in method failure. There were 674 serious adverse events (5.15%), mainly due to method failure. Infection (15; 0.11%) and haemorrhage (17; 0.13%) were rare. One death was recorded (<0.01%); however, an association between EMA and cause of death, necrotising pneumonia, was not established.*

Moreover, the sponsor should make a minor editorial change (in ***bold***).

Succession 2 update

The sponsor has confirmed in their response that the Australian PI will be updated with the completed post-market surveillance study data as part of the next submitted Category 1, Type J application (see Section 6.1, Recommendation 4).

5.7.2. Consumer Medicine Information

The sponsor should ensure any PI updates are captured in the CMI where applicable.

The CMI along with the instruction insert will be included in the pack.

5.8. ADDITIONAL RISK MINIMISATION MATERIALS

The sponsor submitted revised Educational Program material (with tracked changes) with the AU-RMP update submission (as Annex 1; D22-6187939). There were mostly editorial changes to reflect current approved indication and current practices, as well as inclusion of current post marketing data. Of note, the refresher materials have been removed from the package.

In the training manual (Annex 1.1), the sponsor included interim information regarding a pending TGA application to remove PI precautions regarding rhesus alloimmunisation to align

with current Australian and International guidelines. It was recommended that the sponsor only incorporate advice that has been approved.

The previous version of the Educational Program materials can be found here: R14/1181088

Succession 2&3 (Round 1) update

At Succession 2, the sponsor had submitted an updated training manual with the requested changes with their response.

At Succession 3, the Educational program material has been removed from the AU-RMP with the proposed removal of mandatory training program and certification for prescribers. However, it is noted that the sponsor will continue to provide access to prescriber training to support the education of prescribers. Physician education and Patient Information and Consent Agreement are listed as additional risk minimisation measures in the AU-RMP and these materials should be appended to the AU-RMP. Further, the sponsor should ensure prescribers (and dispensers) are made aware of the availability of MS-2 Step training materials and how to access these.

The sponsor should make the minor editorial change to Section 3.6 of the training manual to amend "administration" to "administered" (see Section 5.5.1).

6. EVALUATION OF SPONSOR RESPONSE

6.1. RECONCILIATION OF RECOMMENDATIONS SENT 13 DECEMBER 2022

The sponsor's response, dated 13 January 2023, can be found on

TRIM D23-5035315

docuBridge e004967 (0008-) - Response - 2023-01 Response to RFI

The sponsor has provided and updated AU-RMP version 4.0 (dated 13 January 2023, DLP 31 May 2022) with their response.

Recommendation 1: The sponsor is requested to provide reasons on the difference in potential risk of 'induced bronchial asthma' vs 'severe asthma uncontrolled by treatment'.
Sponsor's response: The Sponsor proposes to update the potential risk of 'severe asthma uncontrolled by treatment' to 'induced bronchial asthma'. As currently detailed in the AU-RMP, bronchospasm may occur with some prostaglandins and prostaglandin analogues. The possibility should be borne in mind in patients with a history of asthma. *The potential risk 'induced bronchial asthma' is currently included in the Canadian RMP and is targeted for review and safety surveillance as part of the annual PBRER (reports of induced bronchial asthma are identified using a prespecified list of preferred terms in MedDRA version 16.0).* *A copy of the proposed updated AU-RMP has been provided in Module 1.8.*
RMP evaluator comment: The important potential risk of 'severe asthma uncontrolled by treatment' has been replaced with 'induced bronchial asthma' in line with Canadian RMP in the updated AU-RMP. This is acceptable.

Recommendation 2: The sponsor is requested to provide a description of the process for maintenance of the AU-RMP (e.g. standard operating procedure document).

In accordance with the guidance on *Risk management plans for medicines and biologicals* throughout the lifecycle of the product, RMPs must be maintained to incorporate new safety information. Any significant updates are required to be submitted to the TGA for evaluation within a timely manner. In accordance with the *Pharmacovigilance Guidelines*, sponsors should have processes in place (with well-defined responsibilities, requirements and timelines) to ensure they comply with their post-approval commitments.

Further, the sponsor is reminded to routinely review the safety concerns in the AU-RMP to ensure it reflects up-to-date safety information. Taking into account the product's reasonable marketing experience (as single ingredient and as combination pack), as well as the fact no additional pharmacovigilance activity is planned to further characterise the risks, the sponsor should evaluate whether any safety concerns can be removed. Further, in the absence of an EU-RMP, any changes to international RMPs should be assessed to determine whether similar updates are warranted in Australia.

Sponsor's response: The maintenance of the AU-RMP is managed via agreements in place with their supplier (Linepharma International Limited). Specifically, the Safety Data Exchange Agreement (SDEA) held between MS Health Pty Ltd and Linepharma International Limited (supplier)includes the responsibilities relating to the AU-RMP. The SDEA specifies that the supplier coordinates an update to the RMP if a significant safety signal is detected, including immediate notification to MS Health of any significant safety issues. Following the receipt of a notification of a significant safety issue from the supplier, MS Health is then responsible for preparation and maintenance of the AU-RMP including any required submission to TGA (according to TGA guidelines including any specified timelines). MS Health is also responsible for implementation of any applicable risk minimisation measures.

Additionally, s47 *(the service provider) have a standard operating procedure in place for the management of safety information. This dictates that the updated AU RMP be submitted to the TGA in accordance with the TGA RMP guidelines.*

Further to the above, the Sponsor has reviewed the safety concerns listed within the AU-RMP and proposes to remove those that have a low risk in regard to the seriousness of the safety concern, a low risk to the individual patient and have minimal impact on public health. The following identified risks have therefore been removed as part of this response:

- *Bleeding*
- *Contractions / cramping*
- *Uterine infection*
- *Nausea and vomiting*
- *Diarrhoea*
- *Hypotension*
- *Skin rashes / urticaria*

A clean and annotated copy of the proposed AU-RMP has been provided in Module 1.8.

In the absence of the EU-RMP, the Sponsor confirms that the safety concerns that are listed within the AU-RMP and the changes proposed above, align with those detailed in the Canadian RMP (although it is noted that the AU RMP still includes additional potential risks over and above those that are included in the Canadian RMP, or presents these slightly differently). A copy of the Canadian RMP has been provided as Attachment 1 to this response. An assurance is provided that any future changes that are made to Canadian RMP with be assessed to determine whether the same updates are also warranted in Australia (as per the processes defined above).

RMP evaluator comment: The sponsor's commitment to assess future changes made to the Canadian RMP to determine whether similar updates are warranted in Australia is acknowledged. The sponsor's proposal to remove the above important identified risks is consistent with the Canadian RMP and is acceptable.

Recommendation 3: The sponsor should remove information regarding the completed post-market surveillance study from the pharmacovigilance plan in the RMP as final study report/results have been submitted to the TGA for assessment. The study should also be deleted as an additional pharmacovigilance activity in Section V.3 in AU-RMP.
Sponsor's response: The sponsor has removed the information regarding the completed post-market surveillance study from the pharmacovigilance plan in the RMP. The study has also been deleted as an additional pharmacovigilance activity in Sections III.2 and V.3 of the RMP.
RMP evaluator comment: The AU RMP has been updated as requested.
Recommendation 4: The sponsor should confirm whether the data from the completed post-market surveillance study added to Section SIII (Clinical trial exposure) of the AU-RMP version 0.4 (and Section 3.6 of Annex 1.1) will be added to the Australian PI.
Sponsor's response: The sponsor confirms that they propose to update the Australian PI with the completed postmarket surveillance study data as part of the next submitted Category 1, Type J application
RMP evaluator comment: Noted. This is acceptable.
Recommendation 5: The sponsor should make the following minor editorial change (in **bold**): *In an observational cohort study of 15 008 women attending one of 16 Marie Stopes International clinics in Australia for MTOP (gestational age ≤ 63 days) between 1 March 2013 and 30 September 2015, patients were **administered** 200 mg mifepristone orally in-clinic, followed 24- 48 hours later by 800 micrograms of misoprostol buccally, self-administered at home. Method success was defined as complete abortion not requiring surgical intervention. Follow up information was available for 13,078 (87.2%) of the total cohort. Medical abortion was successful in 95.16% (12,445/13,078) of women with follow-up. Higher patient and gestational ages were associated (P < 0.001) with a slight increase in method failure. There were 674 serious adverse events (5.15%), mainly due to method failure. Infection (15; 0.11%) and haemorrhage (17; 0.13%) were rare. One death was recorded (<0.01%); however, an association between EMA and cause of death, necrotising pneumonia, was not established.*
Sponsor's response: The sponsor has updated the RMP in accordance with the requested minor editorial amendment. A copy of the updated RMP has been provided in Module 1.8.
RMP evaluator comment: The AU RMP has been updated as requested.

Recommendation 6: To support the proposals to remove requirements for prescriber recertification training and pharmacist registration, the sponsor should provide justification/discussion on:

- additional risk minimisation activities in other countries where MS-2 Step is available compared to Australia
- any safety concerns on the removal of pharmacist registration and prescriber re-certification
- number/percentage of pharmacies registered to dispense MS-2 Step in Australia
- any reports on evaluation of effectiveness of additional risk minimisation activities

Sponsor's response: As of December 2022, there are 5,472 pharmacists registered to provide MS-2 Step® to Australian patients. The most recent Dept of Health data (Allied Health factsheets) reports a total of 32,904 pharmacists registered in Australia in 2020 (more recent data not available); indicating only ~17% of pharmacists are currently registered to dispense MS-2 Step to patients.
The challenge of having less than 20% of pharmacists registered to dispense MS-2 Step presents a risk from a patient-safety perspective of delayed access to medication. This is especially so for patients in either regional and remote settings where there may not be an easily accessible registered pharmacist; as well as for patients whose gestation is approaching the upper limit of MS-2 Step's registered indication and for whom timely access to MToP is even more critical. MS Health will continue to make the MS-2 Step training materials available to both prescribers and dispensers so that skill levels can be maintained, but removal of these specific requirements (prescriber recertification, dispenser registration) is expected to improve the ability of patients to receive timely access to their medication.
MS Health notes that within the Canadian setting, since 2017 patients seeking a medical termination of pregnancy are dispensed an identically configured Mifepristone + Misoprostol composite pack by pharmacists who are not required to register prior to dispensing; or physicians who need to recertify. There have been no adverse safety signals or additional risk minimisation activities identified in Canada with this change to a broader access regimen.

RMP evaluator comment: Noted. Considering the proposed removal of mandatory training program and certification of prescribers and dispensers, the sponsor should ensure prescribers and dispensers are aware of the availability of MS-2 Step training materials and how to access these.

Recommendation 7: The sponsor has proposed that 'once registered and certified no re-registration or recertification is required' for prescribers. It is assumed that this re-certification refers to the periodic renewal of the certificate for the purpose of knowledge maintenance. The sponsor should provide clarification in the AU-RMP on whether and how it plans to inform prescribers of the updated safety information when new evidence becomes available.

Sponsor's response: The Sponsor confirms that re-certification refers to the periodic renewal of the certificate for the purpose of knowledge maintenance.
The MS-2 Step composite pack product has been available in Australia for over 8 years (registered 4/6/2014, marketed 1/2/2015). The pack components (Mifepristone + Misoprostol) have been registered for the Medical Termination of Pregnancy in Australia (and globally) prior to this. The product's characteristics, safety and AE profile are relatively well understood. There is no proposed change in the patient population as part of this application and as such, it is unlikely that a significant change to the product's existing safety profile is going to be encountered.
It is noted that prescribing Medical Practitioner's must remain up-to-date on changes to the safety profile for any product that they prescribe. This information is communicated to prescribers via PI updates and notices on the TGA website (as appropriate). In the event of a significant change to the product safety profile and a need to rapidly disseminate information to prescribers, MS Health would utilise the channels mentioned above and also utilise the MS-2 Step prescriber database (which is being proposed to remain in place). MS Health proposes to continue to utilise the standard channels used for other registered medicines when providing updated information to prescribers.

RMP evaluator comment: The sponsor's response is acceptable.

Recommendation 8: The sponsor has stated under 'Restricted Access to MS-2-Step' that the program is to ensure that "distribution of MS-2-Step is controlled and monitored". With the proposed removal of pharmacist registration, the sponsor should clarify how this is achieved. The sponsor should note, according to the EMA GVP Module XVI, controlled distribution and controlled access programs are different measures that serve different purposes.

Sponsor's response: The European Medicines Agency (EMA) guidance; Guideline on good pharmacovigilance practices (GVP), Module XVI, Section XVI.B.2.2 states the following:

"Since a controlled access programme has large implications for all stakeholders, the use of such a programme should be limited and should be guided by a clear therapeutic need for the product based on its demonstrated benefit"

The sponsor's proposed RMP amendments i.e. removing the need for prescriber recertification and removing the need for dispenser registration, is endeavouring to minimise impacts on patients who may otherwise struggle to access their medication in a timely manner. MS Health proposes to continue providing prescriber education and maintain the database of certified prescribers to act as a control on any potential product misuse or abuse.

In addition to this, MS Health highlights the fact that it is the responsibility of the prescriber to ensure that they are compliant with relevant requirements to provide any therapeutic product e.g. they have completed any relevant training and have the required knowledge to prescribe the therapeutic product in question. With respect to the MS-2 Step product, an additional extra level of control is provided during the PBS-script approval process. The majority of MS-2 Step scripts are PBS-scripts; the approval process requires the prescriber to affirm that they are certified to prescribe.

NB: this need to affirm certification exists regardless of whether the product is designated Authority Required or Streamlined Authority.

Given the above, it is unlikely for additional restricted access controls to be required and MS Health highlights the fact that the impetus for removing the requirement for dispenser registration is to improve patient access. Especially those patients located in rural and/or remote settings; and those later in their gestation and for who the timely access to medication is critical (and can be more challenging).

Within this context, the term "Restricted Access to MS-2 Step" (compared to the EMA GVP Module XVI definition, as provided below for ease of reference) may be inappropriate and appears to be a carryover from the preceding RMP document. The sponsor proposes amending this to "Restricted Distribution of MS-2 Step" as the product will continue to be distributed through controlled pharmaceutical supply chains; thus minimising the potential for product misuse or abuse.

EMA GVP Definitions

XVI.B.2.3.1. Controlled distribution system A controlled distribution system refers to the set of measures implemented to ensure that the stages of the distribution chain of a medicinal product are tracked up to the prescription and/or pharmacy dispensing the product. Orders and shipments of product from a single or multiple identified distribution points facilitate traceability of the product. For instance, this sort of measures could be considered for those products controlled in each country under the respective national legislations to prevent misuse and abuse of medicines.

XVI.B.2.2. Controlled access programme A controlled access programme consists of interventions seeking to control access to a medicinal product beyond the level of control ensured by routine risk minimisation measures, i.e. the legal status. Since a controlled access programme has large implications for all stakeholders, the use of such a programme should be limited and should be guided by a clear therapeutic need for the product based on its demonstrated benefit (e.g. it treats a serious disease without alternative therapies; it treats patients who have failed on existing therapies), the nature of the associated risk (e.g. risk is lifethreatening), and the likelihood that this risk can be managed by such a programme. Therefore, controlled access should only be considered as a tool for minimising an important risk with significant public health or individual patient impact for a product with clearly demonstrated benefits but which would not otherwise be available without a programme where patient access is contingent on fulfilling one or more requirements prior to a product being prescribed or dispensed in order to assure its safe use.

Examples of requirements that need to be fulfilled before the product is prescribed and/or dispensed and/or used in a controlled access programme are listed below (they may be included individually or in combination): • specific testing and/or examination of the patient to ensure compliance with strictly defined clinical criteria; • prescriber, dispenser and/or patient documenting their receipt and understanding of information on the serious risk of the product; • explicit procedures for systematic patient follow-up through enrolment in a specific data collection system e.g. patient registry; • medicines made available for dispensing only by pharmacies that are registered and approved to dispense the product. On occasions, a requirement to test or to monitor a patient in a specific way can also be used as a controlled access tool. For example,

monitoring of the patient's health status, laboratory values or other characteristic prior to and/or during treatment, e.g. electrocardiogram, liver function tests, regular blood tests, pregnancy tests (which can be part of a pregnancy prevention programme). Measures should be put in place to ensure that monitoring takes place according to the SmPC where this is critical to risk-benefit balance of the product.

RMP evaluator comment: The section regarding restricted distribution has been removed with the proposed removal of mandatory training program and certification for prescribers.

Recommendation 9: The sponsor should amend Section V.3 Summary (table) of risk minimisation measures as follows:

- Completed post-marketing surveillance study is still listed as an additional pharmacovigilance activity – this should be removed from the table
- 'Special attention in PSURs' was listed as an additional pharmacovigilance activity – this is considered part of routine pharmacovigilance.
- 'Physician education' is not described as an additional risk minimisation activity for potential risks: Potential interaction with CYP3A4 inhibitors or inducers, Potential interaction with products interacting with the glucocorticoid receptor, Severe asthma uncontrolled by treatment, Incorrect determination of gestational age – this should be revised accordingly
- 'Potential for loss to follow up' is not included – this should be added for completeness

Sponsor's response: The Sponsor has amended Section V.3 Summary (table) of risk minimisation measures in accordance with the above requested changes and in other sections as applicable. A copy of the update AU RMP has been provided in Module 1.8.

RMP evaluator comment: Further changes to the table in Section V.3 are required:

- **Identified risk 'Cardiac disorders' is missing and needs to be added**
- **Potential risks 'Incorrect determination of gestational age' and 'Potential for loss to follow-up' are missing and need to be added**

Additionally, the sponsor should make the below changes to Table 11 in Section V.1:

- **Remove 'physician education' as a routine risk minimisation measure.**
- **Potential risks 'Potential for off-label use beyond the first trimester' and 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up' are missing and need to be added**

Recommendation 10: In the revised training manual (Annex 1.1), the sponsor has included interim information regarding a pending TGA application to remove PI precautions regarding rhesus alloimmunisation to align with current Australian and International guidelines. The sponsor should note, the content of additional risk minimisation materials, including training manual should always align with the approved PI and CMI. Updates to training materials should occur concurrently with, or following TGA approved PI changes.

Sponsor's response: The reference to the TGA application to remove PI precautions regarding rhesus alloimmunisation has been removed from the training manual Annex 1.1. An updated training manual (Annex 1.1) has been provided in Module 1.8.

RMP evaluator comment: Reference to interim information regarding the pending TGA application (PM-2022-03010-1-5) has been removed from the training manual as requested.

Recommendation 11: The most recently evaluated AU-RMP was version 03 (dated 13 November 2014; DLP 28 April 2013). MS Health Pty Ltd has submitted updated AU-RMP version 0.4 (dated 24 November 2022; DLP 31 May 2022) for MS-2 Step, noting that the EU-RMP is not available. Chronologically, going from Version 03 to 0.4 is confusing. The sponsor should consider amending the proposed version number.
Sponsor's response: The applicant inadvertently included 0.4 as the next sequential version. To avoid any further confusion (and subsequent errors), the version number has been updated to 4.0.
RMP evaluator comment: Noted. The sponsor has submitted an updated AU-RMP version number 4.0.

6.2. Reconciliation of Round 1 recommendations – dated 27 February 2023

The sponsor's response after Succession 3 evaluation, dated 6 April 2023, can be found on

TRIM D23-5289076

docuBridge e004967 (0012-) - Response - 2023-04 Response to S31 Request, MS3

The sponsor has provided and updated AU-RMP version 4.1 (dated 5 April 2023, DLP 31 May 2022) with their response.

Recommendation 12: The sponsor has submitted the updated RMP version 4.0 (dated 17 February 2023). This RMP has the same version number with a different date from version 4.0 (dated 13 January 2023). To avoid confusion, for future submissions, the sponsor should update the version number and date for each revision.
Sponsor's response: To avoid further confusion, the version number of the RMP has been updated along with the date for each new revision.
RMP evaluator comment: It is noted the sponsor has submitted an updated AU-RMP version 4.1 (dated 5 April 2023, DLP 31 May 2022) with this response.
Recommendation 13: The findings from the Canadian Phase IV study are applicable to Australia and should be included in the AU-RMP as an additional pharmacovigilance activity. The sponsor should include planned submission dates of study reports. When available a revised RMP which considers the completed study outcomes should be submitted to the TGA for review.
Sponsor's response: The Canadian Phase IV study has been included in Section III.2 of the proposed RMP. The proposed study to determine the effectiveness and safety of combination mifepristone/misoprostol for medical abortion under 63 days gestation among 3,000 Canadian women (the MiMAC study) is currently ongoing and is estimated to be completed in Q1 2024 with the final study report currently planned to be available in Q4 2024. *Once the study has been completed, the sponsor provides the assurance that the study reports together with a revised RMP (which considers the completed study outcome) will be submitted to the TGA. The submission is planned for Q4 2024 / Q1 2025.*
RMP evaluator comment: The sponsor has included information on the Canadian Phase IV study in Section III.2 of the AU-RMP, as requested. This additional pharmacovigilance activity should also be added to the tables in Section III.3 and V.3 as appropriate. It is acknowledged that the sponsor commits to submitting a revised RMP that considers completed study outcomes to the TGA when available. The sponsor should submit key findings from the study as an accompanying document. The full study report is only required upon TGA's request.

Recommendation 14: Further changes to Section V.3 Summary (table) of risk minimisation measures of the AU-RMP, are required:

- Identified risk 'Cardiac disorders' is missing and needs to be added
- Potential risks 'Incorrect determination of gestational age' and 'Potential for loss to follow-up' are missing and need to be added

Sponsor's response: The Sponsor notes that the identified risk 'cardiac disorders' was added to the previously submitted version of the RMP. Section V.3 has been updated further to include the missing potential risk 'incorrect determination of gestational age'.

The Sponsor proposes to remove the potential risk 'potential for loss to follow-up'. This will align with the current Canadian RMP and will bring the potential risks in line with other prescription products with a similar risk profile.

The current Product Information and Consumer Medicines Information includes the requirement for prescribers to ensure that upon discharge from the treatment centre, all women should be provided with appropriate medications as necessary and be fully counselled regarding the likely signs and symptoms she may experience and have direct access to the treatment centre by telephone or local access. Further to this they will receive precise instruction as to whom they should contact and where to go in the event of problems emerging. This will ensure that if a patient does not participate in a follow up visit, they possess the information they need about where to go for further advice or treatment.

A copy of the updated annotated (with the recent changes highlighted with a blue comment) and clean RMP has been provided in Module 1.8.

RMP evaluator comment: The table in Section *V.3 Summary of risk minimization measures* (from page 38) in the AU-RMP does not include the missing potential risk 'incorrect determination of gestational age' as stated. This should be addressed by the sponsor. It is noted the sponsor has added information on 'incorrect determination of gestational age' to Table 5 in Section VII.3.1.

The sponsor's proposal to remove the potential risk 'Potential for loss to follow-up' is acceptable from an RMP perspective, given:

- this will align with the current Canadian RMP
- there are no additional pharmacovigilance activities or additional risk minimisation measures proposed to specifically address potential loss to follow-up
- the importance of follow-up examination 14 to 21 days after taking mifepristone to ensure termination is complete and that there are no complications is well described (as a "must") in the PI/CMI black box warnings.

However, it was noted the sponsor has also removed 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up'. This should remain in the SOSC as there are additional considerations to this risk with regards to access to further advice or treatment if follow-up does not occur. It is noted that this safety concern is not discussed in the PSUR, which uses the Canadian RMP as the reference document. It is requested that the sponsor provide an assessment of this safety concern with the PSUR submission expected August 2023. This assessment may serve to support the removal of this safety concern (can be submitted as an RMP update).

Recommendation 15: Changes to Table 11 in Section V.1 of the AU-RMP are required:

- Remove 'physician education' as a routine risk minimisation measure as this is considered additional risk minimisation.
- Potential risks 'Potential for off-label use beyond the first trimester' and 'Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up' are missing and need to be added

Sponsor's response: The Sponsor has updated Table 11 in Section V.1 of the RMP to remove physician education as a routine risk minimisation measure and to include the following potential risks:

- *Potential for off-label use beyond the first trimester*

As proposed in Recommendation 14 above, the potential risk for loss to follow up is proposed to be removed.

A copy of the updated annotated and clean RMP has been provided in Module 1.8.

RMP evaluator comment: As per comments above, the removal of the potential risks relating to loss to follow-up from the summary of safety concerns is acceptable.
The Sponsor has updated Table 11 in Section V.1 of the AU-RMP to remove physician education as a routine risk minimisation measure as requested. However, 'Potential for off-label use beyond the first trimester' has not been added as a potential risk as stated.

Recommendation 16: The Educational program material has been removed from the AU-RMP with the proposed removal of mandatory training program and certification for prescribers. However, it is noted that the sponsor will continue to provide access to prescriber training to support the education of prescribers. Physician education and Patient Information and Consent Agreement form are listed as additional risk minimisation measures in the AU-RMP and these materials should be appended to the AU-RMP. Further, the sponsor should ensure prescribers (and dispensers) are made aware of the availability of MS-2 Step training materials and how to access these.

Sponsor's response: The sponsor confirms that prescribers and dispenses will continue to be made aware of the availability of the MS-2 Step training materials and how to access them.

RMP evaluator comment: Noted. The Patient Information and Consent Agreement form is listed as an additional risk minimisation measure in the AU-RMP and the Educational program material will continue to be supplied - these materials should be appended to the AU-RMP.
The TGA requires that copies of Australian educational materials to be provided in Annex 3 of the Australia Specific Annex. Materials should be provided with content and intended layout, including images and graphic presentations of information. For digital additional risk minimisation tools, provide content and images of the onscreen layout of the information, and/or the login details or access codes to enable the TGA to evaluate the safety content in the format in which it is provided to the end user. In the absence of an ASA, the same requirement applies to the Australian RMP.
Additionally, the following revisions to V.2 Additional Risk Minimisation Measures are requested:

- Under 'Inclusion of Instruction Insert in Composite Pack Carton' remove text relating to the mandatory training program and certification for prescribers:

  "These arrangements are set up and are accessible via the Sponsor's secure healthcare professional website www.ms2step.com.au, or by calling the company directly. The Sponsor may change the restrictions on supply if in the future an effective control mechanism on prescriber access becomes possible via the PBS."
- Under 'Prescriber Training', specify availability via the website www.ms2step.com.au.

Recommendation 17: In Section 3.6 of the training manual provided in Succession 2, the sponsor should make the minor editorial change of "administration" to "administered"

Sponsor's response: In accordance with the response to Question 1 above, the Sponsor is proposing to remove the Medical Education Program from the RMP and therefore the training manual will not be provided as an attachment. The Sponsor however provides an assurance that the minor editorial change will be made to the training manual that will be available for all healthcare practitioners that prescribe MS-2 Step via the existing online website (www.ms2step.com.au).

RMP evaluator comment: As per the response above, the educational material will need to be provided as an attachment to the AU-RMP.

Recommendation 18: The advice on 24-hour phone service is also provided in the Consumer Medicine Information (CMI). The sponsor should submit the updated CMI to ensure consistent information in the RMP, Product Information (PI), and CMI.

Sponsor's response: The Consumer Medicine Information (CMI) and Product Information (PI) have been updated to remove the reference to the 24-hour phone service. A copy of the revised annotated and clean CMI and PI have been provided in Module 1.3.2 and 1.3.1 respectively.

RMP evaluator comment: Reference to the 24-hour phone service has been removed from the CMI and PI as requested.

Recommendation 19: This is a recommendation for the TGA delegate/clinical evaluator. The requirement for prescriber certification is included in the approved PI. The sponsor has advised that it will remove this requirement and submit the updated PI following the completion of round 1 evaluation. From the RMP perspective, assessing prescriber competencies is more related to clinical practice than to product risk management. Therefore, the removal of prescriber certification from the RMP is acceptable. It is recommended that the delegate/clinical evaluator considers the proposed PI change from the clinical perspective, and whether advisory committee advice is needed.
Sponsor's response: The Sponsor notes that this recommendation is for the TGA delegate / clinical evaluator. However, as previously proposed, the sponsor has updated the PI and CMI to remove the prescriber certification and has provided a copy of the annotated and clean CMI and PI in Module 1.3.2 and 1.3.1 respectively.
RMP evaluator comment: Noted.
Recommendation 20: This is a recommendation for the TGA delegate/clinical evaluator. The provision of 24-hour phone service for patients is included in the approved PI. The sponsor has advised that it will remove this service and submit updated PI following the completion of round 1 evaluation. It is noted that the PI also advises that 'patients must have the ability to access 24-hour emergency care'. This would ensure timely access to urgent medical attention and intervention. Therefore, the removal of 24-hour phone service is acceptable from the RMP perspective. It is recommended that the delegate/clinical evaluator considers the proposed PI change from the clinical perspective, in particular, whether and how much value the 24-hour phone service adds to patient safety outcomes.
Sponsor's response: As above, the Sponsor notes that this recommendation is for the TGA delegate / clinical evaluator. However, as previously proposed (and in accordance with the response to Question 19 above), the sponsor has updated the PI and CMI to remove the provision of the 24-hour phone service. A copy of the revised annotated and clean CMI and PI has been provided in Module 1.3.2 and 1.3.1 respectively.
RMP evaluator comment: Noted.

APPENDIX 1 – LIST OF ACRONYMS

AE	Adverse Event
ACM	Advisory Committee on Medicines
AU-RMP	Australian Risk Management Plan
CMI	Consumer Medicine Information
DLP	Data Lock Point
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
MHRA	Medicines & Healthcare Products Regulatory Agency
PI	Product Information
PMAB	Prescription Medicines Authorisation Branch
RMP	Risk Management Plan
SOSC	Summary of Safety Concerns
TGA	Therapeutic Goods Administration

APPENDIX 2 – INFORMATION ON INTERNATIONAL LANDSCAPE

On 17 February 2023, the MHRA provided the following information regarding prescriber/pharmacist certification requirements for mifespristone:

> *There are no certification requirements in the SmPC [product information] or RMP for mifepristone/misoprostol for medical abortion for prescribers or dispensers. Abortions in the UK fall under the jurisdiction of The Abortion Act 1967 (as amended) which regulates the provision of abortion services in. England, Wales and Scotland. The Department of Health & Social Care (DHSC) issues guidance on procedures and legal requirements for abortion services under the act.*
>
> *In December 2018, the then Secretary of State for Health & Social Care approved that the act should be amended so the misoprostol tablets could be administered at a woman's home in England after taking the mifepristone tablet in a clinic. In March 2020, temporary approval of home use was granted for both components for some abortions (up to 9 weeks and 6 days) without the need to first attend a clinic to ensure continued access during the pandemic lockdown(s). Scotland and Wales implemented temporary measures for early medical abortion, along the same lines as England, using the same powers under the Abortion Act 1967. This provision was made permanent in England and Wales in 2022 and remains in place (but under review) in Scotland.*
>
> *Additionally, there are risk materials available (https://www.medicines.org.uk/emc/product/3380/rmms) for mifepristone/misoprostol in the form of:*
> - *Educational Material for healthcare professionals:*
> - *Medical and Service Delivery Guideline*
> - *Medical Guidelines for Providers of Emergency Care*
> - *Educational Material for patients - Patient card*

The US FDA's Mifepristone REMS Program was modified on January 3, 2023 after a comprehensive review in 2021. Changes consisted of[6]:

- Removing the requirement that mifepristone be dispensed only in certain health care settings, specifically clinics, medical offices, and hospitals (referred to as the "in-person dispensing requirement")
- Adding a requirement that pharmacies that dispense the drug be certified

Under the current Mifepristone REMS Program[7]:

- Mifepristone must be prescribed by a health care provider that meets certain qualifications and is certified under the Mifepristone REMS Program.
- In order to become certified to prescribe mifepristone, health care providers must complete a Prescriber Agreement Form.

[6] Questions and Answers on Mifepristone for Medical Termination of Pregnancy Through Ten Weeks Gestation | FDA (accessed 22 Feb 2023)
[7] Information about Mifepristone for Medical Termination of Pregnancy Through Ten Weeks Gestation | FDA (accessed 22 Feb 2023)

- The Patient Agreement Form must be reviewed with and signed by the patient and the health care provider, and the risks of the mifepristone treatment regimen must be fully explained to the patient before mifepristone is prescribed.
- The patient must be provided with a copy of the Patient Agreement Form and mifepristone Medication Guide (FDA-approved information for patients).
- Mifepristone may only be dispensed by or under the supervision of a certified prescriber, or by a certified pharmacy on a prescription issued by a certified prescriber.
- To become certified to dispense mifepristone, pharmacies must complete a Pharmacy Agreement Form.
- Certified pharmacies must be able to ship mifepristone using a shipping service that provides tracking information.
- Certified pharmacies must ensure mifepristone is dispensed to the patient in a timely manner.

Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

The Managing Director
MS Health Pty Ltd
Suite 60, 278 Church Street,
Richmond, VIC, 3121

Submission No: PM-2022-05475-1-5
Clinical file: 2013/012449
RMP file: 2013/020378
PI file: 2014/008932
Coordination file: E22-638632
Initial data: e004967 (0007)

Attention: s22
Senior Consultant, Regulatory, Quality & Compliance
s47 (Agents on behalf of MS Health Pty Ltd)

Dear Sir/Madam

I refer to your submission dated 22 December 2022 regarding amendments to the Product Information document for MS-2 Step composite pack containing mifepristone and misoprostol.

In accordance with Section 9D(3) of the *Therapeutic Goods Act 1989*, the variations to the register for

- 210574 - MS-2 Step composite pack [MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet blister; GyMiso misoprostol 200 microgram tablet blister]

as described in your email of 28 June 2023 are approved. This approval is based on the evaluation of the information and data provided with the original letter of application and with any subsequent correspondence and submissions relating to the application.

The current Product Information for the product(s) is deemed to be approved under subsection 25AA(2) of the Act. The text of the approved product information varied as set out in the version at **Attachment 1** is approved under subsection 25AA(4) of the Act. The 'Date of revision' included in the Product Information is to be the date of this letter.

For the product(s) approved in this submission, the:

- Product Information (PI) document approved by the TGA must be lodged with the TGA **within 2 weeks** of the date of approval of the variation, and
- related Consumer Medicine Information (CMI) document (if a revision is required to align with the approved PI) must be lodged with the TGA **within 2 weeks** of the date of approval of the variation.

The documents must be lodged in the TGA eBusiness Services system (eBS) - information on how to lodge these documents is available at www.ebs.tga.gov.au

Note that documents lodged must be in text PDF format – please be aware that scanned PDF documents will not be accepted by the system.

You are reminded that there is a continuing obligation to ensure that at all times the patient information document (Consumer Medicine Information - CMI) complies with the statutory requirements. If the related Consumer Medicine Information (CMI) document needs to be changed as a consequence of the change to the approved PI, it must be lodged with the TGA **within 2 weeks** of the date of the changed PI. In the case of changes relating to the safety or safe use of the product, more rapid change of the CMI may be warranted.

New condition(s) of registration

Pursuant to subsection 28(3) of the *Therapeutic Goods Act 1989*, I am notifying you of my decision to impose the following new condition(s) of registration to MS-2 Step composite pack (AUST R 210574) containing mifepristone 200 mg tablet and misoprostol 200 microgram tablet:

> *The MS-2 STEP Australian Risk Management Plan (AU-RMP) (version 4.2, dated 9 May 2023, data lock point 31 May 2022), included with submission PM-2022-05475-1-5, to be revised to the satisfaction of the TGA, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*
>
> *An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).*
>
> *Reports are to be provided in line with the current published list of EU reference dates* ***no less frequently than annually*** *until the period covered by such reports is not less than three years from the date of this approval letter.*
>
> *The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.*

Request for reconsideration of an initial decision

This decision is a reviewable initial decision under section 60 of the Act. Under section 60, a person whose interests are affected by a 'reviewable' initial decision, can seek reconsideration of the initial decision.

As this document constitutes written notice of the making of an initial decision being given by the Secretary, a request for reconsideration of this initial decision must be given to the Minister in writing within 90 (calendar) days after the initial decision notice is given and be accompanied by any information that you wish to have considered by the Minister. A request for reconsideration given to the Minister outside the statutory 90 day reconsideration period cannot be accepted.

The Minister may either personally undertake a request for reconsideration of an initial decision or delegate this function to an officer of the Department with the appropriate delegation.

Under section 60(3A) of the Act, the Minister (or the Minister's delegate) is not able to consider any information provided after the making of a request for reconsideration of an initial decision unless the information is provided in response to a request from the Minister (or the Minister's delegate), or it is information that indicates that the quality, safety or efficacy of the relevant therapeutic goods is unacceptable.

Guidelines for requesting reconsideration of an initial decision

Prior to requesting reconsideration of an initial decision, persons affected by an initial decision are advised to refer to the TGA website <https://www.tga.gov.au/reconsideration-reviewable-initial-decisions> for specific information and detailed guidance for making a request for reconsideration. A request for reconsideration should then be made in writing, signed and dated by the person requesting reconsideration and should include the following:

- a copy of the initial decision notification letter, i.e. this letter (or other evidence of notification);
- identify, and describe with as much specificity as possible, which component(s) of the initial decision should be reconsidered and set out the reasons why reconsideration is requested;
- any information/documentation in support of the request, clearly labelled to correspond with (any or each of) the reasons why reconsideration is requested; and
- an email address nominated for the purposes of receiving correspondence in relation to the request for reconsideration.

All requests for reconsideration should be given to the Minister by email:

Email: '**decision.review@health.gov.au**'

Subject: "**<insert name of person/company making request>** - Request for Reconsideration Under Section 60 of the *Therapeutic Goods Act 1989*"

Requests for reconsideration that include material which cannot be attached to a single email, may be submitted under multiple, sequentially numbered emails (e.g. "… - Email 1 of 3", "… - Email 2 of 3" etc). All sequentially numbered emails must be given to the Minister on the same date.

Under section 60 of the Act, the decision upon reconsideration by the Minister (or the Minister's delegate) must be to either 'confirm', 'revoke' or 'revoke and substitute' the initial decision. The Minister (or the Minister's delegate) must give notice in writing of the outcome of the decision upon reconsideration to the person whose interests are affected, within 60 (calendar) days after making a request for reconsideration. If the Minister (or the Minister's delegate) fails to give such notice within 60 days, the Minister (or the Minister's delegate) is deemed to have confirmed the initial decision.

Subject to the *Administrative Appeals Tribunal Act 1975* (AAT Act), if you are dissatisfied with the decision upon reconsideration by the Minister (or the Minister's delegate), you can apply to the Administrative Appeals Tribunal (AAT) for a review of that decision upon

reconsideration.

NOTE: This initial decision remains in effect unless and until it is revoked or revoked and substituted by the Minister (or the Minister's delegate) as a result of a request for reconsideration under section 60 of the Act OR is set aside, varied or remitted by the AAT or is otherwise overturned or stayed.

Yours faithfully,

Electronically signed and authorised by

s22
Delegate of the Secretary
Clinical Evaluators Team Section
Prescription Medicines Authorisation Branch

Email: s22 @health.gov.au

28 June 2023

Attachment:

1. Approved Product Information

AUSTRALIAN PRODUCT INFORMATION
MS-2-STEP
(Mifepristone and Misoprostol)
Tablets

It is very important that all patients receiving these medications are followed up by a healthcare practitioner, preferably the prescriber, to ensure that the medication has been effective. Even if no adverse events have occurred all patients must receive follow-up 14 to 21 days after taking mifepristone. Read the **Section *4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE*** carefully*.*

This document refers to the use of ***MS-2 Step***, which consists of Mifepristone Linepharma 200 mg tablet and GyMiso® misoprostol 200 microgram tablets in combination. These medicines are indicated in females of childbearing age for the medical termination of an intrauterine pregnancy, up to 63 days of gestation. The Mifepristone Linepharma 200 mg tablet component of this therapy is also used to treat another condition. For information about the treatment of the other condition, refer to the full Product Information for Mifepristone Linepharma 200 mg tablet individual product (AUST R 175671).

1 NAME OF THE MEDICINE

Mifepristone and Misoprostol

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

MS-2 Step is a composite pack containing:

Mifepristone Linepharma

Each tablet contains 200 mg of mifepristone.

For the full list of excipients, see **Section 6.1 LIST OF EXCIPIENTS**.

GyMiso®

Each tablet contains 200 micrograms of misoprostol as a 1% dispersion of misoprostol-hypromellose. Misoprostol is a clear, colourless or yellowish oily liquid.

For the full list of excipients, see **Section 6.1 LIST OF EXCIPIENTS**.

3 PHARMACEUTICAL FORM

Mifepristone Linepharma

White to off-white, round biconvex tablets, diameter 11 mm, with “MF” debossed on one side of the tablet.

GyMiso®

White, flat round tablet with “ML” debossed on one side and “200” on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

MS-2 Step is indicated in females of childbearing age for the medical termination of an intrauterine pregnancy, up to 63 days of gestation.

It is recommended that the duration of pregnancy (i.e., up to 63 days gestation) be confirmed by ultrasound. In the event that an ultrasound is not possible, extra caution should be exercised.

Ultrasound is also useful to exclude ectopic pregnancy

4.2 DOSE AND METHOD OF ADMINSTRATION

MS-2 Step is indicated for medical termination of intrauterine pregnancy, up to 63 days of gestation.

The method of administration is as follows:

Mifepristone: 200 mg of mifepristone (1 tablet containing 200 mg) orally, followed 36 to 48 hours later by the administration of GyMiso®.

GyMiso®: 800 micrograms of misoprostol (4 tablets, each tablet containing 200 micrograms) buccally, i.e: kept between the cheek and the gum for 30 minutes before any fragments being swallowed with water.

When ***MS-2 Step*** fails to cause termination of intra-uterine pregnancy, the patient should return to the treating healthcare practitioner for assessment and discussion of treatment options, which may include pregnancy termination by surgery.

No dosage adjustment of misoprostol or mifepristone is necessary with renal or hepatic insufficiency when administered at the recommended doses.

There are no data available on the effect of food intake on the absorption of mifepristone or misoprostol. MS-2 Step should be taken 2 hours before or 2 hours after a meal.

Refer also to **4.3 CONTRAINDICATIONS**, and **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.**

MS-2 Step should only be prescribed by healthcare practitioners with the appropriate qualifications and training. Ectopic pregnancy should be excluded, an intrauterine device (IUD) (if present) must be removed, consent must be obtained and patients must have the ability to access 24-hour emergency care if and when required for incomplete abortion or bleeding.

4.3 CONTRAINDICATIONS

MS-2 Step should not be prescribed in the following situations:

- Lack of access to emergency medical care in the 14 days following start of the treatment (i.e. administration of mifepristone);
- Suspected or confirmed ectopic pregnancy;
- Asthma uncontrolled by therapy;
- Intrauterine device (IUD) in place;
- Uncertainty about gestational age;
- Chronic adrenal failure;
- Concurrent long term corticosteroid therapy;
- Suspected or known haemorrhagic disorders or treatment with anti-coagulants;
- Hypersensitivity to mifepristone, misoprostol (or any prostaglandin), or any of the excipients used in ***MS-2 Step****;*
- Pregnancy not confirmed by an ultrasound or biological test such as urine or serum HCG;

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The prescriber must ensure that consent and treatment of the patient is in accordance with the appropriate state or territory legislation.

If applicable, medical practitioner's advice should be sought in the event that further management of patients with medical comorbidities or adverse events is required.

Take special care in case of suspected acute adrenal failure. In case of suspected acute adrenal failure, dexamethasone administration is recommended (please refer to the dexamethasone Product Information).

Due to the antiglucocorticoid activity of mifepristone, the efficacy of long-term corticosteroid therapy, including inhaled corticosteroids in asthmatic patients, may be decreased during the 3 to 4 days following intake of mifepristone. Therapy should be adjusted.

Rare serious cardiovascular accidents have been reported following administration of prostaglandins including misoprostol. For this reason women with risk factors for cardiovascular disease or established cardiovascular disease should be treated with caution.

Although no epileptic seizures have been reported with misoprostol, some have been reported with prostaglandins and other prostaglandin analogues, and therefore this possibility should be borne in mind in patients with a history of epilepsy.

Bronchospasm may occur with some prostaglandins and prostaglandin analogues. The possibility should be borne in mind in patients with a history of asthma.

Severe cutaneous adverse reactions, including toxic epidermal necrolysis and acute generalised exanthematous pustulosis, have been reported in association with mifepristone (see **Section 4.8 ADVERSE EVENTS (UNDESIRABLE EFFECTS))**. In patients who experience severe cutaneous adverse reactions, treatment with mifepristone should be immediately discontinued. Re-treatment with mifepristone is not recommended.

Cases of skin rash following misoprostol administration were reported by patients in clinical trials. Angioedema of the face, lips, tongue, and/or larynx, including cases of anaphylaxis have been reported in post-market surveillance with the use of mifepristone and misoprostol, including angioedema occurring within an hour of misoprostol intake. Angioedema associated with upper airway swelling may be life threatening. If the tongue, hypopharynx, or larynx has been involved, appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided**.**

No data is available in patients with inherited porphyria.

In the case of a pregnancy occurring with an intra-uterine device in situ, this device must be removed before administration of Mifepristone Linepharma.

- ***Populations not studied:***

In the absence of specific studies, MS-2 Step is not recommended in patients with:

- Cardiovascular disease
- Hypertensive disease
- Hepatic disease
- Respiratory disease
- Renal disease
- Diabetes
- Severe anaemia
- Malnutrition
- Heavy smokers

Women who are older than 35 years and who also smoke 15+ cigarettes per day should be treated with caution because such patients were generally excluded from clinical trials of mifepristone.

- ***Specific precautions relating to medical termination of an intra-uterine pregnancy:***

- Ectopic pregnancy

Ectopic pregnancy should be excluded and gestation confirmed prior to medical abortion.

- Rhesus alloimmunisation

The need for rhesus determination and prevention of rhesus alloimmunisation should be assessed in line with the current clinical guidelines for induced abortions.

- Explanation of requirements for the method

This method requires the involvement of the woman who should be informed of the requirements of the medical method, which involves:

- The necessity to take both Mifepristone Linepharma and GyMiso® in sequence according to instructions
- The need for follow-up within 14 to 21 days after intake of Mifepristone Linepharma in order to confirm that the abortion is complete
- The non-negligible risk of failure (see **Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical Trials**) of the medical method which may require termination by another method
- On discharge from the treatment centre all women should be provided with appropriate medications as necessary and be fully counselled regarding the likely signs and symptoms she may experience and have direct access to the treatment centre by telephone or local access

The expulsion may take place before GyMiso® administration (in about 3% of cases). This does not preclude the need for follow-up to confirm complete expulsion.

The following risks related to the medical method must be taken into account and explained to the woman:

- Failures

The non-negligible risk of failure (including continuing pregnancy and incomplete abortion), which occurs in up to 7% of cases prior to 63 days gestation, makes follow up mandatory in order to check that the expulsion is completed. Up to 63 days about 1% women will have continuing pregnancies, the rest needing curettage for other reasons.

Exposure of the fetus to misoprostol or mifepristone increases the risk of developing Moebius syndrome and/or an amniotic band syndrome and/or central nervous system anomalies (see **Section 4.6 FERTILITY, PREGNANCY AND LACTATION - Use in Pregnancy**). A second termination of pregnancy procedure shall be considered. In case of continuation of the pregnancy close monitoring by ultrasound scan must be performed in specialised centres.

In cases of non-complete expulsion, a surgical intervention may be necessary.

- Bleeding

The patient must be informed of the occurrence of prolonged vaginal bleeding (an average of 10 to 16 days after Mifepristone Linepharma and GyMiso® intake) which may be heavy. Bleeding occurs in almost all cases and is not in any way proof of complete expulsion. Persistent bleeding can be the consequence of incomplete expulsion. Bleeding can be large enough to necessitate a blood transfusion, in up to 0.2 % of cases up to 63 days gestation and to lead to a significant decrease in haemoglobin levels.

The patient should be informed not to travel far away from the prescribing centre as long as complete expulsion has not been recorded. She will receive precise instructions as to whom she should contact and where to go, in the event of any problems emerging, particularly in the case of very heavy vaginal bleeding.

As per the Royal College of Obstetricians and Gynaecologists guideline, *(The Care of Women Requesting Induced Abortion, November 2011)*, the following is recommended:

"Following abortion, women should be provided with verbal and written information about:

• symptoms they may experience, emphasising those which would necessitate an urgent medical consultation

• symptoms suggestive of continuing pregnancy.

Independent providers of abortion services should have arrangements in place for referring women to a public hospital emergency department for assessment and admission. "

"On discharge, all women should be given a letter providing sufficient information about the procedure to allow another practitioner elsewhere to manage any complications".

Follow-up must take place within a period of 14 to 21 days after administration of Mifepristone Linepharma to verify by the appropriate means (clinical examination, ultrasound scan, or beta-hCG measurement) that expulsion has been completed and that vaginal bleeding has stopped. In case of persistent bleeding (even light) beyond this follow-up, the disappearance of bleeding should be checked within a few days.

If an ongoing pregnancy is suspected, a further ultrasound scan may be required to evaluate its viability.

Persistence of vaginal bleeding at this point could signify incomplete abortion, or an unnoticed extra-uterine pregnancy, and appropriate treatment should be considered. In the event of an ongoing pregnancy diagnosed after follow-up, termination by another method will be offered to the woman.

Since heavy bleeding requiring haemostatic curettage occurs in up to 5 % of cases during the medical method of pregnancy termination, special care should be given to patients with haemostatic disorders with hypocoagulability, or with anaemia. The decision to use the medical or the surgical method should be decided with specialised consultants according to the type of haemostatic disorder and the level of anaemia.

o Infection

As with other types of abortion, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of mifepristone and misoprostol. No causal relationship between these events and the use of mifepristone and misoprostol has been established. Treating healthcare practitioners evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event and immediately seek a medical practitioner's (doctors) advice. In particular, a sustained fever of 38ºC or higher, severe abdominal pain, or pelvic tenderness in the days after a medical abortion may be an indication of infection.

A high index of suspicion is needed to rule out sepsis (from e.g. *Clostridium sordellii* or other species e.g. Streptococcus) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhoea) more than 24 hours after taking misoprostol. However, the symptoms of *Clostridium sordellii* infection are sometimes not the usual symptoms of sepsis and very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, haemo-concentration, and general malaise. Therefore, the possibility of sepsis should be considered in all women who are undergoing medical termination and who present with nausea, vomiting, or diarrhoea and weakness with or without abdominal pain. These symptoms, even without a fever, may indicate *Clostridium sordellii* infection. Strong consideration should be given to obtaining a complete blood count in these patients. Significant leukocytosis with a marked left shift and haemo-concentration may be indicative of sepsis. Doctors should consider immediately initiating treatment with antibiotics that includes coverage of anaerobic bacteria such as *Clostridium sordellii*. Most of the reported deaths occurred in women who used vaginally administered misoprostol however deaths following other forms of administration have been reported. No causal relationship between mifepristone and misoprostol use and an increased risk of infection or death has been

established. *Clostridium sordellii* and other infections such as *Streptococcus* and other bacteria have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynaecologic and non-gynaecologic conditions. Reviews have estimated overall serious infection rates after medical abortion at less than 1%.

Use in the elderly

There is no relevant use of ***MS-2 Step*** in the elderly population in the indication.

Paediatric use

Limited data are available for use of ***MS-2 Step*** in women under 18 years of age.

There is no relevant use of ***MS-2 Step*** in the prepubertal paediatric population in the indication. Administration to adolescents less than 18 years of age should be undertaken with caution.

Effects on laboratory tests

There are no known effects of mifepristone or misoprostol on laboratory tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Mifepristone Linepharma

No interaction studies have been performed.

On the basis of mifepristone's metabolism by CYP3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum levels of mifepristone). Furthermore, rifampicin, dexamethasone, St. John's Wort and certain anticonvulsants (phenytoin, phenobarbital (phenobarbitone), carbamazepine) may induce mifepristone metabolism (lowering serum levels of mifepristone).

Based on *in vitro* information showing that mifepristone acts as a mechanism-based inhibitor of CYP3A4, co-administration of mifepristone may lead to an increase in serum levels of drugs that are CYP3A4 substrates. Due to the irreversible nature of the CYP binding and the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP3A4 substrates and have narrow therapeutic range, including some agents used during general anaesthesia.

GyMiso®

Misoprostol has no known drug interactions. No induction of the hepatic cytochrome P-450 enzyme system has been observed. The serum protein binding of misoprostol acid was not affected by indometacin, ranitidine, digoxin, phenylbutazone, warfarin, diazepam, methyldopa, propranolol, triamterene, cimetidine, paracetamol, ibuprofen, chlorpropamide and hydrochlorothiazide. With salicylic acid (300 µg/mL), the protein binding of misoprostol was lowered from 84 to 52% which is not considered clinically significant since the binding of misoprostol acid is not extensive and its elimination half-life is very short.

In laboratory studies, misoprostol has no significant effect on the cytochrome P450 linked hepatic mixed function oxidase system, and therefore should not affect the metabolism of theophylline, warfarin, benzodiazepines or other drugs normally metabolised by this system. No drug interactions have been attributed to misoprostol in extensive clinical trials. As such, other drugs would be unlikely to interfere with misoprostol's metabolism in either normal or hepatically-impaired patients.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

During clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses.

Mifepristone Linepharma

Mifepristone inhibited oestrus cycling in rats at oral doses of 0.3-1 mg/kg/day (less that the clinical dose adjusted for body surface area) in a 3-week study. This was reversed over the following 2-3 weeks and no subsequent effects on reproductive performance were found.

GyMiso®

In fertility studies in rats in which treated females were mated with treated males, increased pre-implantation losses were observed with misoprostol at oral doses greater than 1 mg/kg/day (11 times the recommended human dose, on a mg/m^2 basis). Post-implantation loss was also increased at 10 mg/kg/day (114 times the recommended human dose, on a mg/m^2 basis).

Use in pregnancy

Mifepristone Linepharma

In animals, the abortifacient effect of mifepristone precludes the proper assessment of any teratogenic effect of the molecule.

Fetal skull/brain malformations, presumed to be related to treatment, have been observed in rabbits and monkeys, but not mice or rats, treated with sub-abortive doses of mifepristone. These most likely occurred secondary to mifepristone's effect on the uterus due to antagonism of progesterone.

Delayed development of the righting reflex and slight inhibition of locomotor development were observed in rats when administered mifepristone at the high-dose level (1 mg/kg/day) from day 15 of gestation to the end of the lactation period (postnatal day 21).

A review of births from 105 pregnancies exposed during first trimester of pregnancy to mifepristone alone (46 cases) or to both mifepristone and misoprostol (59 cases) has recently been published. There were 94 live births (90.4%) and 10 (9.6%) miscarriages (including one with major malformation). Elective termination of pregnancy was performed after the subsequent diagnosis of trisomy 21 in one case. The overall rate of major congenital malformations was 4.2% (95% CI: 1.2 – 10.4%), with two cases among 38 patients exposed to mifepristone alone and two cases among 57 patients exposed to both mifepristone and misoprostol. In conclusion, this unique prospective study found that the rate of major malformations after exposure to mifepristone during the first trimester of pregnancy is only slightly higher than the expected 2 – 3% rate in the general population. Nevertheless, data in humans are still too limited to determine whether the molecule is a human teratogen.

GyMiso®

Use of misoprostol has been associated with birth defects. In a few cases where misoprostol was self-administered (orally or vaginally) in order to induce an abortion, the following deleterious effects of misoprostol have been suggested: malformations of limbs, of fetal movements and of cranial nerves (hypomimia, abnormalities in suckling, deglutition, and eye movements). To date, a risk of malformation cannot be excluded.

Reproductive toxicity studies in animals showed embryotoxicity (increased resorptions) with oral doses of 1 mg/kg/day in rabbits, 10 mg/kg/day in rats, and 20 mg/kg in mice when treatment occurred during the period of organogenesis. An increased incidence of skeletal abnormalities was observed with an oral dose of 1 mg/kg/day in rabbits (possibly due to maternal toxicity) while an increased incidence of cleft palate was seen at a single oral dose

of 30 mg/kg in mice (28 and 170 times the recommended human dose, on a mg/m^2 body surface area basis, respectively).

Failure of pregnancy termination (continuing pregnancy)

Use in pregnancy has been associated with an increased risk of birth defects/malformations for ongoing pregnancies exposed to mifepristone and misoprostol or misoprostol alone, compared to control group. In particular, prenatal exposure to misoprostol has been associated with Moebius syndrome (congenital facial paralysis leading to hypomimia, troubles of sucking and deglutition and eye movements, with or without limb defects) and with amniotic band syndrome (limb deformities/ amputations, especially clubfoot, acheiria, oligodactyly, cleft palate inter alia), and central nervous system anomalies (cerebral and cranial anomalies such as anencephaly, hydrocephaly, cerebellar hypoplasia, neural tube defects).

Women considering medical termination of pregnancy should be precisely counselled on the risks to their fetus if an abortion failure occurs and a second termination of pregnancy procedure is not desirable.

MS-2 Step

As a consequence of the above information on mifepristone and misoprostol:

- Women should be informed that due to the risk of failure of the medical method of pregnancy termination and to the unknown risk to the fetus, follow-up is very important (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).
- Should a failure of the medical method be diagnosed at follow-up (viable ongoing pregnancy), and should the patient still agree, pregnancy termination should be completed by another method.

Should the patient wish to continue with her pregnancy, she should be appropriately counselled as to the risk of birth defects. In that event of continuation of the pregnancy, careful ultra-sonographic monitoring of the pregnancy should be carried out.

To avoid the potential exposure of a subsequent pregnancy to MS-2 Step it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after administration of ***MS-2 Step***.

Use in lactation

Mifepristone is a lipophilic compound and may theoretically be excreted in the mother's breast milk. However, limited data are available. Misoprostol is rapidly metabolised in the mother to misoprostol acid, which is biologically active and is excreted in breast milk. This could cause undesirable effects such as diarrhoea in breast feeding infants. ***MS-2 Step*** use should be avoided during breast-feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most frequent undesirable effects which are observed during treatment with ***MS-2 Step*** are the following:

- Gastrointestinal disorders: nausea (transient and mild), vomiting, diarrhoea, abdominal pain.
- Reproductive system disorders: very frequent uterine contractions observed in the hours following the intake of the misoprostol component of the MS-2 Step pack; vaginal bleeding, sometimes heavy and prolonged (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

- General disorders: headache, dizziness, and chills and fever. (Because castor oil is an excipient of the misoprostol component of the ***MS-2 Step*** pack, digestive symptoms (nausea, vomiting, abdominal pain) can be observed).

The adverse events reported with mifepristone and a prostaglandin analogue such as GyMiso®, classified according to frequency and system organ class, are summarised as shown in Table 1.

Table 1: **Adverse Events for the Combined Use of Mifepristone and Misoprostol**

MedDRA	**Adverse events (frequency)**				
System Organ Class	**Very common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1000 to < 1/100**	**Rare ≥ 1/10000 to < 1/1000 and very rare (< 1/10000)***	**Unknown frequency**
Infections and infestations			Infection	Toxic shock syndrome	
Neoplasms benign, malignant and unspecified				Elevated alpha-foeto protein Elevated carcinoembryonic antigen	
Blood and lymphatic system disorders				Thrombotic thrombocytopenic purpura Thrombocytopenia Induced systemic lupus erythematosus	
Psychiatric disorders				Mania	
Nervous system disorders	Headache Dizziness			Epilepsy Neurogenic tinnitus	
Eye disorders				Ophthalmoplegia	
Cardiac disorders				Myocardial infarction Induced Adam-Stokes syndrome Arrhythmia	
Vascular disorders			Hot flush Hypotension (0.25%)	Superficial thrombophlebitis	
Respiratory, thoracic and mediastinal disorders				Bronchospasm Induced bronchial asthma	

Table 1: Adverse Events for the Combined Use of Mifepristone and Misoprostol					
MedDRA	**Adverse events (frequency)**				
System Organ Class	**Very common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1000 to < 1/100**	**Rare ≥ 1/10000 to < 1/1000 and very rare (< 1/10000)***	**Unknown frequency**
Gastrointestinal disorders	Nausea Vomiting Diarrhoea Gastric discomfort Abdominal pain	Cramping, light or moderate		Gastric bleeding Necrotising pancreatitis	
Hepatobiliary disorders				Abnormal liver function tests Hepatic failure Hepatorenal failure	
Skin and subcutaneous tissue disorders			Skin rash / pruritus	Urticarial reaction Toxic epidermal necrolysis Erythema nodosum Angioedema*	Acute generalized exanthematous pustulosis
Musculoskeletal and connective tissue disorders				Limb spasm	
Renal and urinary disorders				Renal failure	
Pregnancy, puerperium and perinatal conditions	Uterine contractions or cramping (10 to 45%) in the hours following prostaglandin intake.	Heavy bleeding occurs in about 5% of the cases and may require haemostatic curettage in up to 1.4% of the cases. Fetal malformations		Hydatiform mole Ectopic pregnancy Amniotic band syndrome Gestational trophoblastic tumor Uteroplacental apoplexy	
Reproductive system and breast disorders	Vaginal bleeding Uterine spasm	Prolonged post-abortion bleeding Spotting Severe haemorrhage Endometritis Breast tenderness Heavy bleeding	Haemorrhagic shock Salpingitis	Bilateral adnexal mass Intrauterine adhesion Ovarian cyst rupture Breast abscess Haematosalpynx Uterine rupture	

Table 1: Adverse Events for the Combined Use of Mifepristone and Misoprostol					
MedDRA	**Adverse events (frequency)**				
System Organ Class	**Very common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1000 to < 1/100**	**Rare ≥ 1/10000 to < 1/1000 and very rare (< 1/10000)***	**Unknown frequency**
General disorders and administration site conditions	Fatigue Chill / fever	Fainting		Anaphylaxis Periorbital edema Vagal symptoms	

*Including occasional case reports

- Post-marketing experience indicates that death can occur as a result of medical termination of pregnancy (although this is a very rare outcome, <1 in 100,000). The reported deaths were due to sepsis (fatal toxic shock syndrome) associated with *Clostridium sordellii*, which also occurs in association with childbirth and spontaneous termination. The symptoms of *Clostridium sordellii* infection are sometimes not the usual symptoms of sepsis. Therefore, the possibility of sepsis should be considered in all women who are undergoing medical termination and who present with nausea, vomiting, or diarrhoea and weakness, with or without abdominal pain. These symptoms, even without a fever, may indicate *Clostridium sordellii* infection. Strong consideration should be given to obtaining a complete blood count in these patients. Significant leukocytosis with a marked left shift and haemo-concentration may be indicative of sepsis. Doctors should consider immediately initiating treatment with antibiotics that includes coverage of anaerobic bacteria such as *Clostridium sordellii*. Refer to **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**.

- Bleeding is an almost constant part of the procedure, whatever the prostaglandin analogue used, and at any pregnancy term, although it is usually more abundant when pregnancy age increases. It can occur after mifepristone alone. When heavy, it usually reflects incomplete abortion and is observed in approximately 3 to 12% of cases, depending on the pregnancy age and the prostaglandin analogue used, and needs specific treatment. It can necessitate a blood transfusion in up to 0.2% of cases. It can be prolonged for several days after prostaglandin analogue administration and sometimes leads to a decrease in haemoglobin levels. This potentially severe complication justifies that after intake (i) follow-up takes place approximately 14 to 21 days after Mifepristone Linepharma administration to ensure that expulsion is complete with no persisting bleeding and (ii) until follow-up has taken place, the woman remains close to a facility where she can be treated at any moment in case of severe or prolonged bleeding. Refer to **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**.

The issue of the outcome of persisting pregnancy in the case of failure of the medical method remains incompletely solved; a risk of malformation attributable to mifepristone or to prostaglandin analogues such as misoprostol cannot be excluded, and women should be adequately counselled in such a situation. Another fact to take into consideration is the possibility of a pregnancy persisting in the form of an ectopic pregnancy, since evidence suggests that the method does not appear able to terminate an ectopic pregnancy.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems and to MS Health at 1300 515 883.

4.9 OVERDOSE

Mifepristone Linepharma

No case of overdose has been reported.

In the event of massive ingestion signs of adrenal failure might occur. Signs of acute intoxication may require specialist treatment including the administration of dexamethasone.

GyMiso®

The toxic dose of misoprostol in humans has not been determined. Cumulative total daily doses of 1600 micrograms have been tolerated, with only symptoms of gastrointestinal discomfort reported.

Clinical signs that may indicate an overdose are sedation, tremor, convulsions, dyspnoea, abdominal pain, diarrhoea, fever, palpitations, hypotension or bradycardia. Hypertension and tachycardia have also been reported following overdoses. Overdose in pregnancy has resulted in uterine contractions with fetal death.

There is no specific antidote. Treatment should be symptomatic and supportive. Consider administration of activated charcoal in the event of a potentially toxic ingestion. Activated charcoal may reduce absorption of misoprostol if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Mifepristone Linepharma

Pharmacotherapeutic group: Other Sex Hormone and Modulator of the Reproductive function/ Antiprogestogen. ATC code: GO3XB01

Mifepristone is a synthetic steroid with an antiprogestational action as a result of competition with progesterone at the progesterone receptors.

Mifepristone binds to human progesterone receptors with nanomolar affinity. In animals, oral administration was shown to inhibit the action of endogenous or exogenous progesterone in multiple species (rat, mouse, rabbit, dog and monkey). This action is manifested in the form of pregnancy termination.

In women at doses of greater than or equal to 1 mg/kg, mifepristone antagonises the endometrial and myometrial effects of progesterone. During pregnancy it sensitises the myometrium to the contraction inducing action of prostaglandins. While clinical data have demonstrated that mifepristone facilitates dilatation of the cervix, no data are available to indicate that this results in a lowering of the rate of early or late complications to the dilatation procedure.

In the event of an early termination of pregnancy, the combination of a prostaglandin analogue used in a sequential regimen after mifepristone leads to an increase in the success rate and accelerates the expulsion of the conceptus.

Mifepristone binds to the glucocorticoid receptor with affinity comparable to that for the progesterone receptor. Full inhibition of the action of dexamethasone was evident in rats at oral doses 0.5-1.1 times the human dose adjusted for body surface area. In man the

antiglucocorticoid action is manifested at a dose equal to or greater than 4.5 mg/kg by a compensatory elevation of ACTH and cortisol.

Mifepristone also has some anti-androgenic activity. In toxicological studies in rats and monkeys up to a duration of 6 months, mifepristone produced effects related to its antihormonal (antiprogesterone, antiglucocorticoid and antiandrogenic) activity.

GyMiso®

Pharmacotherapeutic group: Other gynecological medicines – prostaglandins. ATC code: G02AD06

Misoprostol is a synthetic analogue of prostaglandin E1. At the recommended dosages, misoprostol induces contractions of the smooth muscle fibers in the myometrium and relaxation of the uterine cervix. The uterotonic properties of misoprostol should facilitate cervical opening and evacuation of intrauterine debris.

In the event of an early termination of pregnancy, the combination of GyMiso® used in a sequential regimen after mifepristone leads to an increase in the success rate and accelerates the expulsion of the conceptus.

Pharmacodynamic studies in early pregnancy have found an increase in uterine tone around 8 minutes after oral and 40 minutes after buccal misoprostol, with sustained contractions achieved by a mean of around 90 minutes and uterine activity peaking prior to 5 hours. Following oral administration uterine activity rises earlier than other routes, but is lower overall. Pretreatment with mifepristone has previously been shown to increase uterine contractility in response to misoprostol.

Clinical trials

Clinical efficacy of early medical abortion is defined as complete abortion without surgical intervention, regardless of the reason for the intervention, which may include continuing pregnancy, missed or incomplete abortion, prolonged or heavy vaginal bleeding or a woman's request.

An open-label single-group prospective trial performed in Mexico by Gynuity Healthcare, USA, involving 971 women available for efficacy treated with 200 mg mifepristone followed by 800 micrograms misoprostol administered buccally indicated that efficacy was 98.0, 96.8 and 95.9% for women with gestational age 49 days and below, 50-56 days and 57-63 days, respectively. In these 3 gestational age groups, the rate of surgical evacuation was 2.0, 3.2 and 4.1% respectively. In this study 25 women received a second dose of misoprostol, in each case, a dose of 800 micrograms by the buccal route. Of those 25, 20 had a successful outcome with medication alone, 4 had a surgical intervention and 1 woman did not return for follow up. In this study, bleeding occurred in all women independent of outcome, and was judged as more than expected in 27.1% of the women.

In an Authorised Prescribers Program in Australia in 2012 that included 7,166 women, efficacy was 97.4% for women with gestational age <49 days, and 95.2% for women with gestational age of 49-63 days. The rate of incomplete termination requiring aspiration was: <49 days: 2.3%; 49-63 days: 4.8%. The rate of ongoing pregnancies was: <49 days: 0.3%; 49-63 days: 0.6%. Bleeding was considered as an adverse event in 0.24% of women, independent of pregnancy age.

Studies published in the literature have reported mifepristone and oral or buccal misoprostol regimens. In one study of 966 patients[1] with pregnancies up to gestational age of 63 days, randomised to 200 mg mifepristone followed 24-36 hours later by 800 micrograms of misoprostol orally or buccally, reported efficacy rates were 91.3% for the oral and 96.2% for the buccal group (RR 0.95, 95% CI 0.92-0.98, p=0.003).

[1] Winikoff B et al. Obstetr Gynecol 2008, 1303-10

Studies published on the combination of mifepristone 200 mg and misoprostol 800 micrograms buccally, and reporting outcomes by gestational age, encompass 399 women with gestational ages 50 – 56 days and 344 women with gestational ages 57 – 63[2][3][4][5][6][7] days. Efficacy ranged from 86.5 to 98.5% in women with gestational age 50 – 56 days and from 93.0 to 100% in those with gestational age 57 – 63 days. In these studies, the rate of ongoing pregnancies ranged from 0 to 7.1% in women with gestational age 50 – 56 days and from 0 to 2.3% in those with gestational age 57 – 63 days.

Literature data provides information on the bleeding and expulsion pattern after termination of pregnancy with mifepristone and misoprostol: approximately half of women start to bleed before prostaglandin administration. Median bleeding time is 10 to 16 days. Bleeding is judged more or much more abundant than usual menses for 2 to 3 days after prostaglandin. In studies where it was measured, there was a slight but significant decrease in haemoglobin level after compared to baseline. In one study blood loss was quantified: the median blood loss was 83 mL and 5.4% of women had a blood loss above 200 mL. Expulsion usually takes place within 3 hours after misoprostol in approximately half of the women, and within 4 hours after misoprostol in approximately 50 to 90% of women.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Mifepristone Linepharma

After oral administration of a single dose of 200 mg, mifepristone is rapidly absorbed. The peak concentration of 2.3 to 2.7 mg/L is reached after 0.75 hours (mean of 49 subjects). The half-life of mifepristone is 36.5 to 38.3 hours.

Mifepristone shows non-linear pharmacokinetics. Following the distribution phase the elimination is at first slow, with a half-life of approximately 12 to 72 hours, and then the concentration is more rapidly reduced with a half-life of 18 hours. With radio-receptor analysis, the final half-life is shown to be up to 90 hours, including all mifepristone metabolites that can bind to progesterone receptors.

After administration of low doses of mifepristone (20 mg orally or intravenously), the absolute bioavailability is 69%.

GyMiso®

When administered orally, misoprostol is rapidly absorbed and metabolised. Peak concentrations around 1.1 ng/mL were reached about 15 minutes after a 400 µg dose in the fasting state. Plasma concentrations of its main degradation metabolite, misoprostol acid, reach their peak of 2 - 2.5 ng/mL after a 2 µg/kg oral dose within approximately 30 minutes and rapidly decline thereafter. As a result, uterine contractility increases and then plateaus after about one hour. Absorption is almost complete, measured at levels between 64 - 73% from urinary data.

For a single oral administration of 800 micrograms misoprostol (4 tablets of 200 micrograms GyMiso®), AUC_{0-t} was 1.9709 ± 0.8130 hr.ng/mL, $AUC_{0-\infty}$ was 2.0192 ± 0.8032 hr.ng/mL and C_{max} was 2.6830 ± 1.2161 ng/mL. For a single buccal administration of 800 micrograms misoprostol (4 tablets of 200 micrograms GyMiso®), AUC_{0-t} was 1.9095 ± 0.2909 hr.ng/mL, $AUC_{0-\infty}$ was 2.0726 ± 0.3578 hr.ng/mL and C_{max} was 1.3611 ± 0.3436 ng/mL. For a single sublingual administration of 800 micrograms misoprostol (4 tablets of 200 micrograms

[2] Chong et al 2012 Contraception 86, 251–256
[3] Fjerstad et al 2009 Contraception 80, 282-286
[4] Boersma et al 2011 Eur J of Contraception & Reproductive Health Care 16, 61-66
[5] Ngoc et al 2011 Contraception 83, 410 – 417
[6] Blum et al 2012 Int J Gynecol Obstetr 118, 166 - 171
[7] WHO 2000 Br J Obstetr Gynecol 107, 524-30

GyMiso®), AUC_{0-t} was 3.0574 ± 0.9872 hr.ng/mL, $AUC_{0-\infty}$ was 3.2094 ±1.0417 hr.ng/mL and C_{max} was 2.4391 ± 1.1567 ng/mL. For log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}, there were statistically significant differences between 3 treatment groups (p = 0.0159, 0.0162 and 0.0083, respectively). Sublingual administration of misoprostol had a higher $AUC_{0-\infty}$ compared with buccal and oral administration which indicated bioavailability was higher by the sublingual route. Misoprostol sublingual and oral administration resulted in higher C_{max} compared with buccal. The C_{max} of buccal administration was achieved later compared with other routes of administration. No difference was found when comparing oral, sublingual and buccal half-lives (p= 0.4495).

Distribution

Mifepristone Linepharma

In plasma, mifepristone is 98% bound to plasma proteins: albumin and principally alpha-1-acid glycoprotein (AAG), to which binding is saturable. Due to this specific binding, the volume of distribution and plasma clearance of mifepristone are inversely proportional to the plasma concentration of AAG.

GyMiso®

Serum protein binding of labeled misoprostol acid was studied in man and was similar in young (81-88%) and elderly (81-89%) subjects. Accumulation in erythrocytes was not seen.

Metabolism

Mifepristone Linepharma

N mono- and di-demethylation and terminal hydroxylation of the 17-propynyl chain are primary metabolic pathways of hepatic oxidative metabolism. Metabolites are detectable in plasma 1 hour after ingestion of mifepristone. Plasma AUC for the dominant metabolite, monodemethylated mifepristone, is approximately double that of the unchanged mifepristone at the clinical dose, and this metabolite retains significant affinity for the progesterone receptor. The other metabolites also display some progesterone receptor affinity (approximately 10 to 15% that of mifepristone). The metabolites may contribute to the pharmacological effects of mifepristone.

In vitro CYP3A4 appears as the isoenzyme primarily responsible for mifepristone demethylation and hydroxylation in human liver microsomes. CYP3A4 substrates progesterone and midazolam inhibited metabolite formation by up to 77%. Other isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1) had apparently no action on mifepristone metabolism.

GyMiso®

Metabolism of misoprostol to misoprostol acid is rapid with no intact misoprostol found in plasma consistent with an *in vitro* half-life of 6.4 minutes for de-esterification of misoprostol in human plasma at 37ºC. Elimination of misoprostol and its metabolites is also rapid with a plasma elimination half-life of 35 minutes.

Excretion

Mifepristone Linepharma

After administration of 600 mg radiolabelled mifepristone, 10% of the total radioactivity was recovered in urine and 90% in faeces.

GyMiso®

The liver is the primary site of metabolism and between 1-4% of misoprostol acid is excreted in the urine.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Mifepristone Linepharma

Mifepristone has been evaluated in tests for mutagenicity in bacterial, yeast and mammalian cells; gene conversion in yeast; unscheduled DNA synthesis in HeLa cells; and for clastogenicity *in vitro* (Chinese hamster ovary cells) and in vivo (mouse bone marrow micronucleus test). No evidence of genotoxicity was observed.

GyMiso®

Misoprostol has been evaluated in tests for mutagenicity in bacterial, yeast and mammalian cells; and for clastogenicity *in vitro* (Chinese hamster ovary cells) and *in vivo* (mouse bone marrow micronucleus test). No evidence of genotoxicity was observed.

Carcinogenicity

Mifepristone Linepharma

No long-term animal carcinogenicity studies have been conducted with mifepristone. Based on the negative genotoxicity results, findings in general repeat-dose toxicity studies and considering the pattern of clinical use, mifepristone is not predicted to pose a particular carcinogenic risk.

GyMiso®

The potential carcinogenicity of misoprostol has been evaluated in both mice and rats. There was no evidence of an effect of misoprostol on tumour occurrence or incidence in rats receiving oral doses up to 2.4 mg/kg/day for 24 months. Similarly, there was no effect of misoprostol on tumour occurrence or incidence in mice receiving oral doses up to 16 mg/kg/day for 21 months. These doses are at least 27 times the recommended human dose, on a mg/m^2 body surface area basis.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mifepristone Linepharma 200 mg tablet contains the following excipients: maize starch, povidone, microcrystalline cellulose, colloidal anhydrous silica and magnesium stearate.

GyMiso® contains the following excipients: hypromellose, microcrystalline cellulose, sodium starch glycollate type A and hydrogenated castor oil.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Do not use after the expiry date printed on the carton labels of the composite pack and the individual components.

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C, keep in the original container to protect from light.

Keep out of reach of children.

Mifepristone Linepharma

Keep in the original green carton in order to protect from light

GyMiso®

Keep in the original purple carton

6.5 NATURE AND CONTENTS OF CONTAINER

Each ***MS-2 Step*** composite pack consists of:

- 1 green carton containing Mifepristone Linepharma 200 mg tablet packaged in a PVC/PVDC/Aluminium blister. Pack size of 1 tablet.
- 1 purple carton containing GyMiso® misoprostol 200 microgram tablet packaged in a dual-faced Aluminium blister. Pack size of 4 tablets (2 tablets per blister).

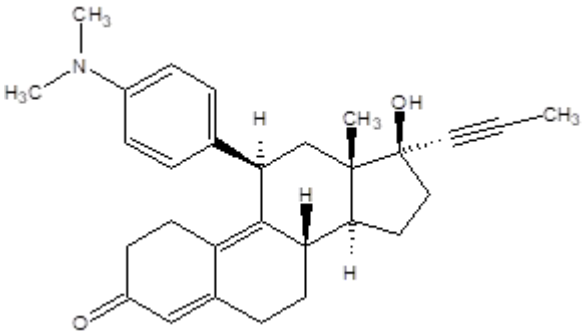
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Mifepristone

Chemical structure



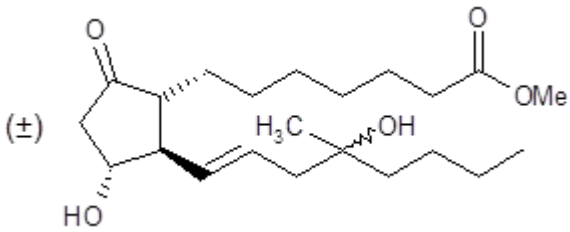
Molecular formula: $C_{29}H_{35}NO_2$ Molecular weight: 429.6

CAS number

CAS Registry Number: 84371-65-3

GyMiso®

Chemical Structure



Molecular formula:$C_{22}H_{38}O_5$ Molecular weight: 382.5

CAS number

CAS Registry Number: 59122-46-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8 SPONSOR

MS Health Pty Ltd
Suite 60, 278 Church Street,
Richmond, VIC, Australia, 3121

Ph: 1300 515 883MS-2 Step® is a registered trademark of MSI Reproductive Choices (UK). Mifepristone Linepharma and GyMiso® are licensed from Linepharma International Limited (UK).

9 DATE OF FIRST APPROVAL

4 June 2014

10 DATE OF REVISION

TBC

11 SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
Black box and 4.2	Medical practitioner /doctor changed to healthcare practitioner
4.2	Certification of doctors removed
4.4	Reference to 24-hour help line in guideline removed and instructions for further medical advice added.

Document 8

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Clinical Evaluation Report – Type J
Prescription Medicines Authorisation Branch

Active substance: Mifepristone and misoprostol

Product name: MS-2 Step composite pack

Sponsor: s47 [redacted] on behalf of MS Health Pty Ltd

Submission number: PM-2022-05475-1-5

eSubmission number: e004967

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989*, applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

Contents

List of abbreviations

Abbreviation	Meaning
ITT	Intention-to-treat
MLP	Mid-level healthcare provider
MToP	Medical termination of pregnancy
MVA	Manual vacuum aspiration
PI	Product Information
PP	Per protocol
SAE	Serious adverse event
WHO	World Health Organization

List of tables

1. Submission details

1.1. Identifying information

Submission number	PM-2022-05475-1-5
eSubmission number	e004967
eSubmission sequences covered in this report	0007, 0012
Sponsor	s47 [redacted] on behalf of MS Health Pty Ltd
Trade name	MS-2 Step composite pack
Active substance	Mifepristone and misoprostol

1.2. Submission type

This is a Category 1, Type J application (variation to the register entry resulting in a change of product information requiring evaluation of clinical, non-clinical or bioequivalence data) to update the PI for MS-2 Step composite pack.

Section 4.2 of the current PI advises MS-2 Step can only be prescribed by doctors with the appropriate qualifications and certified training. The Sponsor proposes to amend 'medical practitioner' in the boxed warning and 'doctors' in Section 4.2 of the PI to 'healthcare practitioners'.

1.3. Drug class and therapeutic indication

As per the MS-2 Step PI [1]:

Mifepristone belongs to the Pharmacotherapeutic group: Other sex hormone and modulator of the reproductive function/antiprogestogen, ATC code GO3XB01.

Misoprostol belongs to the Pharmacotherapeutic group: Other gynaecological medicines – prostaglandins, ATC code G02AD06.

Mifepristone is a synthetic steroid with an antiprogestational action as a result of competition with progesterone at the progesterone receptors. In women at doses of greater than or equal to 1 mg/kg, mifepristone antagonises the endometrial and myometrial effects of progesterone. During pregnancy it sensitises the myometrium to the contraction inducing action of prostaglandins. Misoprostol is a synthetic analogue of prostaglandin E1. At the recommended dosages, misoprostol induces contractions of the smooth muscle fibres in the myometrium and relaxation of the uterine cervix. In the event of an early termination of pregnancy, the combination of a prostaglandin analogue used in a sequential regimen after mifepristone leads to an increase in the success rate and accelerates the expulsion of the conceptus.

The approved indication is [1]:

MS-2 Step is indicated in females of childbearing age for the medical termination of an intrauterine pregnancy, up to 63 days of gestation.

It is recommended that the duration of pregnancy (i.e., up to 63 days gestation) be confirmed by ultrasound. In the event that an ultrasound is not possible, extra caution should be exercised.

Ultrasound is also useful to exclude ectopic pregnancy.

1.4. Dosage forms and strengths

The following dosage forms and strengths are currently registered:

MS-2 Step composite pack (MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet blister; GyMiso misoprostol 200 microgram tablet blister) AUST R 210574

No new dosage forms or strengths are proposed.

2. Background

2.1. Clinical rationale

The Sponsor's rationale was provided in the Cover letter (dated 22nd December 2022), summarised as follows:

Currently the MS-2 Step PI defines MS-2 Step can only be prescribed by doctors with the appropriate qualifications and certified training, with the subsequent post administration follow up to be conducted by a medical practitioner, preferably the prescriber. Therefore, access to early medical abortion (as indicated up to 63 days of gestation) is restricted to where a certified medical practitioner is located.

To ensure timely access to patients, and to ensure that the product is prescribed by the persons authorised by state and territory legislation, the application proposes to amend the black box warning from referencing 'medical practitioner' to 'healthcare practitioner', and for the reference to 'doctors' in section 4.2 to be amended to 'healthcare practitioners'.

2.2. Regulatory history

2.2.1. Australian regulatory history

The individual components of MS-2 Step, Mifepristone Linepharma (mifepristone 200 mg tablet) and GyMiso (misoprostol 200 microgram tablet) were registered in Australia on 29th August 2012 for medical termination of developing intrauterine pregnancy up to 49 days gestation as follows:

Mifepristone Linepharma (AUST R 175671):

Medical termination of a developing intra-uterine pregnancy. In sequential combination with a prostaglandin analogue up to 49 days of gestation; and preparation for the action of registered prostaglandin analogues that are indicated for the termination of pregnancy for medical reasons beyond the first trimester.

GyMiso (AUST R 188015):

GyMiso is indicated in females of childbearing age for the medical termination of a developing intrauterine pregnancy in sequential combination with a mifepristone 200 mg tablet, up to 49 days of gestation.

MS-2 Step composite pack containing Mifepristone Linepharma (mifepristone) 200 mg tablet and GyMiso (misoprostol) 200 microgram tablets was registered on 4th June 2014 (Submission PM-2013-01037-1-5). As part of this submission, the indication was extended to the medical termination of a developing intrauterine pregnancy from 49 days up to 63 days gestation.

Following registration of MS-2 Step composite pack, the Sponsor withdrew the GyMiso mono product from the market, and removed the indication for medical termination of pregnancy up to 49 days for the Mifepristone Linepharma mono product (Submission PM-2014-03311-1-5).

2.2.2. Related submissions

• The Sponsor submitted an updated AU-RMP (version 04) to the TGA on 1st December 2022 (eSubmission e004967, sequence 0006) for review by the Risk Management Section.

Evaluator comment*: The RMP was submitted to TGA prior to submission of the current application. The Evaluator notes the Sponsor proposes to remove the requirement for re-certification training for prescribers from the RMP. This is drawn to the attention of the Delegate. An updated RMP was submitted during the evaluation phase of the current submission (See Section 3 below).*

2.2.3. Overseas regulatory history

Module 1.11 was not provided in the dossier (i.e. no foreign regulatory information).

MS-2 Step combination pack is not registered in other countries/regions.

The combination product Mifegymiso (mifepristone 200 mg tablet and misoprostol 200 microgram tablet combination pack, Linepharma International Limited) is approved in Canada for a comparable indication to MS-2 Step composite pack [2]:

'*Mifegymiso (mifepristone tablet/misoprostol tablets) is indicated for:*

• medical termination of a developing intra-uterine pregnancy with a gestational age up to 63 days as measured from the first day of the Last Menstrual Period (LMP) in a presumed 28-day cycle.

Mifegymiso is not intended for routine use as a contraceptive.'

Mifepristone is registered in the USA, UK and various countries in Europe. In the USA, Mifeprex (mifepristone) is only available through the mifepristone risk evaluation and mitigation strategy (REMS) Program [3].

2.3. Guidance

The following TGA guidelines are considered relevant to the current submission:

• Form for providing product information https://www.tga.gov.au/form-providing-product-information

• Boxed warning guidance https://www.tga.gov.au/resources/resource/guidance/boxed-warning-guidance

3. Contents of the clinical dossier

The dossier was submitted in eCTD format. The submission contained the following clinical information:

- Module 1
  - Application letter, application form, draft Australian PI, draft Australian Consumer Medicine Information (CMI)
- Module 2

- Clinical Overview Addendum

- Module 5
  - Periodic Safety Update Reports covering the intervals 1st June 2016 – 31st May 2017, 1st June 2021 – 31st May 2022
  - Literature references

***Evaluator comment**: As noted in Section 2.2.2 above, an updated AU-RMP (version 04) was submitted separately to the TGA on 1st December 2022. In the Cover letter for the current submission (dated 22nd December 2022), the Sponsor states 'An updated RMP was submitted to the TGA for review on the 1st December 2022 (version 04). Following the completion of the evaluation of this Category 1 application, the version 04 of the RMP will be updated in accordance with the approved changes and is proposed to be submitted with the next safety update.'*

Following discussion with TGA, a separate updated RMP (v4.0, 17th February 2023) was submitted to TGA (on 20th February 2023) during the evaluation phase of the current submission and is under review by the Risk Management Section. The Evaluator notes in the Cover letter for this updated RMP the Sponsor proposes removal of the mandatory medical education program.

This evaluation is based on the data provided in Module 2.5 to support the proposed changes to the PI provided in Module 1.3 (e004967 (0007-) - Product Information - Annotated). The Delegate is advised the proposed change to the RMP regarding removal of the mandatory medical education program was not discussed in the Clinical Overview Addendum.

4. Proposed changes to the PI

The following comments relate to the proposed MS-2 Step PI (e004967 (0007-) - Product Information - Annotated) provided in Module 1.3. Existing text in black, proposed additional text in blue, text for deletion in red strikethrough.

Proposed MS-2 Step PI change
Boxed warning It is very important that all patients receiving these medications are followed up by a ~~medical~~ healthcare practitioner, preferably the prescriber, to ensure that the medication has been effective. Even if no adverse events have occurred all patients must receive follow-up 14 to 21 days after taking mifepristone. Read the Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE carefully.
4.2 Dose and method of administration MS-2 Step is indicated for medical termination of intrauterine pregnancy, up to 63 days of gestation. The method of administration is as follows: Mifepristone: 200 mg of mifepristone (1 tablet containing 200 mg) orally, followed 36 to 48 hours later by the administration of GyMiso®. GyMiso®: 800 micrograms of misoprostol (4 tablets, each tablet containing 200 micrograms) buccally, i.e: kept between the cheek and the gum for 30 minutes before any fragments being swallowed with water. When MS-2 Step fails to cause termination of intra-uterine pregnancy, the patient should return to the treating doctor for assessment and discussion of treatment options, which may include pregnancy termination by surgery.

No dosage adjustment of misoprostol or mifepristone is necessary with renal or hepatic insufficiency when administered at the recommended doses.

There are no data available on the effect of food intake on the absorption of mifepristone or misoprostol. MS-2 Step should be taken 2 hours before or 2 hours after a meal.

Refer also to 4.3 CONTRAINDICATIONS, and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

MS-2 Step should only be prescribed by healthcare practitioners ~~doctors~~ with the appropriate qualifications and certified training. Ectopic pregnancy should be excluded, an intrauterine device (IUD) (if present) must be removed, consent must be obtained and patients must have the ability to access 24-hour emergency care if and when required for incomplete abortion or bleeding.

4.1.1. Supporting evidence

Supportive evidence was provided in the Clinical Overview Addendum. The Clinical Expert states as MS-2 Step can only be prescribed by doctors with the appropriate qualifications and certified training, with the subsequent post administration follow up to be conducted by a medical practitioner (preferably the prescriber), access to early medical abortion is restricted to patients and locations where a certified medical practitioner is accessible. The availability of prescribers is particularly limited in regional and remote areas of Australia, based on data from the Sponsor's certification program (see Table 1).

The Clinical Expert stated further:

- Allowing mid-level healthcare practitioners such as nurses, midwives and nurse practitioners to prescribe MS-2 Step (and as defined by the current state and territory legislation) will improve the current access for women by increasing the number of certified prescribers and removing the need for women to travel long distances to access a certified prescriber and safe abortion services.

- MS Health proposes to continue providing the same (existing) standardised training for all potential prescribers (as detailed in the current approved Australian RMP) which will ensure a minimum baseline of education regardless of training background.

- Use of the term 'healthcare practitioner' will encompass any variability in the state and territory terminology therefore allowing the specific state and territory legislation to define the persons authorised to perform or assist with medical termination of pregnancy (MToP).

The proposed changes are also stated to align with WHO recommendations for provision of MToP. The following points are noted from the WHO Abortion Care Guideline 2022 [4]:

• Strengthening access to comprehensive abortion care within the health system is fundamental to meeting the Sustainable Development Goals (SDGs) relating to good health and well-being (SDG3) and gender equality (SDG5).

• Quality abortion care must be both accessible (timely, affordable, geographically reachable, and provided in a setting where skills and resources are appropriate to medical need) and acceptable (incorporating the preferences and values of individual service users and the cultures of their communities).

• Recommendations regarding health worker roles are appropriate for, and intended for, all resource settings (high, middle and low-resource settings).

• The recommendations all assume that health workers who are in a category that is recommended or suggested to perform specific tasks will have received the appropriate task-specific training and information prior to performing that task.

• Medical abortion includes information provision (including reasons to seek urgent care at any point during the process) and the following components or subtasks: assessing eligibility for

medical abortion (diagnosing and dating the pregnancy, ruling out medical contraindications), administering the abortion medicines with instructions on their appropriate use and managing the common side-effects, and assessing whether the abortion process has had a successful outcome and whether any further intervention is required.

Supportive evidence from the literature was provided:

4.1.1.1. Randomised controlled trials (RCTs)

(i) Kopp Kallner et al. (2014) [5]

Kopp Kallner *et al*. conducted a randomised, controlled, single-centre equivalence trial to assess the efficacy and safety of early MToP provided by doctors or nurse-midwives at an out-patient family planning clinic of the Karolinska University Hospital, Stockholm, Sweden. The study included women ≥ 18 years of age in good general health with no continuing medication for chronic disease, pregnancy of less than 63 days gestation according to LMP, and no contraindication to MToP.

There were 1180 eligible subjects randomised in 1:1 ratio to nurse-midwife arm (n = 597) or to the standard-care (doctor) arm (n = 583) using computer-generated randomisation allocation code. The nurse-midwife arm included 2 nurse-midwives experienced in MToP who received training in vaginal ultrasound of early pregnancy, and the doctor arm included 34 doctors with variable training and experience. Ultrasound was performed in all cases by the allocated provider. In the nurse-midwife group, subjects were examined, counselled, informed, and treated by a single nurse-midwife. In the doctor group, counselling and examination was provided by a doctor, and additional information and medication provided by a nurse-midwife as per clinical routine.

MToP was as per WHO protocol. All participants received mifepristone 200 mg in the clinic and administered 800 micrograms misoprostol vaginally in the clinic or at home 24 hours later. Subjects were advised to take prophylactic pain relief (paracetamol and diclofenac). Follow-up in all cases comprised urinary hCG performed by a nurse-midwife (not involved in the study) approximately 3 weeks later. If this was positive, serum hCG was performed and patients referred for ultrasound to assess for continuing pregnancy. Subjects who did not attend for follow-up were contacted on two attempts, and considered lost to follow up thereafter.

Efficacy was the primary outcome, defined as the successful completion of TOP without need for vacuum aspiration. Safety was a secondary outcome, defined as need for hospitalisation or blood transfusion. Efficacy and safety outcomes were assessed by self-administered patient questionnaires and electronic patient records (completed after initial examination and follow-up visit).

Baseline demographics were comparable between the 2 groups. The median age of subjects was 27 years and median duration of gestation 45 days (see Table 2). Overall, 1068 subjects received and completed the allocated treatment (n = 535 nurse-midwife group, n = 533 doctor group). There were 105 subjects who did not have MToP (n = 62 nurse-midwife, n = 43 doctor group), most commonly due to choosing surgical ToP and advanced gestational age. There were 3 subjects in each group with ectopic pregnancy. The proportion of subjects lost to follow up was comparable between arms (n = 54 [10.1%] nurse-midwife arm, n = 76 [14.3%] doctor group), and stated by the authors to be comparable with studies in TOP. A total of 938 subjects were included in the analyses (n = 481 nurse-midwife group, n = 457 doctor group).

Sample size calculations determined 400 subjects per group sufficient to demonstrate equivalence within a 5% margin with 80% power. Analyses were per-protocol.

Efficacy (i.e. complete TOP without need for surgical intervention) was attained for 99% and 97.4% subjects allocated to the nurse-midwife and doctor arms respectively; risk difference

1.6% with 95% CI within the margin of equivalence (0.2 - 3.0%). There were 5 subjects in the nurse-midwife arm and 12 in the doctor arm requiring surgery, most commonly due to incomplete ToP (n = 5 nurse-midwife group, n = 7 doctor group) and bleeding (unscheduled) (n = 3 doctor group); see Table 3. The authors stated there were no serious complications and no blood transfusions given.

There were 9% and 9.7% subjects in the nurse-midwife and doctor groups respectively with unscheduled visits. The proportion of subjects with complications (defined as need for causal treatment at an unscheduled visit up to 6 weeks after ToP) was comparable; 4.1% and 6.1% patients in the nurse-midwife and doctor groups respectively. The main between-group differences were pain (1.5% doctor group vs. 0.4% nurse-midwife group) and signs of infection (1.3% doctor group vs. 0.6% nurse-midwife group). See Table 4.

Second opinion consultation (doctor for nurse-midwives or second doctor for doctor group; all second opinions performed immediately by other doctors at the clinic to avoid delay to MToP) were reported for 26% (139/535) cases in the nurse midwife group and 4% (21/533) cases in the doctor group. The most common reasons for second opinion in the nurse-midwife group were ultrasound (59 cases) and prescription/second opinion for suspected bacterial vaginosis (54 cases). The authors stated the '*frequency of ultrasound consultations for nurse-midwives went down as the study progressed, indicating a learning curve*'.

Evaluator comment*: The inclusion of only healthy women in the study is not reflective of the general population and is a limitation of the study acknowledged by the authors.*

The reasons for surgery and complications are generally consistent with the known risks of MToP with mifepristone/misoprostol [1].

The proportion of cases requiring second opinion in each group is noted. However, in the Australian setting, patients would generally be referred to a radiology facility for ultrasound assessment. The authors stated nurse-midwives are not able to prescribe antibiotics for bacterial vaginosis in Sweden, which likely accounts for this between-group difference. Excluding these reasons, the main between-group difference was for 'medical reasons' (2.4% nurse-midwife group vs. 0.8% doctor group) for which no further information was provided (see Table 5).

(ii) Warriner et al. (2011) [6]

Warriner and colleagues reported a randomised, controlled, multicentre, equivalence trial in Nepal to assess whether early first trimester MToP provided by midlevel health care providers (MLP; nurses and nurse-midwives) was as safe and effective as MToP provided by doctors. The study was conducted in 5 rural district hospitals in Nepal from 15th April 2009 – 17th March 2010. The authors stated that at the time of the study, MToP service provision by nurses was limited to government facilities where a doctor was present, i.e. not independent of physician oversight. Clinical procedures for medical abortion followed the Nepalese medical abortion protocol.

Women ≥ 16 years of age with pregnancy ≤ 63 days gestation per date of LMP and as estimated by bimanual pelvic examination by the assigned healthcare provider, and residing ≤ 90 minutes from the study clinic with no contraindications to MToP were eligible to participate. Exclusion criteria included known or suspected ectopic pregnancy or undiagnosed adnexal mass, long-term corticosteroid therapy, chronic adrenal failure, inherited porphyria, haemorrhagic disorder or anticoagulant therapy, or an intrauterine device that could not be removed before administration of mifepristone.

Evaluator comment*: The exclusion criteria are generally consistent with contraindications to MS-2 Step as per the current PI [1]. The authors stated pregnancy tests and ultrasound are not routine for MToP in Nepal, although ultrasound machines were available for the study at the discretion of the*

health care provider. Use of ultrasound in the study to assess gestation was low; 0.4% MLP, 4.3% doctors.

The study included providers trained in manual vacuum aspiration (MVA); n = 11 MLP (8 staff nurses, 3 auxiliary nurse-midwives) and n = 14 doctors (6 obstetrician/gynaecologists, 3 GPs and 5 other doctors [with MBBS]). All providers received 3 day training in MToP and were certified.

Subjects were randomly assigned to MLP or doctor via a computer-generated randomisation scheme stratified by study centre. All subjects received mifepristone 200 mg orally on Day 1 and 800 microgram misoprostol tablets vaginally on Day 3 administered by the assigned provider. Subjects returned to the assigned provider for follow-up clinical assessment after 10-14 days.

The primary endpoint was complete abortion without MVA within 30 days of treatment. The secondary endpoint measured case-management decisions by recording case-management discussions and referrals between providers to assess the extent to which each group provided medical abortion services independently. Serious adverse events (SAEs; haemorrhage necessitating blood transfusion, conditions necessitating hospitalisation) were recorded and completeness of abortion and any complications identified via patient interview and clinical examination.

A sample size of 1086 women was determined to provide 80% power to demonstrate equivalence assuming a 5% margin of equivalence and 10% loss to follow-up. The primary analysis was ITT with a supplementary PP analysis on the primary endpoint conducted.

Overall, 1104 subjects were randomised, 1077 treated and 1032 included in analyses of the primary endpoint (n = 518 MLP group, n = 514 doctor group). There were 25 subjects excluded (n = 10 MLP group, n = 15 doctor group), mostly due to gestation > 9 weeks. One subject in each group had signs of ectopic or adnexal mass. Loss to follow up was low (4% both groups).

Baseline characteristics were comparable in the 2 provider groups. The mean (SD) duration of gestation by clinical examination was 6.8 (1.0) weeks and mean age of subjects 28.0 years. Complete abortion was reported for 97.3% subjects in the MLP group and 96.1% in the doctor group; risk difference within the predefined equivalence range (1.24% [95% CI: -0.53, 3.02]). PP analysis was consistent (see Table 6). The proportion of incomplete abortions was similar in both groups (n = 14 [2.7%] MLP group, n = 15 [2.9%] doctor group). All incomplete abortions and continuing pregnancies (n = 0 MLP group, n = 5 [1.0%] in doctor group) were terminated by MVA by the assigned provider. No SAEs were reported. The authors stated '*women reported typical side-effects such as nausea, vomiting, diarrhoea, abdominal pain, chills, and fever with no difference by type of provider*' although these data were not shown. In terms of the secondary endpoint, MLPs discussed < 2% cases with doctors and referred < 1% cases to doctors.

4.1.1.2. Observational studies

Jejeebhoy et al. (2012) [7]

These authors performed an observational cohort study at 5 clinics in urban areas in 2 states in India with limited access to health services, to assess whether medical abortions performed by nurses and ayurvedic physicians were as safe and effective as those done by allopathic physicians. The study was conducted from 2008 - 2010. At the time of the study, only gynaecologists and other certified allopathic physicians were able to provide abortions in India. To control for provider experience, providers with no experience in surgical or medical abortion, pelvic examination (other than academic training) or gestational age assessment were recruited; n = 10 nurses, n = 10 ayurvedic physician and n = 10 allopathic physician. All providers received medical abortion training (including classroom training, practice sessions, and training in the field with a minimum of 10 cases each of gestational age dating and assessment of completion of MToP). Assessment of subject eligibility and completed abortion

status was based on pelvic examination; ultrasonography was not used. The provider evaluations were verified by a certified abortion provider (verifier) who also prescribed the medication for MToP.

All 3 types of service providers were placed sequentially at each clinic until 35-40 medical abortions were completed, approximately 6 weeks. The study was not randomised, although subjects were not aware of which healthcare professional would provide services on the visit day.

Evaluator comment*: It is likely some subjects may have had follow-up with a different type of service provider if they presented during the latter part of a particular provider's placement. Overall, the number of subjects screened for eligibility and for abortion completeness was similar across the groups (n = 464 - 491 and n = 412 - 435 respectively). These assessments were also conducted by the verifier.*

Eligible subjects were those with pregnancy up to 8 weeks gestation (based on urine pregnancy test and pelvic examination) with no contraindications to MToP, haemoglobin ≥ 9 g/dL and residing within an hour of study site. Contraindications included suspected ectopic pregnancy, hypertension, cardiovascular disease and bronchial asthma. Subjects received mifepristone 200 mg orally on Day 1 and misoprostol 400 micrograms orally on Day 3, in line with government guidelines. Subjects returned for pelvic examination to assess for completeness of the abortion on Day 15, and Day 21 for those deemed to have an incomplete abortion.

Evaluator comment*: The study included pregnant women up to 8 weeks gestation which is more restrictive than the approved Australian population (up to 63 days gestational age). Further, the dose of misoprostol used is different (lower) than that used with MS-2 Step. No information was provided as to whether repeat doses of misoprostol were required.*

Sample size calculations estimated 380 subjects per provider arm would provide 80% power to establish equivalence between allopathic physicians and each of the other provider groups, assuming equivalence margin of 5.5% and 5% loss to follow-up. There were 1414 subjects screened and 1225 (87%) recruited. The reasons for screen failure were not stated. Loss to follow-up was small; 4 – 6% across groups.

Although this was not a randomised study, baseline demographic characteristics were generally consistent across the 3 groups. The mean age of subjects ranged from 26.6 – 27.1 years. Gestational age was not stated.

The key outcome measure was observed failure rate (proportion of subjects for whom complete information was available who had an ongoing pregnancy on Day 15, or an incomplete abortion on Day 15 or Day 21 if extended follow-up was advised). The observed failure rate was 4.6% in the nurse and allopathic physician group and 5.5% in the ayurvedic physician group with differences in failure rates (allopathic physicians vs. nurses and allopathic vs. ayurvedic physicians) within the predefined margin of statistical equivalence (Table 7). The proportion of subjects with incomplete abortion and ongoing pregnancy was comparable across groups (1.8 - 2.1% and 2.8 - 3.4% respectively). Convergence between assessments by the different healthcare providers and verifiers was high. All subjects with an ongoing pregnancy or incomplete abortion underwent MVA by the verifier. There were no serious complications and no subjects required blood transfusion or hospitalisation. Unscheduled visits (5%) or phone calls (4%) were stated to be related mostly to extent and duration of bleeding or uncertainty regarding procedure; these data were not shown.

4.1.1.3. Cochrane review – Barnard et al. (2015) [8]

A Cochrane Collaboration review by Barnard *et al.* assessed the safety and effectiveness of abortion procedures administered by MLPs compared to doctors. The review included RCTs,

prospective cohort or observational studies comparing safety and/or effectiveness of any first trimester abortion procedure by any type of MLP or doctors. Of the 8 studies meeting eligibility criteria, 5 studies assessed surgical abortions which are not considered relevant to the current submission. The 3 studies assessing medical abortion (2 RCTs, 1 cohort study); were those by Kopp Kallner *et al*., Warriner *et al*., and Jejeebhoy *et al.* discussed above [5, 6, 7].

Barnard and colleagues stated '*For medical abortion procedures the risk of failure was not different for mid-level providers or doctors (RR 0.81, 95% CI 0.48 to 1.36 from RCTs; RR 1.09, 95% CI 0.63 to 1.88 from observational studies). The quality of evidence of this outcome for the RCT analysis was considered to be high, although the quality of evidence of the observational studies was considered to be very low'.*

4.1.1.4. International experience

• The Clinical Expert stated MToP provision by MLPs such as nurses, midwives and nurse practitioners is already available and part of the standard of care in countries including Canada and the USA, with nurse practitioners in Canada able to prescribe mifepristone since 7th November 2017.

Evaluator comment*: The Health Canada Regulatory Decision Summary document to register Mifegymiso (29th July 2015, available in public domain [9]) states risk management activities included physician only dispensing and education and registration program for prescribers. In the Regulatory Decision Summary document (7th November 2017) to extend the indication for Mifegymiso from 49 to 63 days gestation, Health Canada stated 'the term "Doctors" was replaced by "health professionals" throughout the Mifegymiso product monograph as practice of medicine, including who can prescribe Mifegymiso, varies by province' [10].*

• Schummers *et al*. [11] noted mifepristone (in combination with misoprostol) was marketed in Canada in January 2017 with restrictions that were removed by the Canadian regulator in November 2017 such that mifepristone could be prescribed and dispensed as a normal prescription. The Clinical Expert stated '*Since 2017, there has not been an increase in the incidences of serious adverse events in Canada due to the change in prescriber indicating no increased risk to patients when MToP is provided by mid-level healthcare professionals*.'

The Evaluator notes Schummers and colleagues reviewed population-based administrative data from Ontario, Canada to assess abortion use, safety and effectiveness prior to availability of mifepristone (January 2012 – December 2016) and availability of mifepristone without restrictions (7th November 2017 – 15th March 2020). The dataset comprised linked records from practitioner visits, all hospital visits, and outpatient prescriptions for female Ontario residents aged 12 – 49 years who had received abortion services from 1st January 2012 - 15th March 2020.

Safety outcomes within 6 weeks after abortion included SAEs and complications of abortion. Effectiveness outcomes included incidence of subsequent uterine evacuation, ongoing intrauterine pregnancy and ectopic pregnancy diagnosed within 6 weeks of abortion. Although not the primary objective of the study, the data for first trimester medical abortions when mifepristone was available with restrictions (1st January 2017 – 6th November 2017) and when mifepristone was available without restrictions (7th November 2017 – 15th March 2020) are of most relevance to the current application to expand prescriber eligibility for MToP. These subgroup analysis results were included as supplementary tables (not provided with the reference in Module 5.4, however available in the public domain [12]); see Table 8 and Table 9.

Evaluator comment*: The short time period during which mifepristone was available with restrictions is noted and does limit interpretation of the results. Overall, SAEs and complications were low in both groups. For effectiveness outcomes, the proportion of women with ongoing pregnancy and ectopic pregnancy was similar whilst the proportion requiring subsequent uterine evacuation was lower in the mifepristone without restrictions group. The authors acknowledge early mifepristone uptake may*

be underestimated as mifepristone prescriptions dispensed after 10th August 2017 (following introduction of a universal subsidy) were universally captured whilst only mifepristone prescriptions among patients with income-based prescription subsidies and under 25 years of age were captured from January to 9th August 2017. Schummers et al. consider this limitation was mitigated by identification of medical abortions by other data. Whether this impacts the data presented for the mifepristone available with restrictions group, taking into consideration the short time period, is uncertain, and no firm conclusions can be drawn from these data.

The Clinical Expert stated '*as shown in the current Periodic Safety Report (PSUR; 1st June 2021-31st May 2022) there has been no increase or additional changes in the safety concerns monitored in Canada prior to the approval of the change of prescriber (*PSUR 1st June 2015 – 31st May 2016*) versus those that are currently monitored*'.

Evaluator comment*: The summary of safety concerns in these 2 documents is different (e004967 (0007-) - Periodic Safety Update Report 01 June 2016 to 31 May 2017 (#21) and e004967 (0007-) - Periodic Benefit Risk Evaluation Report 01 June 2021 to 31 May 2022 (#26)). The Clinical Expert did not elaborate on this point and it is not clear to the Evaluator the 'safety concerns' the Expert is referring to. The PBRER covering the period 01 June 2021 – 31st May 2022 has been submitted previously and reviewed by the TGA. Additional information was requested from the Sponsor following TGA review of the PSUR including provision of an updated RMP.*

• In the USA, trained advanced practice clinicians (including nurse practitioners, nurse-midwives and physician assistants) have been providing medical and, in some cases, early surgical abortion in 15 states since 2005 [13]. Schummers *et al*. [11] state mifepristone is approved for use in the USA with REMS restrictions (including mandatory prescriber certification, observed dosing, dispensing by the prescriber or medical facility with the exclusion of pharmacies, and submission of a prespecified patient consent form).

Evaluator comment*: From information available on the FDA website, the Mifepristone REMs Program was modified in December 2022 to remove the 'in-person' dispensing requirement and addition of certification of pharmacies. The Mifeprex product label (revised 01/2023) states Mifeprex is only available through the REMS program which includes prescriber certification, dispensing by, or under supervision of, the prescriber, or certified pharmacies [3].*

• Prescriber status for mifepristone in Europe or UK was not discussed in the Clinical Overview.

Berer (2009) [13] stated the following:

- In France and Great Britain, both medical and surgical abortions must be performed by a physician.

- In France, physicians confirm the pregnancy and conduct the follow-up visit but nurses are often responsible for all the other procedures involved in medical abortion.

- Regulations in Great Britain are already interpreted to allow nurses to administer medical abortion drugs, as long as the drugs are prescribed by a physician.

Evaluator comment*: The Evaluator notes this paper was published in 2009 and there may have been updates to medical abortion practices and prescriber eligibility in countries in Europe and the UK since then. The UK SPC for Mifepristone Linepharma [14] includes the following statement in Section 4.1, Therapeutic indications 'For termination of pregnancy, Mifepristone Linepharma 200mg tablet and prostaglandins can only be prescribed and administered in accordance with countries national laws and regulations.'*

In summary, the Clinical Expert concluded '*The proposed amendments to broaden the definition of prescriber do not pose a risk to patient safety. Evidence provided within this submission demonstrates there to be no detectable impact of MToP by appropriately trained healthcare*

professionals on patient outcomes; and that the provision of education for all prescribers will ensure a minimum baseline regardless of prescriber's background.'

4.1.2. Evaluator's assessment and recommendations

The main evidence provided to support the proposed change is from 3 studies, including data for approximately 1800 women receiving MToP up to 63 days gestation [5, 6] and approximately 1100 women receiving MToP up to 8 weeks gestation [7].

The Kopp Kallner *et al*. [5] study is considered most relevant to use in Australia. This study was conducted in a high-resource setting with ultrasound as part of the protocol, whereas the studies by Warriner *et al*. [6] and Jejeebhoy *et al*. [7] were conducted in low-resource settings. Neither of the latter 2 studies included ultrasound assessment per study protocol, nor was hCG testing utilised in the Warriner study. This does not generally align with the Australian MS-2 Step PI [1], which recommends confirmation of pregnancy duration by ultrasound in the indication, and lists 'pregnancy not confirmed by an ultrasound or biological test such as urine or serum HCG' as a contraindication. Furthermore, the study population and dose of misoprostol used in the Jejeebhoy *et al*. [7] study differs from approved use in Australia.

Although the Warriner *et al*. and Jejeebhoy *et al*. studies [6, 7] are less applicable to the Australian setting, overall there were no safety concerns with provision of MToP by MLPs identified in any of the 3 studies, with effectiveness outcomes comparable for MLPs and doctors. The risk of failure was comparable for MToP performed by MLPs and doctors in all studies and is a known risk described in the MS-2 Step PI [1]. There were no serious adverse events reported. The reasons for complications were provided by Kopp Kallner *et al*. [5] and noted to be consistent with the safety profile of MToP with mifepristone/misoprostol.

There was variability in provider experience across the 3 studies. Nurse-midwives experienced in MToP were recruited in the Kopp Kallner *et al*. [5] study with additional early pregnancy ultrasound training provided. All providers underwent MToP training in the Warriner *et al*. and Jejeebhoy *et al*. studies [6, 7]. The importance of education with regard to the MToP process was endorsed by the Clinical Expert who reiterated *'MS Health proposes to continue providing the same (existing) standardised training for all potential prescribers (as detailed in the current approved Australian RMP) and doing so will ensure a minimum baseline of education regardless of training background',* stating further *'The PI amendments proposed by MS Health simply enable individual jurisdictions to make decisions appropriate for their population'.*

Broadening the prescriber eligibility to include non-physician prescribers (in accordance with individual state and territory requirements) is consistent with established practice in Canada and the USA, noting the USA has REMS program requirements for all prescribers [3].

Overall, the Evaluator considers the evidence provided supports the proposed changes to the boxed warning of the MS-2 Step PI to amend '*medical practitioner'* to '*healthcare practitioner*' and to amend '*doctors with the appropriate qualifications and certified training'* in Section 4.2 to '*healthcare practitioners with the appropriate qualifications and certified training*' given the Sponsor proposes to maintain the existing standardised training for prescribers. However, the Evaluator was advised by the Risk Management Section the Sponsor proposes to remove the requirement for prescriber certification from the PI as part of the updated RMP provided to TGA (dated 17th February 2023). The proposed removal of prescriber certification from the PI does potentially bring into question the Sponsor's justification for the proposed changes to the PI as the Clinical Expert's assertion regarding a minimum baseline of education irrespective of training background would not hold if the requirement for prescriber certification is removed.

The proposed changes to the boxed warning and Section 4.2 give rise to inconsistencies in the PI which have not been addressed, and are drawn to the attention of the Delegate:

• Section 4.2 Dose and method of administration:

The Sponsor states in the Cover letter the application proposes to amend the reference to 'doctors' in Section 4.2 to 'healthcare practitioners'.

However Section 4.2 includes the text '*When MS-2 Step fails to cause termination of intra-uterine pregnancy, the patient should return to the treating doctor for assessment and discussion of treatment options, which may include pregnancy termination by surgery*.'

This text is not consistent with the proposed changes advising patients receiving these medications are followed up by a healthcare practitioner, preferably the prescriber.

• Section 4.4 Special warnings and precautions for use:

Section 4.4 includes information regarding particular co-morbidities as follows:

Take special care in case of suspected acute adrenal failure. In case of suspected acute adrenal failure, dexamethasone administration is recommended (please refer to the dexamethasone Product Information).

Due to the antiglucocorticoid activity of mifepristone, the efficacy of long-term corticosteroid therapy, including inhaled corticosteroids in asthmatic patients, may be decreased during the 3 to 4 days following intake of mifepristone. Therapy should be adjusted.

Patients with these medical comorbidities may require additional medical management such as adjustment of inhaled corticosteroid (ICS) therapy for asthma patients for example, that may be outside the scope of practice of non-physician healthcare providers. The Sponsor has not specifically addressed how patients with relevant medical comorbidities as described in the PI will be managed by non-physician healthcare providers.

• Section 4.4 Special warnings and precautions for use and Section 4.8 Adverse effects (undesirable effects):

Section 4.4 includes text regarding cases of serious bacterial infection, including very rare cases of fatal septic shock, with statements in the 'Infection' subsection specifically referring to 'doctors' as follows:

- *'Treating doctors evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event.'*

This text is not consistent with the proposed changes advising patients receiving these medications are followed up by a healthcare practitioner, preferably the prescriber. It would seem appropriate all healthcare providers would need to be aware of this risk.

- *'These symptoms, even without a fever, may indicate Clostridium sordellii infection. Strong consideration should be given to obtaining a complete blood count in these patients. Significant leukocytosis with a marked left shift and haemo-concentration may be indicative of sepsis. Doctors should consider immediately initiating treatment with antibiotics that includes coverage of anaerobic bacteria such as Clostridium sordellii.'*

This text is also included in Section 4.8 of the PI.

These statements refer to clinical management of a potentially serious infection/possible sepsis including initiation of appropriate antibiotic therapy. As aforementioned, it is not clear whether this is within the scope of practice of non-physician healthcare providers.

• Section 4.6 Fertility, pregnancy and lactation:

Section 4.6 includes the following text*:*

'To avoid the potential exposure of a subsequent pregnancy to MS-2 Step it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after administration of MS-2 Step.'

This is considered important safety information. It is not clear whether prescription of reliable contraceptive methods is within the scope of practice for all healthcare providers for whom expanded prescriber eligibility is proposed (acknowledging different state/territory legislation), and therefore if some patients may need to be referred to a different healthcare provider. Of note to the Delegate, 'Return to fertility' is included in the 'Serious warnings and precautions' box in the Canadian Mifegymiso product monograph [2].

These outstanding issues may require appropriate risk minimisation strategies such as updates to the educational materials.

5. Other issues

As discussed in Section 3, the Sponsor provided an updated RMP (v4.0, 17th February 2023) during the evaluation phase of the current submission. The RMP Evaluator advised 2 recommendations for Delegate/Clinical evaluator consideration:

(i) The Sponsor proposes to remove the requirement for prescriber certification from the PI. The RMP Evaluator recommended the Delegate/Clinical evaluator consider the proposed PI change from the clinical perspective, and whether advisory committee advice is needed.

Evaluator comment*: This Type J application proposes to expand prescriber eligibility for MS-2 Step. Removal of prescriber certification was not proposed in the PI submitted with the application, and not discussed in the Clinical Overview Addendum. On the contrary, to support the expansion of prescriber eligibility, the Clinical Expert stated 'MS Health proposes to continue providing the same (existing) standardised training for all potential prescribers (as detailed in the current approved Australian RMP) and doing so will ensure a minimum baseline of education regardless of training background …. The PI amendments proposed by MS Health simply enable individual jurisdictions to make decisions appropriate for their population'. This statement is not considered consistent with the proposed change to remove prescriber certification.*

Whether advisory committee advice is needed regarding the proposed change is for the consideration of the Delegate.

(ii) The Sponsor proposes to remove the requirement for a Sponsor provided 24-hour phone service. The RMP Evaluator recommended the Delegate/Clinical evaluator consider the proposed PI change from the clinical perspective, in particular, whether and how much value the 24-hour phone service adds to patient safety outcomes.

Evaluator comment: *The Sponsor has not provided any data in the current submission regarding use of the 24-hour phone service in Australia nor was removal of this statement from Section 4.4 of the PI discussed in the Clinical Overview Addendum. No clinical comment regarding this proposed change is therefore able to be provided.*

6. First round recommendation regarding authorisation

At this stage, approval of the variation to the register entry and Australian PI for MS-2 Step composite pack (mifepristone/misoprostol) is not able to be recommended for the following reasons:

- The Evaluator considers the data provided in the submission supports the proposed changes to the boxed warning to amend '*medical practitioner'* to '*healthcare practitioner'* and to amend '*doctors with the appropriate qualifications and certified training'* in Section 4.2 to '*healthcare practitioners with the appropriate qualifications and certified training*' (in accordance with individual state and territory requirements) on the basis the existing standardised training for

all potential prescribers is maintained as stated by the Clinical Expert. However, the Sponsor's proposal to remove the mandatory education program as proposed in an updated RMP subsequently submitted to the TGA is inconsistent with the Clinical Expert's assertion that a minimum baseline level of education will be provided for all prescribers, and does not support the justification for the prescriber eligibility changes.

7. Clinical questions

1. The RMP (dated 17th February 2023) provided to the TGA separate from the Type J dossier proposes removal of the requirement for prescriber certification. Please state how this proposed amendment aligns with the justification provided in the Clinical Overview Addendum to support the proposed expansion of prescriber eligibility - '*MS Health proposes to continue providing the same (existing) standardised training for all potential prescribers (as detailed in the current approved Australian RMP) and doing so will ensure a minimum baseline of education regardless of training background'.*

2. Please confirm whether the standardised training program will remain in place for all prescribers of MS-2 Step in Australia.

If not, please state how the risk with the proposed expansion of prescriber eligibility from medical professional to healthcare professional will be minimised.

8. Review of Sponsor's response

The Sponsor stated the evaluation report was reviewed for errors of fact or omissions and no corrections are required.

As part of the Section 31 response the Sponsor provided an updated PI (e004967 (0012-) - Product Information - Annotated) which includes additional proposed changes to Section 4.2 to remove '*and certified training'* as follows:

MS-2 Step should only be prescribed by healthcare practitioners~~doctors~~ with the appropriate qualifications ~~and certified training~~. Ectopic pregnancy should be excluded, an intrauterine device (IUD) (if present) must be removed, consent must be obtained and patients must have the ability to access 24-hour emergency care if and when required for incomplete abortion or bleeding.

The Sponsor response to the Clinical Questions (e004967 (0012-) - Response - 2023-04 Response to S31 Request, MS3) is copied below:

Question 1: The RMP (dated 17th February 2023) provided to the TGA separate from the Type J dossier proposes removal of the requirement for prescriber certification. Please state how this proposed amendment aligns with the justification provided in the Clinical Overview Addendum to support the proposed expansion of prescriber eligibility - '*MS Health proposes to continue providing the same (existing) standardised training for all potential prescribers (as detailed in the current approved Australian RMP) and doing so will ensure a minimum baseline of education regardless of training background'.*

Sponsor response: The Sponsor confirms that the existing standardised training (the Medical Education Program) will still be available for all healthcare practitioners that prescribe MS-2 Step via the existing online website (www.ms2step.com.au). The change proposed in the most recent submitted update to the RMP was to remove the mandatory aspect of the training and

the subsequent certification. As detailed in Question 2 below, it is the prescriber's obligation to acquire the knowledge and skill to prescribe a drug safely (which is a fundamental aspect of their practice), regardless of whether the RMP includes mandatory certification of prescribers. In the decade since the registration of MS-2 Step, the Sponsor has seen a number of education and training resources developed to support prescribers beyond that offered by the Medical Education Program included in the initial registration of the product. Examples include:

- Women's Health Victoria (https://whvtraining.com.au/product/early_medical_abortion/),

- Family Planning NSW (https://www.fpnsw.org.au/medical-abortion-online),

- the AusCAPPS network, an online community of practice network to support providers of early medical abortion (https://medcast.com.au/communities/auscapps)

- the compulsory module for RANZCOG trainees

- electronic Therapeutic Guidelines.

These resources are all available for clinicians who have an interest and wish to understand more about this area of medicine. The Sponsor notes that these alternate training resources are not subject to TGA oversight via incorporation into formal documentation such as an RMP. The need for the current approved restriction criteria (i.e. mandatory certification and training), while prudent and likely necessary at the time of first registration, is diminished in view of such extensive experience and availability of training.

The Sponsor would also request the assessor consider MS-2 Step in comparison with other products on the ARTG (with greater risk profiles), but which don't have the same restrictions or mandatory programs in place before the product can be prescribed. The expectation for these other products being that a prescriber would be professionally competent before prescribing any product. The Sponsor is simply asking the same standard to be applied to MS-2 Step.

Therefore, to reiterate the above, the Sponsor does not plan to remove the Medical Education Program, they only propose to remove this from being mandatory and subsequently not part of the RMP.

Question 2: Please confirm whether the standardised training program will remain in place for all prescribers of MS-2 Step in Australia.

If not, please state how the risk with the proposed expansion of prescriber eligibility from medical professional to healthcare professional will be minimised.

Sponsor response: As above, the Sponsor proposes to remove the mandatory component and associated certification of the Medical Education Program (currently included as part of the approved RMP and PI for MS-2 Step).

As detailed in the recently submitted draft RMP, the Medical Education Program will still be available to all treating healthcare practitioners. The sponsor is committed to continuing to improve patient access to the product by ensuring that training is available for prescribers and dispensers.

In accordance with the Australian Health Practitioner Regulation Agency (AHPRA) position, when a practitioner's practice is believed to be, or may be, unsatisfactory:

"Unsatisfactory professional performance, of a registered health practitioner, means the knowledge, skill or judgment possessed, or care exercised by, the practitioner in the practice of the health profession in which the practitioner is registered is below the standard reasonably expected of a health practitioner of an equivalent level of training or experience [[1]]."

Therefore, the prescriber's obligation to acquire the knowledge and skill to prescribe a drug safely is a fundamental aspect of their practice, regardless of whether the prescriber is a medical professional or healthcare professional. This is the case for most (if not all) other medicines where a prescriber is expected to understand when the medication can and cannot be prescribed; any testing, monitoring or other activity that must occur before administration; obtaining informed consent; and providing follow-up care as appropriate.

Therefore, the Sponsor does not believe that the removal of the mandatory certification (by completion of the Medical Education program) will result in any additional risk when the prescriber eligibility is changed from a medical professional to a healthcare professional as the Medical Education Program will continue to be available online via the existing website (www.ms2step.com.au), along with other education and training resources that are available over and above the Sponsor specific training.

Evaluator comment: The Sponsor's responses are noted. The justification provided by the Clinical Expert in the Clinical Overview Addendum to expand prescriber eligibility to include non-physician prescribers (in accordance with individual state and territory requirements) included assurance the existing standardised training for all potential prescribers as per current approved Australian RMP (i.e. mandatory practitioner training and certification) would be maintained, and was supported by data provided in the dossier. As noted in this report, all providers underwent MToP training in the Warriner *et al*. and Jejeebhoy *et al*. studies (including certification in the Warriner *et al*. study) [6, 7], and the Kopp Kallner study [5] recruited nurse-midwives experienced in MToP who received additional ultrasound training. The proposed removal of '*and certified training*' from the proposed PI provided with the Section 31 response does not align with the Clinical Expert's assertion that '*a minimum baseline of education regardless of training background will continue to be provided*' and data included in the submission to support the proposed expansion of prescriber eligibility.

9. Second round recommendation regarding authorisation

A recommendation regarding authorisation of the Type J application for MS-2 Step composite pack is not able to be provided.

As stated at Round 1, the data provided in the submission support the proposed changes to the boxed warning to amend '*medical practitioner'* to '*healthcare practitioner'* and to amend '*doctors with the appropriate qualifications and certified training'* in Section 4.2 to '*healthcare practitioners with the appropriate qualifications and certified training*' (in accordance with individual state and territory requirements) on the basis the existing standardised training for all potential prescribers is maintained.

However, the Sponsor also proposes to remove '*and certified training'* from the PI provided with the Section 31 response. The proposed changes to the PI include expansion of prescriber eligibility more broadly with proposed changes to current risk management measures to remove mandatory certified training for prescribers. There is uncertainty regarding the risk of expanding prescriber eligibility and removing the requirement for certified training. ACM advice is recommended.

The Delegate's attention is drawn to inconsistencies noted in Sections 4.2, 4.4, 4.6 and 4.8 of the MS-2 Step composite pack PI with the proposed expansion of prescriber eligibility as discussed in Section 4.1.2 of this report. These are considered outstanding issues to be addressed should the application be approved.

10. References

1. Australian MS-2 Step PI. Available at TGA PI/CMI repository. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent=&id=CP-2014-PI-01965-1&d=20230222172310101

2. Canadian Mifegymiso Product Monograph (date of revision 17th June 2022). Provided in Module 5.4 (e004967 (0007-) - Canada SmPC)

3. US Mifeprex Product Label. Revised 01/2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020687Orig1s025Lbl.pdf

4. WHO Abortion Care Guideline 2022. Geneva: World Health Organization; 2022. Provided in Module 5.4 (e004967 (0007-) - WHO - Abort Care guidelines - 2022)

5. Kopp Kallner H, Gomperts R, Salomonsson E, Johansson M, Marions L, Gemzell-Danielsson K. The efficacy, safety and acceptability of medical termination of pregnancy provided by standard care by doctors or by nurse-midwives: a randomised controlled equivalence trial. *BJOG*. 2015;122:510-517. Provided in Module 5.4 (e004967 (0007-) - Kopp-Kallner 2014).

6. Warriner IK, Wang D, Huong NTM, Thapa K, Tamang A, Shah I *et al*. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomised controlled equivalence trial in Nepal. *Lancet*. 2011;377:1155-1161. Provided in Module 5.4 (e004967 (0007-) - Warriner 2011)

7. Jejeebhoy SJ, Kalyanwala S, Mundle S, Tank J, Zavier AJF, Kumar R *et al*. feasibility of expanding the medication abortion provider baser in India to include ayurvedic physicians and nurses. *Int Perspect Sex Reprod Health*. 2012;38:133-142. Provided in Module 5.4 (e004967 (0007-) - Jejeebhoy 2012)

8. Barnard S, Kim C, Park MH, Ngo TD. Doctors or mid-level providers for abortion. *Cochrane Database of Systematic Reviews* 2015, Issue 7. Art. No.: CD011242. DOI: 10.1002/14651858.CD011242.pub2. Provided in Module 5.4 (e004967 (0007-) - Barnard 2015)

9. Regulatory Decision Summary – Mifegymiso - Health Canada. https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detail.php?linkID=RDS00032

10. Regulatory Decision Summary – Mifegymiso - Health Canada. https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detail.php?linkID=RDS00294

11. Schummers L, Darling EK, Dunn S, McGrail K, Gayowsky A, Law MR *et al*. Abortion safety and use with normally prescribed mifepristone in Canada. *N Engl J Med*. 2022;386:57-67. Provided in Module 5.4 (e004967 (0007-) - Schummers 2022)

12. Schummers L, Darling EK, Dunn S, McGrail K, Gayowsky A, Law MR *et al*. Abortion safety and use with normally prescribed mifepristone in Canada. *N Engl J Med*. 2022;386:57-67. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7489974/

13. Berer M. Provision of abortion by mid-level providers: international policy, practice and perspectives. *Bull World Health Organ*. 2009;87:58-63. Provided in module 5.4 (e004967 (0007-) - Berer 2009)

14. UK SPC Mifepristone Linepharma 200 mg tablet (revised 27/10/22). https://mhraproducts4853.blob.core.windows.net/docs/72e81b0722b04c4d065babba78a7be4e0dbe89fb

11. Supporting information, tables and figures

11.1. Study synopses

Not applicable.

11.2. Other supporting tables and figures

Table 1: Prescribers: number of women of childbearing age per prescriber by region

	ACT	NSW	NT	QLD	SA	TAS	VIC	WA
Metro	2933	2246	-	2173	2681	-	1738	3132
Regional	13	1656	492	1592	2795	1068	1083	1666
Remote	-	2825	612	644	1685	2106	0	961

Note: a zero value indicates there are locations in that state or territory with that classification but no prescribers or dispensers are registered. A dash signifies there are no locations in that state or territory that fall under that classification. Classifications align with definitions provided by the Australian Bureau of Statistics (ABS).

Source: MS Health – July 2022 Update, Dispenser and prescriber program, Module 5.4 (e004967 (0007-) - MS Health 2022 - Update)

Table 2: Demographic characteristics of women

	Allocated to nurse-midwife *n* = 535 Median (range)	Allocated to doctor *n* = 533 Median (range)
Age	27 (18–47)	27 (18–46)
Gestational age at ultrasound (days)	45 (30–63)	45 (28–63)
Gravidity	2 (0–13)	2 (0–14)
Parity	0 (0–5)	0 (0–6)
Miscarriage	0 (0–4)	0 (0–5)
TOP, surgical	0 (0–3)	0 (0–5)
TOP, medical	0 (0–4)	0 (0–5)
Vaginal deliveries	0 (0–5)	0 (0–6)
Caesarian section	0 (0–3)	0 (0–3)

There were no statistically significant differences between the groups.

Source: Table 1, Kopp Kallner et al. [5]

Table 3: Reasons for surgery

Reason for surgery	Allocated to nurse midwife (N=5)	Allocated to physician (N=12)	Total of women
Incomplete TOP	5	7	12
Bleeding (unscheduled)	0	3	3
Prolonged bleeding	0	1	1
Pain	0	1	1
Total	5	12	17

None of the differences reached statistical significance

Source: Table S2, Kopp Kallner et al. [5]

Table 4: Reason for complication (defined as an unscheduled visit for symptoms that led to further treatment)

Reason for the unscheduled visit	Allocated To nurse midwife (%) (n=493, 41 missing)	Allocated to physician (%) (n=472, 61 missing)	Total (%) (n=965, 102 missing)
Bleeding	2 (0.4)	4 (0.8)	6 (0.6)
Bleeding due to incomplete TOP	8 (1.6)	5 (1.1)	13 (1.3)
Symptoms of continuing pregnancy	0 (0)	1 (0.2)	1 (0.1)
Pain	2 (0.4)	7 (1.5)	9 (0.9)
Positive u-hCG[1]	4 (0.8)	2 (0.4)	6 (0.6)
Prolonged bleeding	0 (0)	2 (0.4)	2 (0.2)
Signs of infection	3 (0.6)	6 (1.3)	9 (0.9)
Unknown	1 (0.2)	2 (0.4)	3 (0.3)
Total	20 (4.1)	29 (6.1)	49 (5.1)

None of the differences reached statistical significance (p>0.05).U-hcg= urinary human chorionic gonadotropin with cut off 500 IE/ml (specified in the text)

Source: Table S3, Kopp Kallner et al. [5]

Table 5: Reason for second opinion consultation

Reason for consultation	Allocated to nurse-midwife *n* (%)	Allocated to doctor *n* (%)	Total *n* (%)
Multiple pregnancy	7 (1.3)	1 (0.2)	8 (0.7)
High serum hCG*	0 (0)	1 (0.2)	1 (0.9)
Information	3 (0.6)	1 (0.2)	4 (0.4)
Medical reasons	13 (2.4)	4 (0.8)	17 (1.6)
Ultrasound	59 (11)	8 (1.5)	67 (6.3)
Unknown	3 (0.6)	4 (0.8)	7 (0.7)
Prescription/second opinion for suspected bacterial vaginosis	54 (10)	4 (0.8)	58 (5.4)
Total	535	533	1068

*hCG, human chorionic gonadotropin.

Source: Table 3, Kopp Kallner et al. [5]

Table 6: Outcomes of medical abortion by type of provider

	MLP	Doctors	Risk difference for the primary endpoint* (95% CI)	Risk difference for the primary endpoint-adjusted analysis† (95% CI)
ITT analysis				
Number of women	518	514	..	..
Complete abortion	504 (97·3%)	494 (96·1%)	1·24% (–0·53% to 3·02%)	1·49% (–0·17% to 3·14%)
Incomplete abortion	14 (2·7%)	15 (2·9%)	..	..
Continuing pregnancy	0	5 (1·0%)	..	..
PP analysis				
Number of women	504	472	..	..
Complete abortion	490 (97·2%)	455 (96·4%)	0·89% (–1·11% to 2·88%)	1·12% (–0·70% to 2·93%)
Incomplete abortion	14 (2·8%)	12 (2·5%)	..	..
Continuing pregnancy	0	5 (1·1%)	..	..

MLP=midlevel health-care providers. ITT=intention to treat. PP=per protocol. *Estimated from a generalised estimating equation model with treatment as the fixed effect and service provider as a random effect. †Adjusted for woman's age and duration of gestation.

Source: Table 4, Warriner et al. [6]

Table 7: Medication abortion failure rates, by provider type, and differences in failure rates between provider types (and 95% CI)

Indicator	Provider type			Difference	
	Ayurvedic physicians (N=382)	Nurses (N=393)	Allopathic physicians (N=389)	Ayurvedic vs. allopathic	Nurses vs. allopathic
Observed failure rate	5.5	4.6	4.6	0.9 (–2.2 to 4.0)	–0.1 (–3.0 to 2.9)
Ongoing pregnancy	2.1	1.8	1.8	0.3 (–1.7 to 2.3)	0.0 (–1.9 to 1.8)
Incomplete abortion	3.4	2.8	2.8	0.6 (–1.9 to 3.0)	0.0 (–2.4 to 2.3)

Note: Equivalence is indicated when the 95% confidence interval for the difference in failure rates between the allopathic physician group and each of the other two groups (ayurvedic physicians and nurses) lie within the predetermined margin of equivalence (±5.5%).

Source: Table 3, Jejeebhoy et al. [7]

Table 8: Subgroup Analysis: First Trimester Medication Abortion - Safety and Effectiveness

Abortion safety and effectiveness outcomes according to mifepristone regulatory period among first trimester medication abortions only in Ontario, Canada: January 2012 – December 2016 vs. November 7 2017 - March 15 2020

Policy period	Pre-mifepristone Jan 2012- Dec 2016	Mifepristone with restrictions Jan – Nov 6 2017	Mifepristone as a normal prescription Nov 7 2017 – Mar 2020
First trimester medication abortions per period	2,956	2,671	25,754
	n (%)	n (%)	n (%)
Abortion safety outcomes			
Severe adverse events*	0 (0.00)	0 (0.00)	<6**** (n/a)
Abortion complications**	15 (0.51)	24 (0.90)	196 (0.76)
Abortion effectiveness outcomes			
Subsequent uterine evacuation***	344 (11.6)	239 (8.9)	1,160 (4.5)
Intrauterine pregnancy continuing to subsequent delivery	0 (0.00)	7 (0.26)	34 (0.13)
Ectopic pregnancy detected post-abortion	19 (0.64)	13 (0.49)	89 (0.35)

* Severe adverse event includes blood transfusion, abdominal surgery (laparotomy, laparoscopy, hysterectomy), ICU admission, or sepsis, all concurrent with an abortion complication. See detailed definition in Supplemental Table 1.
** Abortion complications include incomplete or complete abortion complicated by infection, hemorrhage, embolism, damage to pelvic organs, venous complications, or other complications after an induced abortion. See detailed definition in Supplemental Table 1.
***Subsequent uterine evacuation includes aspiration, re-aspiration, or subsequent abortion procedure in the same pregnancy.
**** Cells with fewer than 6 events cannot be reported due to privacy and confidentiality requirements of our data steward.

Source: Table S5, Schummers et al. [9]

Table 9: Subgroup Analysis: First Trimester Medication Abortion - Severe Adverse Event and Complication Components

Incidence of components of severe adverse event and abortion complication outcomes according to mifepristone practice restriction policy periods among first trimester medication abortions only in Ontario, Canada: January 2012 – December 2016 vs. November 7 2017 - March 15 2020

Policy period	Pre-mifepristone Jan 2012- Dec 2016	Mifepristone with restrictions Jan – Nov 6 2017	Mifepristone without restrictions Nov 7 2017 – Mar 2020
	n (%)	n (%)	n (%)
Severe adverse event components			
Blood transfusion	0 (0.00)	0 (0.00)	0.03
Abdominal surgery	0.00	<6*** (n/a)	0.06
ICU admission	0.00	0.00	<6*** (n/a)
Sepsis	0.00	0.00	<6*** (n/a)
Abortion complication components			
Infection	<6***	<6*** (n/a)	0.08
Hemorrhage	0.37	0.60	0.49
Shock	0.00	0.00	0.00
Renal failure	0.00	0.00	0.00
Damage to pelvic organs	0.00	<6***	0.00
Other	<6***	<6***	0.21

*** Cells with fewer than 6 events cannot be reported due to privacy and confidentiality requirements of our data steward.

Source: Table S6, Schummers et al. [9]

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au

s22 [redacted]

From: DUFFY, Tracey
Sent: Wednesday, 24 May 2023 12:39 PM
To: HENDERSON, Nick; s22 [redacted]
Cc: LANGHAM, Robyn
Subject: RE: FW: ACM 39 (June 2023) Report and Agenda [SEC=OFFICIAL]

Ok thanks
s22 [redacted] - I don't need to see the agenda items.
I note the meeting is on during SE so we won't get questions about any outcome either.
Tracey

Sent from Workspace ONE Boxer

On 24 May 2023 at 12:05:50 pm ACST, HENDERSON, Nick <Nick.Henderson@health.gov.au> wrote:

Hi Tracey
The only one that stands out is the consideration of removing the restrictions in the PI for MS- 2Step. This has received media attention and Robyn and I are also fielding calls and text messages form Minister Kearney's office on when a decision will be made. But looking at the comment in the last column (below), it should be well received.
Nick

2.13	Type J (Variation to the registered entry resulting in a change in PI)	mifepristone/misoprostol (**MS-2 Step**) PM-2022-05475-1-5 *MS Health Pty Ltd* TRIM - Delegates Overview: D23-5368342 Full agenda package: Available 25 May	Section 4.2 of the current PI advises MS-2 Step can only be prescribed by doctors with the appropriate qualifications and certified training. The Sponsor proposes to amend 'medical practitioner' in the boxed warning and 'doctors' in Section 4.2 of the PI to 'healthcare practitioners' as well as remove the requirement for prescriber certification. Removal of 24-hour phone service for patients is also proposed.	Same

From: DUFFY, Tracey <Tracey.Duffy@health.gov.au>
Sent: Wednesday, 24 May 2023 11:56 AM
To: s22 [redacted]@health.gov.au>; HENDERSON, Nick <Nick.Henderson@health.gov.au>
Subject: Re: FW: ACM 39 (June 2023) Report and Agenda [SEC=OFFICIAL]
Thanks - Nick are any of the agenda items going to be contentious or have any media scrutiny?

Sent from Workspace ONE Boxer
On 24 May 2023 at 11:20:01 am ACST, s22 [redacted]@health.gov.au> wrote:

Dear Tracey

FYI
Please let me know if you want to see/discuss any of the agenda papers. You are not attending this meeting due to Senate Estimates.
Regards

s22
s22
Health Products Regulation Group
Australian Government, Department of Health and Aged Care
T: s22 | E: s22 @health.gov.au
PO Box 100, Woden ACT 2606, Australia
The Department of Health and Aged Care acknowledges First Nations peoples as the Traditional Owners of Country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

From: s22 @health.gov.au>
Sent: Tuesday, 23 May 2023 3:56 PM
To: s22 @health.gov.au>; LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>; HENDERSON, Nick <Nick.Henderson@health.gov.au>
Cc: s22 @health.gov.au>; SIMPSON, Andrew <Andrew.Simpson@health.gov.au>; s22 @health.gov.au>; s22 @health.gov.au>; s22 @health.gov.au>
Subject: ACM 39 (June 2023) Report and Agenda [SEC=OFFICIAL]
Good afternoon All,
Please see attached the Deputy Secretary brief for ACM 39 (1 and 2 June 2023) including TRIM links to Delegate's Overviews and agenda packages (also available via D23-5399747)
This meeting will be held as a face to face meeting here at the TGA (we note that Tracey will be an apology for this meeting).
The meeting timetable is available at D23-5364821.
Thank you.
Kind regards,

s22
ACM Secretariat and Prescription Medicine Expert Advice Service
Prescription Medicines Authorisation Branch
Phone: s22 | Email: s22 @health.gov.au

Therapeutic Goods Administration
Department of Health and Aged Care
PO Box 100
Woden ACT 2606
www.tga.gov.au

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This response is general information given to you without prejudice; it is not binding on the TGA and you should get your own independent legal advice to ensure that all the legislative requirements are met.

[SEC=OFFICIAL]

[SEC=OFFICIAL]

From: s22
To: LANGHAM, Robyn; s22 ; HENDERSON, Nick; SIMPSON, Andrew; AST Application Support Team; s22 ; Streamlined Submission; DUFFY, Tracey; s22 ; KAY, Elspeth
Cc: s22
Subject: **URGENT MEDIA RELEASE - PBS - MS-2 Step - Type J - PM-2022-05475-1-5 - preparing for imminent decision [SEC=OFFICIAL:Sensitive]
Date: Thursday, 22 June 2023 12:44:28 PM
Attachments: image004.png
image005.png
image007.png
image008.png
MeltWater Release - MS Health - MS-2 Step - Amended PI+ap.docx
image002.png
image003.png
image009.png

Hi All
Please see the attached draft Media Release in relation to the amendments to restrictions on prescribing of MS-2 Step.
The draft has been cleared by Nick and Adriana (TAAD). TAAD are liaising with MS Health on next steps to progress PBS listing.
Happy to discuss

s22
Director – Applications, Exports and Engagement
Prescription Medicines Authorisation Branch
Medicines Regulation Division | Therapeutic Goods Administration
Australian Government, Department of Health and Aged Care
T: s22 | E: s22 @health.gov.au
PO Box 100, Woden ACT 2606, Australia

The Department of Health and Aged Care acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to elders both past and present

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From: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Sent: Wednesday, 21 June 2023 9:39 AM
To: s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 @Health.gov.au>; HENDERSON, Nick <Nick.Henderson@health.gov.au>; SIMPSON, Andrew <Andrew.Simpson@health.gov.au>; AST Application Support Team s22 @health.gov.au>
Cc: s22 @health.gov.au>; Streamlined Submission s22 @health.gov.au>; DUFFY, Tracey <Tracey.Duffy@health.gov.au>; s22 @health.gov.au>; KAY, Elspeth <Elspeth.KAY@Health.gov.au>
Subject: RE: Update - PBS - MS-2 Step - Type J - PM-2022-05475-1-5 - preparing for imminent decision [SEC=OFFICIAL:Sensitive]
Thanks again s22
robyn

From: s22 @health.gov.au>
Sent: Wednesday, 21 June 2023 9:37 AM
To: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>; s22 s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 @Health.gov.au>; HENDERSON, Nick <Nick.Henderson@health.gov.au>; SIMPSON, Andrew <Andrew.Simpson@health.gov.au>; AST Application Support Team

s22 [redacted] @health.gov.au>
Cc: s22 [redacted] @health.gov.au>; Streamlined Submission
s22 [redacted] @health.gov.au>; DUFFY, Tracey <Tracey.Duffy@health.gov.au>;
s22 [redacted] @health.gov.au>; KAY, Elspeth <Elspeth.KAY@Health.gov.au>
Subject: Update - PBS - MS-2 Step - Type J - PM-2022-05475-1-5 - preparing for imminent decision [SEC=OFFICIAL:Sensitive]

Hi Nick and Robyn,

I've talked with the PBAC secretariat this morning. Here're some updates:

- Submission to change to PBS streamlined authority: Yes, this was recommended by the PBAC at its March meeting. It hasn't been announced as the department is waiting for the required documents from the sponsor who didn't know they had to submit the documents.
- Submission to amend/remove treatment criteria under PBS authority 'must be treated by a prescriber who is registered with the MS-2-Step Prescribing Program' (https://www.pbs.gov.au/medicine/item/10211K.): No, no submission was considered by PBAC at its March meeting. The PBS secretariat has received the submissions for PBAC to consider at its next meeting. They will search through the list and confirm whether the sponsor has made a submission.
- Process to amend/change treatment criteria: Unlike submissions for market authorisation, submissions to PBAC do not have to be made by the sponsor. If the sponsor hasn't made the submission, the Department, following the TGA's decision, can decide to find a different applicant, or even be the applicant. The question is whether there is such appetite. They will escalate the question and provide advice after a discussion by the SES.
- Confirmation of the TGA's imminent decision: They have asked us to hold off the public announcement until they have provided their input, but they do understand that we have to make the announcement and the decision very soon. They will provide written advice on the above issues ASAP, hopefully before mid-day.

I'll continue to follow up and send response from TAAD.

Regards,

s22 [redacted]
Principal Evaluator
Risk Management Section
Pharmacovigilance Branch

Phone: s22 [redacted]
Email: s22 [redacted] @health.gov.au

Therapeutic Goods Administration
Department of Health and Aged Care
PO Box 100
Woden ACT 2606
www.tga.gov.au

Important: *This transmission is intended only for the use of the addressee and may contain confidential or legally privileged information. If you are not the intended recipient, you are notified that any use or dissemination of this communication is strictly prohibited. If you receive this transmission in error please notify the author immediately and delete all copies of this transmission.*

From: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Sent: Tuesday, 20 June 2023 5:21 PM

To: s22 @health.gov.au>; s22 @health.gov.au>; s22 @health.gov.au>; s22 @Health.gov.au>; HENDERSON, Nick <Nick.Henderson@health.gov.au>; SIMPSON, Andrew <Andrew.Simpson@health.gov.au>; AST Application Support Team s22 @health.gov.au>
Cc: s22 @health.gov.au>; Streamlined Submission s22 @health.gov.au>; DUFFY, Tracey <Tracey.Duffy@health.gov.au>; s22 @health.gov.au>
Subject: RE: RMS advice: MS-2 Step - Type J - PM-2022-05475-1-5 - preparing for imminent decision [SEC=OFFICIAL:Sensitive]

Thanks,
Would be nice to have it all tidy for an announcement..
robyn

From: s22 @health.gov.au>
Sent: Tuesday, 20 June 2023 5:15 PM
To: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>; s22 @health.gov.au>; s22 @health.gov.au>; s22 @Health.gov.au>; HENDERSON, Nick <Nick.Henderson@health.gov.au>; SIMPSON, Andrew <Andrew.Simpson@health.gov.au>; AST Application Support Team s22 @health.gov.au>
Cc: s22 @health.gov.au>; Streamlined Submission s22 @health.gov.au>; DUFFY, Tracey <Tracey.Duffy@health.gov.au>; s22 @health.gov.au>
Subject: RE: RMS advice: MS-2 Step - Type J - PM-2022-05475-1-5 - preparing for imminent decision [SEC=OFFICIAL:Sensitive]

Hi Robyn,
I'll follow up with TAAD on this question. May not be a quick answer tonight. My understanding is that the request to change to authority streamlined script didn't include the removal of prescriber registration, as the PBAC has made the decision to follow TGA requirements on matters like this several years back.
I'll let you all know as soon as I have any update.
Regards,

s22
Principal Evaluator
Risk Management Section
Pharmacovigilance Branch

Phone: s22
Email: s22 @health.gov.au

Therapeutic Goods Administration
Department of Health and Aged Care
PO Box 100
Woden ACT 2606
www.tga.gov.au

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From: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Sent: Tuesday, 20 June 2023 5:07 PM
To: s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>; s22 s22 @Health.gov.au>; HENDERSON, Nick <Nick.Henderson@health.gov.au>; SIMPSON, Andrew <Andrew.Simpson@health.gov.au>; AST Application Support Team s22 @health.gov.au>
Cc: s22 @health.gov.au>; Streamlined Submission s22 @health.gov.au>; DUFFY, Tracey <Tracey.Duffy@health.gov.au>; s22 @health.gov.au>
Subject: RE: RMS advice: MS-2 Step - Type J - PM-2022-05475-1-5 - preparing for imminent decision [SEC=OFFICIAL:Sensitive]

Thanks all..
I had not realised there was still requirement for registration on the PBS.. is it possible to find out where the request to amend the PBS is up to ?? I know there was a request to change to Authority streamlined script..
Robyn

From: s22 @health.gov.au>
Sent: Tuesday, 20 June 2023 5:00 PM
To: s22 @health.gov.au>; s22 s22 @health.gov.au>; LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>; s22 s22 @Health.gov.au>; HENDERSON, Nick <Nick.Henderson@health.gov.au>; SIMPSON, Andrew <Andrew.Simpson@health.gov.au>; AST Application Support Team s22 @health.gov.au>
Cc: s22 @health.gov.au>; Streamlined Submission s22 @health.gov.au>; DUFFY, Tracey <Tracey.Duffy@health.gov.au>; s22 @health.gov.au>
Subject: RE: RMS advice: MS-2 Step - Type J - PM-2022-05475-1-5 - preparing for imminent decision [SEC=OFFICIAL:Sensitive]

HI all,
Looping in s2 as she is now back
s22 2

From: s22 @health.gov.au>
Sent: Tuesday, 20 June 2023 4:59 PM
To: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>; s22 s22 @Health.gov.au>; HENDERSON, Nick <Nick.Henderson@health.gov.au>; SIMPSON, Andrew <Andrew.Simpson@health.gov.au>; s22 s22 @health.gov.au>; AST Application Support Team s22 @health.gov.au>
Cc: s22 @health.gov.au>; Streamlined Submission s22 @health.gov.au>; DUFFY, Tracey <Tracey.Duffy@health.gov.au>; s22 @health.gov.au>
Subject: RMS advice: MS-2 Step - Type J - PM-2022-05475-1-5 - preparing for imminent decision [SEC=OFFICIAL:Sensitive]

Hi Robyn,

Thanks for seeking confirmation on RMP changes. The relevant changes in the RMP have been evaluated and accepted as part of the evaluation for the same submission. The new RMP condition of registration requires the implementation of the updated RMP that has removed the following:

- Pharmacist registration
- Prescriber certification, and re-certification

Neither the 24-hour phone service, nor being prescribed by a medical practitioner has been an RMP requirement. Therefore, the RMP updates align with those in the approved PI.
It should be noted that the PBS authority requirements still include prescriber registration at this stage: https://www.pbs.gov.au/medicine/item/10211K.
Let me know if you need any further information.
Regards,

s22 [redacted]
Principal Evaluator
Risk Management Section
Pharmacovigilance Branch

Phone: s22 [redacted]
Email: s22 [redacted] @health.gov.au

Therapeutic Goods Administration
Department of Health and Aged Care
PO Box 100
Woden ACT 2606
www.tga.gov.au

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From: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Sent: Tuesday, 20 June 2023 4:44 PM
To: s22 [redacted] @Health.gov.au>; HENDERSON, Nick <Nick.Henderson@health.gov.au>; SIMPSON, Andrew <Andrew.Simpson@health.gov.au>; s22 [redacted] @health.gov.au>; AST Application Support Team s22 [redacted] @health.gov.au>
Cc: s22 [redacted] @health.gov.au>; Streamlined Submission s22 [redacted] @health.gov.au>; DUFFY, Tracey <Tracey.Duffy@health.gov.au>; s22 [redacted] s22 [redacted] @health.gov.au>; s22 [redacted] @health.gov.au>
Subject: RE: MS-2 Step - Type J - PM-2022-05475-1-5 - preparing for imminent decision [SEC=OFFICIAL:Sensitive]
Thanks s22 [redacted]. understand.
I think we need to line up any RMP changes with the PI changes.. in terms of any announcements,
Robyn

From: s22 [redacted] @Health.gov.au>
Sent: Tuesday, 20 June 2023 4:42 PM
To: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>; HENDERSON, Nick <Nick.Henderson@health.gov.au>; SIMPSON, Andrew <Andrew.Simpson@health.gov.au>;

s22 @health.gov.au>; AST Application Support Team s22 @health.gov.au>
Cc: s22 @health.gov.au>; Streamlined Submission s22 @health.gov.au>; DUFFY, Tracey <Tracey.Duffy@health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>
Subject: RE: MS-2 Step - Type J - PM-2022-05475-1-5 - preparing for imminent decision [SEC=OFFICIAL:Sensitive]

Hi Robyn,

There is no mention within the currently approved PI on the ARTG relating to the registration/certification of dispensing pharmacists, only doctors. This is the relevant part of Section 4.2 within the amended PI with tracked changes:

MS-2 Step should only be prescribed by healthcare practitioners~~doctors~~ with the appropriate qualifications and ~~certified~~ training. Ectopic pregnancy should be excluded, an intrauterine device (IUD) (if present) must be removed, consent must be obtained and patients must have the ability to access 24-hour emergency care if and when required for incomplete abortion or bleeding.

I've cc'ed in s22 from RMS who will be able to advise you relating to the RMP.
Kind regards,
s22

From: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Sent: Tuesday, 20 June 2023 4:18 PM
To: HENDERSON, Nick <Nick.Henderson@health.gov.au>; s22 s22 @Health.gov.au>; SIMPSON, Andrew <Andrew.Simpson@health.gov.au>; s22 @health.gov.au>; AST Application Support Team s22 @health.gov.au>
Cc: s22 @health.gov.au>; Streamlined Submission s22 @health.gov.au>; DUFFY, Tracey <Tracey.Duffy@health.gov.au>
Subject: RE: MS-2 Step - Type J - PM-2022-05475-1-5 - preparing for imminent decision [SEC=OFFICIAL:Sensitive]

Thanks s22 and team..
Just to clarify – does the amended PI include removal of registration **and** certification for both prescribers AND dispensing pharmacists??
Also not sure what will happen with the RMP.. grateful for some help if you can,
Robyn

From: HENDERSON, Nick <Nick.Henderson@health.gov.au>
Sent: Tuesday, 20 June 2023 3:59 PM
To: s22 @Health.gov.au>; SIMPSON, Andrew <Andrew.Simpson@health.gov.au>; s22 s22 @health.gov.au>; AST Application Support Team s22 @health.gov.au>
Cc: s22 @health.gov.au>; Streamlined Submission s22 @health.gov.au>; DUFFY, Tracey <Tracey.Duffy@health.gov.au>; LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Subject: RE: MS-2 Step - Type J - PM-2022-05475-1-5 - preparing for imminent decision [SEC=OFFICIAL:Sensitive]

Thanks s22
This is great news. Could you draft an urgent web statement, I would like to share this with MOs ahead of decision being made (at least 24 hours) so we do need to manage the timing of

decision, provision of information and comms
Nick

From: s22 [redacted] @Health.gov.au>
Sent: Tuesday, 20 June 2023 3:56 PM
To: HENDERSON, Nick <Nick.Henderson@health.gov.au>; SIMPSON, Andrew <Andrew.Simpson@health.gov.au>; s22 [redacted] s22 [redacted] @health.gov.au>; AST Application Support Team s22 [redacted] @health.gov.au>
Cc: s22 [redacted] @health.gov.au>; Streamlined Submission s22 [redacted] @health.gov.au>
Subject: MS-2 Step - Type J - PM-2022-05475-1-5 - preparing for imminent decision [SEC=OFFICIAL:Sensitive]

Hi all,

The Type J application for MS-2 Step composite pack (mifepristone and misoprostol) was recently discussed at the June 2023 ACM meeting. This Type J application seeks to amend the PI for MS-2 Step to:

- Change the prescribing from medical practitioner to healthcare practitioner
- Remove the requirement for prescriber certification
- Remove the sponsor managed 24-hour phone service for patients

[NB: MS-2 Step is indicated for medical termination of intrauterine pregnancy up to 63 days gestation]

The Delegate is aiming for a decision as soon as possible, subject to receipt of some final data from the sponsor, which is expected today or tomorrow.

Nick/Andrew -

1. Is the potential decision timing of this week acceptable from your perspective?
2. Do you think any additional comms is required? (e.g. web statement). We can send the decision letter to the sponsor under embargo if needed.

s22 [redacted] - FYI, in case there are additional media enquiries

AST - FYI for ARTG entry timing; in addition to the updated PI, there will be an updated RMP condition of registration imposed within the approval letter

Kind regards,

s22 [redacted]
s22 [redacted]
Prescription Medicines Authorisation Branch

Medicines Regulation Division | Health Products Regulation Group
Australian Government, Department of Health and Aged Care
T: s22 [redacted] | E: s22 [redacted] @health.gov.au
Location: Fairbairn
PO Box 100, Woden ACT 2606, Australia

The Department of Health and Aged Care acknowledges First Nations peoples as the Traditional Owners of Country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

From: s22 [redacted] @health.gov.au>
Sent: Tuesday, 20 June 2023 12:24 PM
To: Approval letter request <PES.request@Health.gov.au>
Subject: PM-2022-05475-1-5 - Type J - Urgent [SEC=OFFICIAL:Sensitive]

Dear s22 [redacted],

Just a heads up. This is urgent request. I am just waiting on one 24 hour phone call change data to come through. If it is not used much, I will be ready to approve this application. We will need to inform s22 and Nick before we can send it out.
Please draft an approval letter for Type J –
Approvable PIs –
e004967 (0016-) - Product Information - Clean
e004967 (0016-) - Product Information - Annotated
Thank you
Kind regards

s22
[redacted]
Director
Prescription Medicine Authorisation Branch
Health Products Regulation Group
Australian Government, Department of Health and Aged Care

Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

MEDIA RELEASE

Amendments to restrictions for prescribing of MS-2 Step (Mifepristone and Misoprostol)

XX July 2023

On XX July 2023, the Therapeutic Goods Administration (TGA) approved an application from MS Health to amend restrictions on the prescribing of MS-2 Step (Mifepristone and Misoprostol).

A number of changes to prescribing requirements have been made. Previously, MS-2 Step was only able to be prescribed by a medical practitioner (a doctor) who had been certified to prescribe the medicine. The TGA's decision means that MS-2 Step can now be prescribed by any healthcare practitioner with appropriate qualifications and training - this may include nurse practitioners and GPs.

Noting these eased restrictions, a new warning/instruction has been included in the Product Information, which provides information about circumstances where a person should be referred to a medical practitioner.

Commented s22 Link

The decision to approve these amendments was informed by expert advice from the Advisory Committee on Medicines, an independent committee with expertise in scientific, medical and clinical fields and including consumer representation.

The TGA has also approved a number of other regulatory changes to MS-2 Step, including removal of pharmacist registration requirements and removal of the sponsor-managed 24-hour telephone helpline for patients.

Commented s22 May not need this

Following these regulatory changes, ~~an application to amend~~ changes to the Pharmaceutical Benefits Schedule (PBS) listing will shortly be considered by Pharmaceutical Benefit Advisory Committee, who will advise on these matters in coming weeks.

Commented s22 Review by TAAD

Contact for members of the media:

- Email: news@health.gov.au
- Phone: 02 6289 7400

From: DUFFY, Tracey
To: MEDIA, TGA
Cc: LANGHAM, Robyn; s22 ; SIMPSON, Andrew; s22 s22 ; s22 ; s22
Subject: RE: ATTN Tracey: URGENT - For clearance ASAP: News request - ABC - Abortion pill - Due ASAP [SEC=OFFICIAL]
Date: Wednesday, 10 May 2023 8:03:00 PM
Attachments: image003.png
image005.png

Thanks – cleared response below that includes some edits.
Tracey

From: s22 @health.gov.au>
Sent: Wednesday, 10 May 2023 7:50 PM
To: DUFFY, Tracey <Tracey.Duffy@health.gov.au>
Cc: s22 @health.gov.au>; LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>; s22 @health.gov.au>; SIMPSON, Andrew <Andrew.Simpson@health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>; s22 @Health.gov.au>; s22 @health.gov.au>; s22 @tga.gov.au>; s22 @health.gov.au>
Subject: ATTN Tracey: URGENT - For clearance ASAP: News request - ABC - Abortion pill - Due ASAP [SEC=OFFICIAL]
Importance: High

Dear Tracey,

Please find response below, to the ABC media query, Nick has cleared.

For your urgent clearance please.

Query:

I'm trying to follow up this story from the Courier Mail regarding access to abortion pill in Queensland.

https://www.couriermail.com.au/lifestyle/abortion-pill-qld-nurses-midwives-to-gain-prescription-powers/news-story/3bb726efd70ebdfdf063a254de2fe608

I'm wondering if the TGA can provide confirmation of this proposed change?

How far away is the TGA approval?

Proposed response:

The TGA can confirm that it is currently expediting an evaluation of MS Health's application to broaden prescribing powers for mifepristone and misoprostol. The application will be considered at the next meeting of the Advisory Committee on Medicines (ACM) in June 2023, after which the TGA delegate will make their final decision. As with all evaluations, the TGA's assessment will carefully consider the risks and benefits a of the proposed change – and will focus on patient safety. Details of the TGA's decision, when made, will be published on our website.

To allow prescribing of MS-2 Step by healthcare practitioners other than doctors, such as nurse practitioners and midwives, changes to state and territory law may be required. This is because in some jurisdictions, prescribing of medicines in Schedule 4 of the Standard for the Uniform Scheduling of Medicines and Poisons (Poisons Standard) by nurses may be unlawful or limited to certain products.

The comments quoted in the article should be read in the context of the rest of the evidence provided by Dr Langham at the Inquiry into Universal access to reproductive healthcare. In particular:

It was universally agreed that what was put in place 10 years ago was no longer relevant. It was really out of step with current international guidelines and it certainly was not meeting the needs of the Australian community in what it did…

Dr Langham's comments refer to the sentiments of the Women's Health Product Advisory Group on the potential changes, they do **not refer to a decision** on MS Health's application.

Kind regards,

s22 [redacted]
HPRG Regulatory Engagement Services
Collaboration Services Section
Regulatory Practice & Support Division | Health Products Regulation Group
Regulatory Engagement Branch
Australian Government Department of Health and Aged Care
P: s22 [redacted]
After Hours: s22 [redacted] | E: s22 [redacted] @health.gov.au
Location: Fairbairn, Level 2 South

Regulatory Engagement Service Gateway

Direct access to our services and resources.

From: HENDERSON, Nick <Nick.Henderson@health.gov.au>
Sent: Wednesday, 10 May 2023 7:43 PM
To: KAY, Elspeth <Elspeth.Kay@health.gov.au>
Cc: s22 [redacted] @health.gov.au>; LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>; s22 [redacted] @health.gov.au>; SIMPSON, Andrew <Andrew.Simpson@health.gov.au>; s22 [redacted] s22 [redacted] @health.gov.au>; s22 [redacted] @health.gov.au>; s22 [redacted] @Health.gov.au>; s22 [redacted] @health.gov.au>
Subject: RE: For clearance: News request - ABC - Abortion pill - Due ASAP [SEC=OFFICIAL]
Thank you approved, please progress to Tracey for clearance
Nick

From: KAY, Elspeth <Elspeth.Kay@health.gov.au>
Sent: Wednesday, 10 May 2023 7:31 PM
To: HENDERSON, Nick <Nick.Henderson@health.gov.au>
Cc: s22 [redacted] @health.gov.au>; LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>; s22 [redacted] @health.gov.au>; SIMPSON, Andrew <Andrew.Simpson@health.gov.au>; s22 [redacted] s22 [redacted] @health.gov.au>; s22 [redacted] @health.gov.au>; s22 [redacted] @Health.gov.au>; s22 [redacted] @health.gov.au>
Subject: For clearance: News request - ABC - Abortion pill - Due ASAP [SEC=OFFICIAL]
Importance: High
Dear Nick, for your clearance - below proposed response incorporates PMAB and PB responses. I have spoken with Robyn and she is comfortable with the response.

Kind regards
Elspeth

From: KAY, Elspeth
Sent: Wednesday, 10 May 2023 7:27 PM
To: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Cc: HENDERSON, Nick <Nick.Henderson@health.gov.au>
Subject: FW: News request - ABC - Abortion pill - Due ASAP [SEC=OFFICIAL]
Hi Robyn, as discussed – pls can you let me know if any concerns about the proposed response.

The TGA is considering an application to broaden prescribing powers of mifepristone and misoprostol through an expedited evaluation process. The application will be considered at the next meeting of the Advisory Committee on Medicines (ACM), after which the TGA delegate will make their final decision. As with all evaluations, the TGA's assessment will carefully consider the risks and benefits a of the proposed change – and will focus on patient safety. Details of the TGA's decision, when made, will be published on our website.
To allow prescribing of MS-2 Step by healthcare practitioners other than doctors, such as nurse practitioners and midwives, changes to state and territory law may be required. This is because in some jurisdictions, prescribing of medicines in Schedule 4 of the Standard for the Uniform Scheduling of Medicines and Poisons (Poisons Standard) by nurses may be unlawful or limited to certain products.
The comments quoted in the article should be read in the context of the rest of the evidence provided by Dr Langham at the Inquiry into Universal access to reproductive healthcare. In particular:
It was universally agreed that what was put in place 10 years ago was no longer relevant. It was really out of step with current international guidelines and it certainly was not meeting the needs of the Australian community in what it did…
Dr Langham's comments refer to the sentiments of the Women's Health Product Advisory Group on the potential changes, they do not refer to a decision to on MS Health's application.

From: s22 [redacted] @health.gov.au>
Sent: Wednesday, 10 May 2023 7:02 PM
To: s22 [redacted] @health.gov.au>; s22 [redacted] @Health.gov.au>
Cc: SIMPSON, Andrew <Andrew.Simpson@health.gov.au>; KAY, Elspeth <Elspeth.Kay@health.gov.au>; s22 [redacted] @health.gov.au>; s22 [redacted] @health.gov.au>
Subject: RE: News request - ABC - Abortion pill - Due ASAP [SEC=OFFICIAL]
Hi All
Draft input, I have included relevant Hansard excerpt below. Not sure if we need to write to the paper and ask them to correct?
The TGA would like to clarify that the application from MS Health, to amend the current prescribing restrictions for MS-2 Step is still under evaluation. The application will be considered at the next meeting of the Advisory Committee on Medicines (ACM), after which the TGA delegate will make their final decision.
The comments quoted in the article must to be read in context with the rest of the evidence provided by Dr Langham at the Inquiry into Universal access to reproductive healthcare. In particular:
It was universally agreed that what was put in place 10 years ago was no longer relevant. It

was really out of step with current international guidelines and it certainly was not meeting the needs of the Australian community in what it did…
Dr Langham's comments refer to the sentiments of the Women's Health Product Advisory Group on the potential changes, they do not refer to a decision to on MS Health's application.

Additionally, the article infers that a decision will made in a matter of weeks. Dr Langham indicated that this application would be discussed at the ACM in a matter a weeks, and a decision would follow soon after. That being said, the TGA is expediting this application.
As with all evaluations, the TGA's assessment will carefully consider the risks and benefits a of the proposed change – and will focus on patient safety.
Details of the TGA's decision, when made, will be published on our website.
Full Hansard is available at: XX

> ***Senator WATERS:*** *I have lots. Thanks very much for being here, Professor Langham and Ms Duffy. Can I just start off with the last reference you made, Professor Langham, to the women's health product advisory group, which, if I heard you correctly—and I'm not hearing very well today—you said was established in June of last year and had a meeting in October of last year discussing abortion access. Can you tell us a little bit more, if you're permitted to, about what was discussed and what the results of that discussion were?*
>
> ***Dr Langham:*** *What was discussed was just that: the barriers to access, and also the data that was presented to the group was the paucity of availability that was, in part, from the very low numbers of general practitioners which were registered to prescribe and also the low number of pharmacists that were registered to dispense. There were a number of other factors that were identified, and most of these were barriers that were put in place when the drug was first registered in Australia about a decade ago, and that was, in part, through a risk management plan and, in part, through the actual regulatory documents that sit around the registration—the product information document. It was universally agreed that what was put in place 10 years ago was no longer relevant. It was really out of step with current international guidelines and it certainly was not meeting the needs of the Australian community in what it did. We discussed several options as to how this could be remedied. Along with my earlier statement that the TGA is not able to evaluate or monitor a drug that's not been presented to us by a sponsor, we're also unable to make any changes to risk management plans or product information without an approach from the relevant sponsor. In Australia, there's just the one sponsor, and that's MS Health. We talked about where others might be able to make approaches, where other options might be moving forward. It was a few weeks after that I think that MS Health came to the TGA with their application to ease some of the restrictions in the risk management plan and in the prescriber information, namely that there wasn't going to be a requirement for pharmacists to register but also that there was going to be a removal of the specific word 'doctor', opening up potentially to all healthcare practitioners, including nurses and midwives, and that after registration healthcare practitioners would not be required to do annual certification programs. Because of the clear messaging that had come out of the working group, I was able to then go to the sponsor and say: 'We thank you for doing this. We think this is a great step forward, but there's certainly a lot of very strong sentiment in the community and in the relevant stakeholder groups that you need to go further.' So we had a discussion trying to share the thoughts of the*

group with the sponsors, and it was after that that the application to amend the current risk management plan and the PI was expanded further so that their application that's currently sitting with the TGA, which is being dealt with in an expedited fashion, includes dropping the requirement for doctors to register with the company altogether. I would anticipate that without this requirement the stigma that might be attached to prescribers having to register with the only company in Australia that provides medical abortion will certainly allow for a greater access and a greater uptake.

Senator WATERS: *Thank you. That's a great run through. I appreciate that. What time frame are you now working to to assess that revised application?*

Dr Langham: *At the moment we're talking a couple of weeks. As is part of our process, I mentioned our external independent clinical advisory committees, and we have one specifically for the evaluation of medicines. That's our Advisory Committee on Medicines. I understand that the evaluators that are currently working with the proposal are planning to take that to the Advisory Committee of Medicine for further comment, and, if that's going to happen in too long a time, then certainly an out-of-session consideration could be managed.*

Senator WATERS: *What further steps are there after that, before such time as hopefully those reforms would then become reality?*

Dr Langham: *That's it, once the TGA approves the amended applications.*

Senator WATERS: *There's no further delay? That just changes like that. You mentioned a couple of weeks, but then you also said waiting for the special Advisory Committee on Medicines. What's the longest you think it could be?*

Dr Langham: *That's a single meeting, and it really has to do with the calendar for the meetings to which they sit. I'm not sure of when their next sitting is. They generally happen every couple of months. If it's too far away, then we could certainly have an out-of-session consideration for something like this.*

Senator WATERS: *That sounds really positive, and that's following on from when we previously spoke in estimates as well. With the proposed removal of the restriction for doctors to register and the removal of the term doctor, will that mean that nurses and midwives—notwithstanding that the PBS won't change or may not change—will be able to prescribe both medicines?*

Dr Langham: *Senator, you've hit upon one of the interesting vagaries of our country, and that is that not all federal law applies on a state basis. Certainly the states and territories have their own powers, and allowing prescription of certain drugs and medicines by nurse practitioners is really on a state-by-state basis.*

From: s22 [redacted] @health.gov.au>
Sent: Wednesday, 10 May 2023 5:59 PM
To: s22 [redacted] @health.gov.au>; s22 [redacted] @Health.gov.au>
Cc: SIMPSON, Andrew <Andrew.Simpson@health.gov.au>; KAY, Elspeth <Elspeth.Kay@health.gov.au>; s22 [redacted] @health.gov.au>; s22 [redacted]

s22 @health.gov.au>
Subject: FW: News request - ABC - Abortion pill - Due ASAP [SEC=OFFICIAL]
Importance: High
For your input asap pls. Can you pls send your input back to E for inclusion on PB response so there is not double up on info
Regards
s22
Phone: s22

From: News <news@health.gov.au>
Sent: Wednesday, 10 May 2023 5:42 PM
To: KAY, Elspeth <Elspeth.Kay@health.gov.au>; News <news@health.gov.au>; s22 @health.gov.au>; s22 @tga.gov.au>
Cc: DUFFY, Tracey <Tracey.Duffy@health.gov.au>; LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Subject: RE: News request - ABC - Abortion pill - Due ASAP [SEC=OFFICIAL]
Importance: High
Hi all,
Courier Mail article is attached.
We will now also need a response as soon as possible tonight please, as its for a story in the AM radio program tomorrow morning.
Suggested line here: *The TGA is actively considering an application to broaden prescribing powers of mifepristone and misoprostol. A decision is expected in coming weeks.*
Thank you,
s22
Media Unit
Australian Government, Department of Health and Aged Care
T: s22 | s22 E: news@health.gov.au
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From: KAY, Elspeth <Elspeth.Kay@health.gov.au>
Sent: Wednesday, 10 May 2023 5:39 PM
To: News <news@health.gov.au>; s22 @health.gov.au>; s22 @tga.gov.au>
Subject: RE: News request - ABC - Abortion pill - Due 11am Thurs [SEC=OFFICIAL]
Hi s22 could we please have a copy of the Courier Mail article?

From: News <news@health.gov.au>
Sent: Wednesday, 10 May 2023 5:18 PM
To: s22 @health.gov.au>; s22 @tga.gov.au>
Cc: News <news@health.gov.au>
Subject: News request - ABC - Abortion pill - Due 11am Thurs [SEC=OFFICIAL]
Hi TGA team,
Can I please get a response for the below by 11am tomorrow? Apologies for the lack of time.
Thanks,
s22
Media Unit

Australian Government, Department of Health and Aged Care
T: s22 [redacted] E: news@health.gov.au
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From: s22 [redacted] @abc.net.au>
Sent: Wednesday, 10 May 2023 5:01 PM
To: News <news@health.gov.au>
Subject: RE: TGA contact [SEC=OFFICIAL]

Hello,
Sorry I missed your call.
I'm trying to follow up this story from the Courier Mail regarding access to abortion pill in Queensland.
https://www.couriermail.com.au/lifestyle/abortion-pill-qld-nurses-midwives-to-gain-prescription-powers/news-story/3bb726efd70ebdfdf063a254de2fe608
I'm wondering if the TGA can provide confirmation of this proposed change?
How far away is the TGA approval?
Many thanks,
s22 [redacted]

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[SEC=OFFICIAL]

From: s22
To: s22 ; LANGHAM, Robyn
Cc: SIMPSON, Andrew; KAY, Elspeth; s22
Subject: Update: MS-2-Step TGA submission PM-2022-05475-1-5 [SEC=OFFICIAL]
Date: Tuesday, 21 February 2023 11:51:26 AM
Attachments: e004967-0009.zip
image001.png
image003.png
image004.png
image006.png
image009.png
image010.png
image011.png

Hi Robyn and s22
I'd like to provide an update following s22 conversation with the sponsor last week (Thanks s22 .
I had a phone call yesterday with s22 from s47 , the agent representing MS Health, the sponsor. s22 advised me that MS Health had agreed with the TGA to submit further proposed changes to the Risk Management Plan (RMP) through the post-market RMP update process to remove the requirement for prescriber certification, and 24 hours phone line service for patients. Neither s22 nor MS Health was aware that both requirements are included in the current Product Information (PI). During our conversation, I showed her the relevant PI content that needs to be updated. s22 revised her plan to submit the updated RMP through the ongoing type J submission PM-2022-05475-1-5 so PI updates can be considered, and proposed to submit updated PI which includes the relevant changes later through the same submission to allow time to draft PI updates. s22 also talked about a meeting with the TGA scheduled at the end of February. However, she wasn't sure what topics would be discussed, and could not advise what information may be sought from the TGA.
We have received the updated RMP as per the revised plan this morning (attachment). We will conduct RMP evaluation as part of submission PM-2022-05475-1-5 as a matter of priority. We are happy to work to the same timeframe as the clinical evaluator for milestone 3. It would be great if we could be provided with the following information to ensure expedited actions:

- The expedited timeframe for milestone 3 for submission PM-2022-05475-1-5
- Any information on the scheduled meeting with MS Health later this month, and if any information and/or advice is required from the RMP evaluator.

Thanks.
Regards,

s22
Principal Evaluator
Risk Management Section
Pharmacovigilance Branch

Phone: s22
Email: s22 @health.gov.au

Therapeutic Goods Administration
Department of Health and Aged Care
PO Box 100
Woden ACT 2606
www.tga.gov.au

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From: s22 @health.gov.au>
Sent: Friday, 17 February 2023 11:29 AM
To: s22 @health.gov.au>; LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Cc: SIMPSON, Andrew <Andrew.Simpson@health.gov.au>
Subject: RE: RE: [EXTERNAL] MS-2-Step TGA submission [SEC=OFFICIAL]

Good morning Robyn/s22
I just got a call from s22, they are preparing to submit the RMP changes today or latest by Monday.
Kind regards
s22

From: s22 @health.gov.au>
Sent: Wednesday, 15 February 2023 4:02 PM
To: s22 @health.gov.au>; LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Subject: RE: RE: [EXTERNAL] MS-2-Step TGA submission [SEC=OFFICIAL]

Great, thanks Robyn and s22
I've asked the case manager to inform us as soon as she receives the dossier. I'll keep you informed of any updates.
Regards,

s22
Principal Evaluator
Risk Management Section
Pharmacovigilance Branch

Phone: s22
Email: s22 @health.gov.au

Therapeutic Goods Administration
Department of Health and Aged Care
PO Box 100
Woden ACT 2606
www.tga.gov.au

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From: s22 @health.gov.au>
Sent: Wednesday, 15 February 2023 3:38 PM
To: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>; s22 s22 @health.gov.au>
Subject: RE: RE: [EXTERNAL] MS-2-Step TGA submission [SEC=OFFICIAL]

Hi Robyn and s22
It is prioritised from my end. s22 is the evaluator. Depending on the amendments request we will do as soon as we can.

Kind regards
s22

Sent from Workspace ONE Boxer

On 15 February 2023 at 15:32:13 GMT+11, LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au> wrote:

> Thanks for that s22 . I had no idea myself.. if (with s22 agreement), I can assure them of prioritisation, I think that will help enormously
> Regards
> Robyn
>
> ---
> Sent from Workspace ONE Boxer
>
> On 15 February 2023 at 3:30:31 pm AEDT, s22 @health.gov.au> wrote:
>
> > Hi Robyn,
> > Thanks for the update.
> > I'm not sure which meeting s22 was talking about. Anyway, if any updates to the submission are submitted that involves RMP updates, I'm happy to prioritise the work if it needs to be discussed by the end of February. s22 do you have more information?
> > Regards,
> > s22
> > Principal Evaluator
> > Risk Management Section
> > Pharmacovigilance Branch
> >
> > Phone: s22
> > Email: s22 @health.gov.au
> >
> > Therapeutic Goods Administration
> > Department of Health and Aged Care
> > PO Box 100
> > Woden ACT 2606
> > www.tga.gov.au
> >
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> >
> > **From:** LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
> > **Sent:** Wednesday, 15 February 2023 3:23 PM

To: s22 @health.gov.au>; s22 s22 @health.gov.au>
Subject: Fwd: RE: [EXTERNAL] MS-2-Step TGA submission [SEC=OFFICIAL]
Hi.. see below
Are you able to advise re s22 question regarding timing?
Thanks
Robyn

Sent from Workspace ONE Boxer

---------- Forwarded message ----------

From: s22 @msiaustralia.org.au>
Date: 15 February 2023 at 2:48:35 pm AEDT
Subject: RE: [EXTERNAL] MS-2-Step TGA submission [SEC=OFFICIAL]
To: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Cc: s22 @mshealth.com.au>
Hi Robyn
We are just finalising the submission and hope to have it to you tomorrow. Hopefully that means it can still go to the meeting at the end of the month.

s22
Managing Director
Pronouns: he, him, his
MSI Australia | Australian Support Office
GPO Box 1635 Melbourne VIC 3001 Australia
tel s22 | **fax** s22 | **book** 1300 003 707
email s22 @msiaustralia.org.au
web msiaustralia.org.au | mshealth.com.au
MSI Australia Logo

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Please consider the environment before printing this email.

From: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>

Sent: Tuesday, 14 February 2023 2:31 PM
To: s22 @msiaustralia.org.au>
Cc: s22 @mshealth.com.au>
Subject: RE: [EXTERNAL] MS-2-Step TGA submission
[SEC=OFFICIAL]

Hi s22

Keen to follow up on progress.. have you had a chance to talk to the staff at the TGA regarding amending your submission?

Regards,

Robyn

Adj. Prof Robyn Langham AM
Chief Medical Adviser

Health Products Regulation Group
Australian Government Department of Health
T: s22 | E: Robyn.Langham@health.gov.au
PO Box 100, Woden ACT 2606, Australia

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From: s22 @msiaustralia.org.au>
Sent: Friday, 3 February 2023 4:14 PM
To: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Cc: s22 @mshealth.com.au>
Subject: Re: [EXTERNAL] MS-2-Step TGA submission
[SEC=OFFICIAL]

Hi Robyn,

Thanks for your time on the phone this morning. As discussed keen to progress an amendment to our submission considering the support shared. I've cc'd s22 who would be the right person to speak to your team and support me in making this change.

Have a good week off and speak soon.

s22

Managing Director
Pronouns: he, him, his
MSI Australia | Australian Support Office
GPO Box 1635 Melbourne VIC 3001 Australia
tel s22 | **fax** s22 | **book** 1300 003 707
email s22 @msiaustralia.org.au
web msiaustralia.org.au | mshealth.com.au

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From: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Sent: Wednesday, February 1, 2023 9:38:21 AM
To: s22 @msiaustralia.org.au>
Cc: s22 @msiaustralia.org.au>; s22 @msiaustralia.org.au>
Subject: RE: [EXTERNAL] MS-2-Step TGA submission [SEC=OFFICIAL]

Hi s22

More than happy to speak – I am on and off planes Thursday and Friday, just short flights - so feel free to call and leave a message – will return your call when I am on the ground

Robyn

s22

From: s22 @msiaustralia.org.au>
Sent: Wednesday, 1 February 2023 9:15 AM
To: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Cc: s22 @msiaustralia.org.au>; s22 @msiaustralia.org.au>
Subject: RE: [EXTERNAL] MS-2-Step TGA submission [SEC=OFFICIAL]

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Thanks s22

Lovely to meet you Robyn

Is there a number to best speak on if I have any questions? Would appreciate a quick chat later in the week if possible

Thanks

s22

Managing Director
Pronouns: he, him, his

MSI Australia | Australian Support Office
GPO Box 1635 Melbourne VIC 3001 Australia
tel s22 | **fax** s22 | **book** 1300 003 707

email s22 @msiaustralia.org.au
web msiaustralia.org.au | mshealth.com.au

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From: s22 s22 @msiaustralia.org.au>
Sent: Monday, 30 January 2023 4:41 PM
To: LANGHAM, Robyn <Robyn.LANGHAM@health.gov.au>
Cc: s22 @msiaustralia.org.au>
Subject: RE: [EXTERNAL] MS-2-Step TGA submission [SEC=OFFICIAL]

Hi Robyn,

Thanks for your email. I appreciate the feedback from our recent conversation and have passed this on. We're currently reviewing this new information and may have further questions. I've also cc'd s22, Managing Director.

Regards,

s22

s22 [redacted]

MSI Australia | MS Health
GPO Box 1635 Melbourne VIC 3001 Australia
mobile s22 [redacted] | **fax** s22 [redacted] | **book** 1300 003 707

email s22 [redacted]@msiaustralia.org.au
web mariestopes.org.au | mshealth.com.au

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From: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Sent: Monday, 30 January 2023 12:30 PM
To: s22 [redacted]@msiaustralia.org.au>
Subject: RE: [EXTERNAL] MS-2-Step TGA submission [SEC=OFFICIAL]

Hi s22 [redacted]

Keen to hear of any progress – let me know if I can help at all.

Regards,

Robyn

From: LANGHAM, Robyn
Sent: Thursday, 19 January 2023 2:39 PM
To: s22 [redacted]@msiaustralia.org.au>
Subject: RE: [EXTERNAL] MS-2-Step TGA submission [SEC=OFFICIAL]

Cool.. I will send you a zoom (will come from my uni email though.. zoom is not TGA friendly

Robyn

From: s22 s22 @msiaustralia.org.au>
Sent: Thursday, 19 January 2023 2:37 PM
To: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Subject: RE: [EXTERNAL] MS-2-Step TGA submission [SEC=OFFICIAL]

Yes, I'm in Sydney, so that's 9:30 AEDT.

From: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Sent: Thursday, 19 January 2023 2:33 PM
To: s22 @msiaustralia.org.au>
Subject: RE: [EXTERNAL] MS-2-Step TGA submission [SEC=OFFICIAL]

Sensational

Tomorrow morning suits.. are you in Sydney still? Can zoom or webex

Robyn

From: s22 s22 @msiaustralia.org.au>
Sent: Thursday, 19 January 2023 2:15 PM
To: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Subject: RE: [EXTERNAL] MS-2-Step TGA submission [SEC=OFFICIAL]

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Hi Robyn,

I have the following availability over the coming week:

1. Fri 19 Jan 9:30-10am
2. Mon 23 Jan 9-10am; 12:30-2pm
3. Tue 24 Jan 9-11am; 11:30am-1pm
4. I'm not available Wed-Fri next week.

Let me know which of these times suits you.

Regards,

s22 [redacted]

[redacted]

MSI Australia | MS Health
GPO Box 1635 Melbourne VIC 3001 Australia
mobile s22 [redacted] | **fax** s22 [redacted] | **book** 1300 003 707

email s22 [redacted]@msiaustralia.org.au
web mariestopes.org.au | mshealth.com.au

<image001.png>

<image002.png>

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From: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Sent: Thursday, 19 January 2023 1:15 PM
To: s22 [redacted]@msiaustralia.org.au>
Subject: [EXTERNAL] MS-2-Step TGA submission [SEC=OFFICIAL]

> You don't often get email from robyn.langham@health.gov.au. Learn why this is important

Hello s22 [redacted]

Am writing regarding the current submission from MS-2-Step that is with our assessment team,

Would really like the chance to discuss this with you

Do you have any time over the next week?

Thanks in advance

Robyn

Adj. Prof Robyn Langham AM

Chief Medical Adviser

Health Products Regulation Group
Australian Government Department of Health
T: s22 [redacted] E: Robyn.Langham@health.gov.au

PO Box 100, Woden ACT 2606, Australia

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s47 [redacted]

Document 12

20 February 2023

Dossier (Prescription Medicines)
Records Management
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606

CATEGORY 1 APPLICATION – TYPE J:
UPDATED RISK MANAGEMENT PLAN

eSubmission Identifier: e004967
Submission Number: PM-2022-05475-1-5
Sequence: 0009; Related Sequence: 0007

ARTG	Product Details
210574	MS-2 Step composite pack [MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet blister; GyMiso misoprostol 200 microgram tablet blister]

Dear Sir / Madam,

On behalf of MS Health Pty Ltd (Client ID 57301) please find enclosed a copy of the updated Australian Risk Management Plan (RMP) v4.0, 17 February 2023 for MS-2 Step which has been updated with additional proposed changes. Please note, a RMP is currently under review with the TGA (version 4.0, 13 January 2023) which was submitted to the RMP unit as a stand-alone document with the associated 'submission of an updated RMP' form.

In accordance with the discussion between MS Health and s22 [redacted] and Prof. Robyn Langham (TGA), this updated RMP is being submitted in addition to the RMP that is currently under review by the RMP unit and is being submitted to both Streamlined submissions and the RMP unit, but has been linked to the Category 1 application that is currently under evaluation (PM-2022-05475-1-5) to facilitate evaluation.

The proposed additional changes, including the removal of the mandatory medical educational program, are being sought after ongoing stakeholder feedback indicated a willingness on behalf of the TGA to consider additional changes to the MS-2 Step RMP. The additional changes would align the MS-2 Step RMP with the expectations of RMPs of the majority of medicines registered with the TGA, and with expectations around prescriber competency for a medicine that has been in-market for many years with hundreds of thousands Australian women having been prescribed MS-2 Step since it was first registered.

The proposed amendments reflect how the medical (and medical abortion) landscape has changed since the product was first registered. For example, there are now multiple sources

s47 [redacted]

for prescriber education (not just the Sponsor's education program). After over 8 years of registration, the product has been widely used, is well understood by both GPs and hospital clinicians, and clinicians better understand the need to provide post-treatment support to their patients (instead of it being provided by the product sponsor) compared to when the product was first introduced.

For ease of review the following versions of the RMP are being submitted:

- A fully annotated copy of the RMP which includes all changes that are currently under review by the TGA and the proposed additional changes (highlighted in blue) (version 4.0 dated 17 February 2023)
- An annotated copy of the RMP in which the proposed changes submitted as part of sequence 0008 (version 4.0 dated 13 January 2023) have been accepted and only the additional changes that are proposed as part of the V4.0, 17 February 2023 updated version are annotated.
- A clean copy of the proposed RMP

Additionally, the proposed changes to the RMP will result in the removal of the associated requirements for prescriber certification and the 24-hour telephone helpline in the Product Information (PI) (Sections 4.2 and 4.4 of the PI refers). The sponsor proposes to provide the amended PI reflecting the proposed changes as part of the response to the Milestone 3 evaluation report.

This dossier is submitted in eCTD format and further technical details pertaining to the electronic submission are provided in Appendix 1.

Please do not hesitate to contact me on s22 [redacted], by facsimile on s22 [redacted] or by email at s47 [redacted] if you require any further regulatory or information technology assistance with this submission.

Yours faithfully,

s22 [redacted]

s22 [redacted]
Senior Consultant, Regulatory, Quality and Compliance
s47 [redacted]
(Agents on behalf of MS Health Pty Ltd)

s47 [redacted]

Appendix 1: Electronic Submission Details

eSubmission identifier	e004967
Format	eCTD
Specification	AU 3.1
eBS Client ID	57301
Approved Name	Mifepristone, Misoprostol
Trade Name	MS-2 Step
ARTG Number(s)	210574
Submission Number	PM-2022-05475-1-5 PV-1
Sequence	0009
Related Sequence	0007
Regulatory Activity Lead	Prescription meds-chemical
Sequence type	Supplementary Information
Sequence description	AU RMP 4.0, 17 February 2023
Submission Mode	Single
Electronic media	Email
Submission size	~ 2.22 Mb
Validation tool and version	Lorenz eValidator v.21.2
Validation Findings	**4.1.24 Warning** • The operation for the risk management plan must always be 'replace' after the initial 'new' Two annotated RMP are included in the dossier. **4.3.2 Warning** • A response document has not been provided as it is not required. A copy of the validation report can be provided upon request.
Virus Protection Software and Assurance	Webroot Secure Anywhere Endpoint Protection v9.0.26.61. An assurance is provided that the electronic dossier is virus free.
Contact email	s47 [redacted]

1.0 Correspondence

1.0.2 Lifecycle Management Tracking Table

Sequence	Sequence Type	Sequence Description	Related Sequence	Regulatory Activity	Date
0009	Supplementary Information	AU RMP 4.0	0007	Removal of prescriber certification and mandatory training	February 2023
0008	Supplementary Information	Response to Request for Information – 2022-12-13	0006	RFI to Updated AU RMP v4.0	January 2023
0007	J – PI change requiring evaluation	Initial	0007	Category 1 Application Type J	December 2022
0006	Risk Management Plan	AU RMP 0.4	0006	Updated AU RMP v0.4	November 2022
0005	9D(1) – Correct an ARTG entry - Indications	Initial	0005	Request to correct the indication in the public ARTG summary to align with the PI approved in the previous submission	September 2022
0004	H-Minor Variation, Not Resulting in a New Register Entry 9D(2C) Notification	Initial	0004	Addition of new Australian site for secondary packaging and release for supply	September 2022
0003	Supplementary Information	Product Information	0003	Provision of finalization sequence for approved PI	August 2022
0002	H-Minor Variation, Not Resulting in a New Register Entry 9D(2C) Notification	Initial	0002	Addition of new site for excipient Povidone K - 30	August 2022
0001	J – PI change requiring evaluation	Initial	0001	Category 1 Application Type J	July 2022
Sequences submitted below were submitted in NeeS format					
0010	9D(1) - Correction of Register Entry	Initial	0010	Shelf life correction	January 2020
0011	H-Minor Variation, Not Resulting in a New Register Entry 9D(3) – Change to PI (not J)	Initial	0011	PI reformat and TGO 91 label update	April 2020
0012	Supplementary Information	Response to Request for Further Information – 2020-06-16	0011	RFI TGO91 Label update	June 2020

0013	Periodic Safety Update Report	PSUR for period of 1 June 2019 to 31 May 2020	0013	PBRER No.5	August 2020
0014	9D(2C) Notification	Initial	0014	TGO91 Label updates	October 2020
0015	9D(2) Safety Related Request	Initial	0015	Addition of warning statement regarding severe cutaneous adverse reactions.	July 2021
0016	Periodic Safety Update Report	PSUR for period of 1 June 2020 to 31 May 2021	0016	PBRER No.6	October 2021
0017	H-Minor Variation, Not Resulting in a New Register Entry	Initial	0017	Addition of new testing site	February 2022
0018	9D(2) Safety Related Request	Initial	0018	Safety related changes and Minor Editorial changes to the PI to align with CCDS	June 2022

Sequences 0000-0009 submitted by previous agent.

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

CTD Module 1, Section 1.8.2
Risk Management Plan Version 4.0~~0.34~~

Module 1.8.2 Risk Management Plan

Commented s22 RMP reformatted to the current RMP format

MS-2 Step

Composite pack containing:

MIFEPRISTONE LINEPHARMA 200 mg Tablet mifepristone 200 mg

and

GyMiso® misoprostol 200 µg tablets

RMP version to be assessed as part of this application:	
RMP version number:	4.0~~0.4~~
Data lock point for this RMP:	31 May 2022
Date of final sign off:	17 February 2023
Rationale for submitting an updated RMP	This RMP has been updated as follows: To include the revised Education Program material included as Appendix 1, the format of the RMP has also been updated. To remove the need for pharmacists to be registered to ~~restricted~~be able to dispense the product. To remove the requirement for recertification training. Updated summary concerns and additional risk minimisation activities. To remove the need for prescribers to complete mandatory training and receive certification to be able to prescribe the product. To remove the requirement for a Sponsor provided 24 hours aftercare service
Summary of significant changes in this RMP:	Revised into current EU-RMP template
Other RMP versions under evaluation:	Version 4.0, 14 January 2023~~NA~~
~~RMP version number:~~	~~Not applicable~~
~~Submitted on:~~	~~Not applicable~~
~~Procedure number:~~	~~Not applicable~~
Details of the currently approved RMP:	
Version number:	Version ~~0.3~~3.0; Data lock point 28 April 2013

Commented s22 FI 13 Dec

Commented s22 Minor editorial changes

Commented s22 Version 17 Feb 2023 additional changes

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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Approved with procedure:	Version ~~0.3~~3.0 was submitted on 14 November 2014 and provides documentation as agreed with the Office of Product Review and revised information, following the registration of MS-2 Step in May 2014. (Submission ID: PM-2013-01037-1-5)
Date of approval:	28 May 2013

QPPV name:

Date:

QPPV signature:

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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PART I: PRODUCT(S) OVERVIEW

Table 1 Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	MS-2 Step is a composite pack consisting of one pack of Mifepristone Linepharma (one mifepristone 200 mg tablet) and one pack of GyMiso® (four misoprostol 200 microgram tablets).
Pharmacotherapeutic group(s) (ATC Code)	**Component:** mifepristone G03XB51, mifepristone, combinations **Component:** misoprostol G02AD06, misoprostol
Name of Sponsor	MS Health Pty Ltd
Medicinal products to which this RMP refers	MS-2 Step (containing Mifepristone Linepharma and GyMiso®)
Invented name(s) in Australia	MS-2 Step (containing Mifepristone Linepharma and GyMiso®)
Brief description of the product	Chemical class **Component:** Mifepristone Linepharma Mifepristone is a synthetic competitive progesterone receptor and cortisol receptor antagonist **Component: GyMiso®** Misoprostol is a synthetic analogue of prostaglandin E1.
	Summary of mode of action **Component:** Mifepristone Linepharma. Mifepristone acts via high-affinity reversible binding to the human progesterone and cortisol receptors. **Component: GyMiso®** At the recommended dosages, misoprostol induces contractions of the smooth muscle fibers in the myometrium and relaxation of the uterine cervix. The uterotonic properties of misoprostol should facilitate cervical opening and evacuation of intrauterine debris. In the event of an early termination of pregnancy, the combination of GyMiso® used in a sequential regimen after mifepristone leads to an increase in the success rate and accelerates the expulsion of the conceptus.
	Important information about its composition N/A
Hyperlink to the Product Information	Module 1.3.1

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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Indication(s) in AU	***MS-2 Step*** is indicated in females of childbearing age for the medical termination of ~~a developing~~an intrauterine pregnancy, up to 63 days of gestation. It is recommended that the duration of pregnancy (i.e., up to 63 days gestation) be confirmed by ultrasound. In the event that an ultrasound is not possible, extra caution should be exercised. Ultrasound is also useful to exclude ectopic pregnancy
Dosage in AU	Mifepristone Linepharma: 200 mg of mifepristone (1 tablet containing 200 mg) orally, followed 36 to 48 hours later by the administration of GyMiso®. GyMiso®: 800 micrograms of misoprostol (4 tablets, each tablet containing 200 micrograms) buccally, i.e: kept between the cheek and the gum for 30 minutes before any fragments being swallowed with water.
Pharmaceutical form(s) and strengths	**Component:** Mifepristone Linepharma Tablet Mifepristone 200 mg **Component: GyMiso®** Tablet Misoprostol 200 micrograms
Is/will the product be subject to additional monitoring in AU?	No

Commented [S22]: Updated in accordance with the approved indication, through the RMP

PART II: SAFETY SPECIFICATION

SI – EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

Indication

MS-2 Step is indicated in females of childbearing age for the medical termination of ~~a developing~~an intrauterine pregnancy, up to 63 days of gestation.

It is recommended that the duration of pregnancy (i.e., up to 63 days gestation) be confirmed by ultrasound. In the event that an ultrasound is not possible, extra caution should be exercised.

Ultrasound is also useful to exclude ectopic pregnancy.

Incidence:

Data from a number of Australian states on pregnancy termination rates applied to the Australian female population aged 15 to 44 years as at June 2009 indicates that between approximately 82,000 to 95,000 surgical terminations may occur in Australia each year. (1,2) Assuming that 30 percent of terminations of pregnancies are eligible for the medical method with mifepristone followed by misoprostol, then approximately 24,600 to 28,500 terminations could be performed with the medical method each year.

To this figure should be added the number of cases in which mifepristone will have been used for cervical priming prior to D & C for second trimester termination. The incidence of second term pregnancy termination is very low (approximately 8 / 1,000 births (3), thus may involve 2,000 cases per annum in Australia.

Prevalence:

Not applicable – refer to Incidence.

Demographic profile of target population:

Women of reproductive age, no specific profile.

The main treatment options:

In general, where pregnancy termination is legal (as is the case in most EU countries), D&C or vacuum aspiration, which are the standard surgical procedures for first trimester pregnancy termination are very safe: in a study of more than 14,000 subjects (4), the following complications were reported after suction curettage (SC):

Complication	SC only, *n* (%)	SC with dilatation, *n* (%)
Retention of fetoplacental material	228 (2.7)	129 (2)
Excessive bleeding	168 (2)	128 (2)
Infection	81 (< 1)	60 (< 1)
Perforation	None	7 (0.05)
Persistant fever	None	None
Unintended major surgery	None	None
Hemorrhage requiring transfusion	None	None

As shown in the table, retention of foetoplacental material and excessive bleeding are the most frequent, albeit rare, complications. Death appears exceptional in this indication and is related to general anaesthesia whenever used.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Not applicable.

Important co-morbidities:

No significant co-morbid conditions have been identified in the target population of women of reproductive age.

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Potential health risk:

A review of the safety of mifepristone from first trimester termination of pregnancy in the USA (5) reported an overall complication rate of 2.2 per 1000, with infection (0.2 per 1000), bleeding requiring transfusion (0.5 per 1000) and deaths 1.1 per 100,000.

Improper use of medical termination of pregnancy could lead to potential health risk linked to excessive bleeding, incomplete foetal expulsion and infection. Such risk can be minimized by ensuring medical practitioners have access to education and training resources. ~~adequate training of medical practitioners~~.

Commented S22 Proposed removal of mandatory training program for prescribers

Since the use of mifepristone and misoprostol cannot terminate a pregnancy in 100% of the cases, the background incidence of congenital anomalies is presented below.

Table 2 Epidemiology of congenital anomaly

Identified or potential risk	Congenital anomaly
Incidence of condition	Congenital anomalies are reported in some 2.2% of live births, with the most common anomalies being cardiac malformations (68/10,000 births), orofacial clefts (16/10,000 births) and genital malformations (16/10,000 births) (EUROCAT Central Registry, Report 2004-2005).
Prevalence of condition	Not applicable.
Mortality of condition	Not applicable.
Risk factors	Some congenital anomalies can be attributed to a mother's genetic predisposition. Other risk factors include age (over 35), use of certain drugs and alcohol, and smoking during pregnancy.

SII – NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

Table 3 Safety concerns and relevance to human usage

Mifepristone	
Safety concern	**Relevance to human usage**
Pharmacology: Antiprogesterone activity Mifepristone prevented pregnancy maintenance in rats, rabbits, guinea pigs and monkeys as a consequence of its anti-progesterone activity. Anticortisol activity Mifepristone exerts anticortisol activity (due to receptor antagonism) in a variety of in vitro and in vivo models. Studies in humans have confirmed the existence of anticortisol activity. However, such activity can be	These actions justify the clinical use of mifepristone in humans (pregnancy termination). None given the duration (single-dose administration) of treatment, given the reversibility of cortisol blockade.

Mifepristone	
Safety concern	**Relevance to human usage**
demonstrated after repeated use at daily doses of 200 mg or more, and can be reversed (1 mg dexamethasone reverses the cortisol blockade induced by 400 mg mifepristone). In addition, cortisol blockage results in an increase in ACTH and cortisol blood levels which in turn overcome the cortisol receptor blockade induced by mifepristone. Antiandrogenic, estrogenic and antiestrogenic, mineralocorticoid and antimineralocorticoid activities. At repeated doses, mifepristone exhibits partial androgen antagonism in animal models. It exhibits little estrogen estrogenic or anti-estrogenic activity in spayed and immature animals but caused an increase in ovarian weight and prolonged estrus in mature animals and displays no antimineralocorticoid activity against aldosterone nor any mineralocorticoid activity (see section 2.4.3 of dossier).	None (single-dose administration)
Safety pharmacology: Mifepristone was evaluated in a variety of standard pharmacological tests (see section 2.4.3.3 of dossier). CNS activity - Only effect noted was a potentiation of the hexobarbital sleeping time in rodents with oral doses of 10-100 mg/kg. Autonomous nervous system activity In vitro, mifepristone antagonized acetylcholine, histamine and serotonin in the isolated guinea pig ileum at a concentration of 10-4M. Cardiovascular/respiratory activity No effects were seen at doses up to 10 mg/kg. Gastrointestinal activity No effects at doses up to 100 mg/kg. Genitourinary activity Mifepristone decreased sodium excretion at doses of 10-100 mg/kg, potassium at 30-100 mg/kg and the sodium/potassium ratio. Urine volume was increased at the 100 mg/kg dose. Endocrine activity In fasted rats, mifepristone produced a slight hypoglycemic effect at doses of 30-100 mg/kg. Analgesic / anti-inflammatory activity No effects at doses up to 100 mg/kg.	There is no finding which would be relevant when used as a single administration with a dose of 200 mg.

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Mifepristone	
Safety concern	**Relevance to human usage**
Haematological activity No significant effects.	
Pharmacokinetic interactions: Using in vitro studies, mmifepristone has been shown to be a potent mechanism-based inactivator of human CYP-3A4 (see section 2.4.4.4 of dossier).	The clinical significance of the inactivation of CYP-3A4 by mifepristone is that it would be expected to increase the bioavailability of several clinically used drugs metabolized by CYP-3A4 such as cyclosporine A, tacrolimus and dihydropyridines.
Repeated dose toxicity studies: (See section 2.4.5.2 of dossier) Pituitary, adrenals, mammary, ovary, uterus, vagina, fallopian tubes: The toxicological profile emerging from these studies appears to be a consequence of the anti-progesterone and anti-glucocorticoid properties of mifepristone. Liver and kidney: Increase weight associated with hepatocyte hypertrophy in rats and in monkeys. Thyroid: In a chronic toxicity study, a thyroid follicular adenoma was seen in one high-dose female rat.	The effects observed in the toxicity studies were seen after repeated daily dosing. They appeared unspecific and are unlikely to be of consequence in women after a single 200 mg dose of mifepristone. This effect was observed after repeated daily dosing. It is unlikely to be of consequence in women after a single 200 mg dose of mifepristone.
Reproductive and developmental toxicity: Fertility: Mifepristone was administered orally to groups of 12 female Sprague-Dawley rats for 3 weeks at doses of 0, 0.3 or 1.0 mg/kg/day. After the end of treatment rats were observed for 5 weeks after which they were mated with untreated males. Cycles were monitored by daily vaginal smears. Results: The oestrous cycle was disrupted at both doses within 10 days of treatment. Withdrawal of treatment resulted in gradual dose-dependent restoration of the cycle over 2 - 3 weeks. Reproductive endpoints of mating, gestation, parturition, litter size, morphology of offspring, bodyweight change and survival were not affected by drug treatment. Embryofoetal development: Mouse	These findings suggest that if a woman is exposed to a 200 mg dose of mifepristone early during her pregnancy, no deleterious effects on foetal development are necessarily expected if pregnancy is maintained. Reproductive function should not be altered.

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Mifepristone	
Safety concern	**Relevance to human usage**
Groups of 25 Swiss CD 1 mice were gavaged with vehicle, 0.5, 1 or 2 mg/kg/day mifepristone from day 6 to 17 of gestation. Clinical signs: None Body weight: Almost complete suppression of body weight gain in the 2 mg/kg/day group. Moderate suppression in the 1 mg/kg/day group. Final body weights (day 18) were Controls - 62.8; Low-dose - 58.9; medium-dose - 48.0; high-dose - 34.8 grams. There was a marked dose-related increase in fetal loss. The mean rate was 21% in low-dose; 60% in medium-dose and 100% in high-dose. Foetal weights were normal in the survivors. Foetal examination: There were no treatment related increases in foetal anomalies or malformations. Rat Groups of 25 pregnant Sprague-Dawley rats were gavaged with vehicle, 0.25, 0.50 or 1.0 mg/kg/day mifepristone from day 6 to day 17 of gestation. Clinical signs: None Body weight: weight gain was comparable between groups except for the high-dose group where there was a retardation at the end of treatment. Six high-dose rats had no living foetuses at autopsy. The post-implantation loss was 34% compared to 5.7% in controls (statistically significant). Foetal weights were equal between groups and the sex ratio was the same. Foetal examination: There were no treatment related differences in foetal anomalies or malformations. Rabbit Groups of 15-20 HY rabbits were gavaged with vehicle, 0.25, 0.5,1, 2, or 4 mg/kg/day mifepristone from day 6 to 18 of gestation. The two highest doses increased foetal loss (31% and 67% cf. 6% for controls) and increased the incidence of incomplete ossification of the cranium, sternum and paws, without affecting maternal body weight or producing clinical signs. In a published study in rabbits, treatment with mifepristone on 0.5 or 1 mg/day s.c. for 1-5 days starting on day 11 of gestation was associated with foetal malformations (failure	These data suggest some potential for adverse effects on foetal development, including teratogenicity, with exposure to mifepristone where pregnancy is maintained. The abnormalities observed in animals most likely occurred as a consequence of the mifepristone's effect on the uterus rather than any direct effect of the drug on the foetus. These results indicate that in case a woman carries her pregnancy to term despite exposure to mifepristone during pregnancy, there is some potential for postnatal development to be delayed.

Mifepristone	
Safety concern	**Relevance to human usage**
of the cranium to close and haemorrhagic destruction of the upper part of the head and brain, no spinal column, no closure of eyelids) considered to be treatment-related. Monkey A case of holoprosencephaly in a fetus of a cynomolgus monkey that had been treated with mifepristone at 2.5 mg/kg/day i.m. from day 15 to 18 of gestation is reported in the literature. This was considered most likely to have occurred secondary to disturbed development of the gestational sac and placenta due to an incomplete abortion, reducing blood supply to the conceptus. Pre-/post natal development: Groups of 20-25 Sprague-Dawley rats were gavaged with vehicle or 0.25, 0.5 or 1 mg/kg/day mifepristone from day 15 of gestation to the end of the lactation period (postnatal day 21). Increase morality at birth (not statistically significant) and delayed development of the righting reflex and slight inhibition of locomotor development were observed at the high-dose level. Other developmental parameters and the reproductive performance of the offspring were unaffected. Male and female Sprague-Dawley pups from 15 litters were injected s.c. 1 day after birth with vehicle, 1, 10 or 100 mg/kg mifepristone. On day 4, the number of offspring in each litter was reduced to 8 (4 of each sex) using a random distribution table. The general condition and growth of the offspring was not affected by treatment. Descent of testes was normal but there was a slight delay in vaginal opening in the high-dose females (not significant). At the age of 11 or 15 weeks, histopathology revealed no effects on the testes and activity of the seminiferous tubules. Reproductive function, assessed by mating rate and fertilizing capacity, was not affected by treatment. Disruption of normal sexual development in neonatal Wistar rats given 1 mg mifepristone s.c. every second day from postnatal day 1 or 4 for 14 days is reported in the literature.	

Misoprostol	
Safety concern	**Relevance to human usage**
Misoprostol, 15-deoxy-16-hydroxy-16-methyl-PGE1, is a synthetic analogue of PGE1.	

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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Misoprostol	
Safety concern	**Relevance to human usage**
Prostaglandins contract or relax many smooth muscles. Strips of non-pregnant human uterus are relaxed by PGEs; strips from pregnant women are contracted by low concentrations of PGE2 and relaxed by high concentrations. Intraperitoneal and oral administration of misoprostol induced diarrhoea in mice and rats, respectively, with ED50 values in the rat after oral administration being in the range 366-1305 µg/kg, depending on when in the 8-hour observation period following dosing the effect was measured. Oral administration of 30 µg/kg of misoprostol to conscious dogs did not affect blood pressure, heart rate or the ECG. Misoprostol inhibited histamine-induced bronchoconstriction in the anaesthetized guinea-pig after intravenous administration of 10-1000 µg/kg, the effect depending on the intensity of the histamine challenge; effects against a PGF2α challenge were more variable.	These actions justify the clinical use of misoprostol in humans (pregnancy termination). None (single-dose administration)
Toxicological information Single dose toxicity Oral LD50 values in mice and rats were 27-138 and 81-100 mg/kg, respectively, with corresponding values after intraperitoneal dosing of 70-160 and 40-62 mg/kg. In an ascending dose study in dogs, no deaths were observed at 10 mg/kg, the maximum dose administered. The most prominent clinical signs were diarrhea and reduced motor activity in rodents and, in dogs, emesis, tremors, mydriasis and diarrhea. Most deaths occurred within 24 hours of dosing and surviving animals appeared normal within 3-4 days. Repeat dose toxicity The rat and dog were selected as the species for the repeated dose toxicity studies. Rats Studies in the rat were of 5, 13 and 52 weeks duration; the 52 week study incorporated a 13 week recovery period. Administration 0, 160, 320, 1200, 1600, 8000 and 9000 µg/kg/day. The major clinical signs were diarrhoea, salivation, vaginal dilation and discharge, decreased body weight (mainly males) and increased food consumption. There was no effect on rectal temperature in the 5 week. In the 52 week study, no abnormal clinical signs were observed at 160 µg/kg/day and all signs at the higher doses of 1200 and 9000 µg/kg/day were absent by the end of the 13 week recovery period.	The effects observed in the toxicity studies were seen after repeated daily dosing. They appeared unspecific and are unlikely to be of consequence in women after a single 800 µg dose of misoprostol.

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

CTD Module 1, Section 1.8.2
Risk Management Plan Version 4.0~~0.34~~

Misoprostol	
Safety concern	**Relevance to human usage**
There were no deaths that were attributable to treatment. Principal clinical biochemistry changes were decreases in serum total protein and increases in serum iron, with any changes in other parameters remaining within normal limits and considered incidental. The decrease in protein levels may be a consequence of poor absorption of nutrients resulting from diarrhoea. Serum iron was significantly increased at 9000 µg/kg/day in the 52 week study and at 1600 and 8000 µg/kg/day in the 5 week study. Any changes in laboratory parameters seen at the end of the 52 week study were absent after the 13 week recovery period. Dogs Studies in the dog were of 5, 13 and 52 weeks duration. Doses for the 52 week study were 0, 30, 100 and 300 µg/kg/day. These studies included recovery periods of 4 and 13 weeks. The most important clinical signs in these studies were emesis, diarrhoea, soft and/or mucoid stools and increased rectal temperature; these were dose related and either decreased or were absent by the end of the 4 and 13 week recovery periods. There were two deaths in the 52 week study, both in animals receiving 300 µg/kg/day. Changes in clinical biochemistry parameters were incidental or within normal limits, with the exception of serum chloride, which increased slightly in the 52 week study; there were no abnormal clinical laboratory findings at the end of the recovery periods.	
Genotoxicity Misoprostol was negative in five in vitro tests of genotoxic potential – the Ames test in five strains of Salmonella typhimurium, the mouse lymphoma TK+/- assay, mitotic gene conversion in Saccharomyces cerevisiae, a sister chromatid exchange assay in CHO cells and a C3H/10T 1/2 cell transformation assay. The first four of these were performed in the absence and presence of metabolic activation. In addition to these tests, an abstract (6) cites a negative result in an in vivo mouse micronucleus test.	None

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CTD Module 1, Section 1.8.2
Risk Management Plan Version 4.0~~0~~.~~34~~

Misoprostol	
Safety concern	**Relevance to human usage**
Carcinogenicity The potential carcinogenicity of misoprostol has been evaluated in both mice and rats. The study in mice was of 21 months duration and administered doses of 0, 160, 1600 and 16000 µg/kg/day by gavage. In the rat study, doses of 0, 24, 240 and 2400 µg/kg/day were administered for 24 months by gavage. There was no indication of a carcinogenic effect in either species. In both species, there were statistically significant increases in epithelial hyperplasia and hyperkeratosis of the gastric mucosa; these were non-neoplastic and expected as a consequence of the pharmacological activity of misoprostol. This was also observed in the 52-week study in rats where it was seen to be reversible on stopping treatment. In addition, hyperostosis of the marrow cavity of sternebrae and femurs was observed in mice. This has also been reported for PGE2 in rats, dogs and children. However, this was not seen in the 24-month carcinogenicity study in rats with misoprostol, nor in the 52-week repeated dose toxicity study in dogs. It thus appears to be a phenomenon restricted to mice for misoprostol.	Given the short duration of administration to women covered by the current application, its relevance to the intended use of misoprostol is doubtful.
Reproductive and developmental toxicity: Two fertility studies were performed in the rat. One was with doses of 0, 100, 1000 and 10000 µg/kg/day; males were treated from day 71 premating until mating and females from 15 days premating to parturition. The other used doses of 0, 100, 400 and 1600 µg/kg/day; males were treated from day 70 premating and females from 14 days premating to day 7 of gestation. The number of implantations was decreased at 1600 and 10000 µg/kg/day and an increase in resorptions occurred at 1000 and 10000 µg/kg/day in one study, but not at 1600 µg/kg/day in the other; resorptions were not increased in the rat teratology study at doses up to 10000 µg/kg/day. As a consequence of these events, there were a decreased number of live foetuses or pups at 10000 µg/kg/day and a decreased number of foetuses at 1600 µg/kg/day. Foetal and pup survival and development were not affected. Two teratology studies were performed in rats using the same doses as the fertility studies with dosing on days 6 to 15 or 7 to 17 of gestation; there was no evidence of embryotoxicity, foetotoxicity or teratogenicity. Two rabbit studies, at doses of 0, 100, 300 and 1000 µg/kg/day on days 6 to 18 of gestation also showed no evidence of foetotoxicity or teratogenicity, although there was an increased number of resorptions at 1000 µg/kg/day in one study.	On the basis of the studies summarized in this application, there would not seem to be cause for concern with respect to possible effect on the foetus of misoprostol in circumstances where termination of pregnancy in association with mifepristone was not successful and the pregnancy was allowed to continue. However, misoprostol, through its smooth muscle contracting activity, could have effects on the developing foetus and there are several reports in the literature on the occurrence of congenital defects in children born to mothers who had taken misoprostol to terminate pregnancy; this off-label use of misoprostol appears to have been a particular problem in Brazil, from where considerable evidence has accumulated on its possible teratogenic activity in humans (7,8). Data would suggest a link between misoprostol and congenital malformations, based on a retrospective analysis of cases, and a

Misoprostol	
Safety concern	**Relevance to human usage**
A rat pre/postnatal study used doses of 100, 1000 and 10000 µg/kg/day administered from day 15 of gestation to day 20 postpartum. Pup survival was unaffected, though a decrease in pup weight gain was apparent at 10000 µg/kg/day. The studies summarised above showed effects of misoprostol in decreasing implantations and increasing resorptions in rats and rabbits, but did not show any indication of a teratogenic effect. Moreover, the doses at which effects on implantations and resorptions were observed were 1000 µg/kg/day and above, levels 75 times higher than the 800 µg dose recommended in this application for use in the termination of pregnancy. In a more targeted embryotoxicity / teratogenicity study in the mouse, pregnant Han:NMRI mice were treated with single doses of 20 or 30 mg/kg of misoprostol on day 10 of pregnancy. A slight and reversible decrease in maternal weight gain was seen at both doses. Whereas there was no evidence of embryotoxicity at the 20 mg/kg dose, resorptions were increased at 30 mg/kg and an increased occurrence of cleft palate as well as other skeletal abnormalities was observed in surviving foetuses at this dose level. Embryotoxic effects of other prostaglandins have been reported, including PGE2 and PGF2α and rioprostil, a synthetic PGE1 analogue; these effects were attributed, at least in part, to the disturbances in blood supply to the foetus caused by these potent agents. Misoprostol will also reduce uterine blood flow and this could be the cause of the apparent malformations described in humans, although humans seem much more sensitive to misoprostol than mice, rats or rabbits.	prospective study based on Brazilian data suggested that misoprostol may increase the incidence of congenital anomalies, but that the magnitude of the increased risk is low (9).

SIII – CLINICAL TRIAL EXPOSURE

Clinical efficacy of early medical abortion is defined as complete abortion without surgical intervention, regardless of the reason for the intervention, which may include continuing pregnancy, missed or incomplete abortion, prolonged or heavy vaginal bleeding or a woman's request.

The clinical trial exposure to MS-2 Step includes the following studies.

An open-label single-group prospective trial (Study 1.1.4) performed in Mexico by Gynuity Healthcare, USA, involving 971 women available for efficacy treated with 200 mg mifepristone followed by 800 micrograms misoprostol administered buccally indicated that efficacy was 98.0, 96.8 and 95.9% for women with gestational age 49 days and below, 50-56 days and 57-63 days, respectively. In these 3 gestational age groups, the rate of surgical evacuation was 2.0, 3.2 and 4.1% respectively. In this study 25 women received a second dose of misoprostol, in each case, a dose of 800 micrograms by the buccal route. Of those 25, 20 had a successful outcome with

medication alone, 4 had a surgical intervention and 1 woman did not return for follow up. In this study, bleeding occurred in all women independent of outcome, and was judged as more than expected in 27.1% of the women.

In an observational cohort study of 15 008 women attending one of 16 Marie Stopes International clinics in Australia for MTOP (gestational age < 63 days) between 1 March 2013 and 30 September 2015, patients were administered~~ration~~ 200 mg mifepristone orally in-clinic, followed 24-48 hours later by 800 micrograms of misoprostol buccally, self-administered at home. Method success was defined as complete abortion not requiring surgical intervention. Follow up information was available for 13,078 (87.2%) of the total cohort. Medical abortion was successful in 95.16% (12,445/13,078) of women with follow-up. Higher patient and gestational ages were associated (P < 0.001) with a slight increase in method failure. There were 674 serious adverse events (5.15%), mainly due to method failure. Infection (15; 0.11%) and haemorrhage (17; 0.13%) were rare. One death was recorded (<0.01%); however, an association between EMA and cause of death, necrotising pneumonia, was not established (26)

Commented [S22] RFI 13 Dec 2022

Commented [S22] Updated data added post completion of the post marketing study

Studies published in the literature have reported mifepristone and oral or buccal misoprostol regimens. In one study of 966 patients(10) with pregnancies up to gestational age of 63 days, randomised to 200 mg mifepristone followed 24-36 hours later by 800 micrograms of misoprostol orally or buccally, reported efficacy rates were 91.3% for the oral and 96.2% for the buccal group (RR 0.95, 95% CI 0.92-0.98, p=0.003).

Studies published on the combination of mifepristone 200 mg and misoprostol 800 micrograms buccally, and reporting outcomes by gestational age, encompass 399 women with gestational ages 50 – 56 days and 344 women with gestational ages 57 – 63 days (10–16). Efficacy ranged from 86.5 to 98.5% in women with gestational age 50 – 56 days and from 93.0 to 100% in those with gestational age 57 – 63 days. In these studies, the rate of ongoing pregnancies ranged from 0 to 7.1% in women with gestational age 50 – 56 days and from 0 to 2.3% in those with gestational age 57 – 63 days.

Literature data provides information on the bleeding and expulsion pattern after termination of pregnancy with mifepristone and misoprostol: approximately half of women start to bleed before prostaglandin administration. Median bleeding time is 10 to 16 days. Bleeding is judged more or much more abundant than usual menses for 2 to 3 days after prostaglandin. In studies where it was measured, there was a slight but significant decrease in haemoglobin level after compared to baseline. In one study blood loss was quantified: the median blood loss was 83 mL and 5.4% of women had a blood loss above 200 mL. Expulsion usually takes place within 3 hours after misoprostol in approximately half of the women, and within 4 hours after misoprostol in approximately 50 to 90% of women.

SIV – POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Under the Authorised Prescribers Program in Australia in 2012, there were 7,166 medical terminations. Efficacy was 97.4% for women with gestational age <49 days, and 95.2% for women with gestational age of 49-63 days. The rate of incomplete termination requiring aspiration was: <49 days: 2.3%; 49-63 days: 4.8%. The rate of ongoing pregnancies was: <49 days: 0.3%; 49-63 days: 0.6%. Bleeding was considered as an adverse event in 0.24% of women, independent of pregnancy age.

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Not applicable.

SIV.2 Limitation to detect adverse reactions in clinical trial development programs

Not applicable.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programs

MS-2 Step is for use in women of childbearing age.

There is limited data available for use of ***MS-2 Step*** in women under 18 years of age. There is no relevant use of MS-2 Step in the prepubertal paediatric population in the indication. Administration to adolescents less than 18 years of age should be undertaken with caution.

SV – POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

Seventy nine thousand four hundred and three (79, 403) women ~~,~~ have been exposed to Mifepristone Linepharma 200 mg tablet (Sweden, Norway, Finland, Kenya, United-Kingdom, Denmark and Australia).

Commented s22 Minor editorial changes

For GyMiso®, since launch in 2004, one hundred and eighty seven thousand three hundred and thirty three (187,333) women have been exposed to GyMiso® (as per the most recent PSURs).

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Literature surveys indicate that in Western countries approximately 2 million women have been exposed to mifepristone and misoprostol for termination of pregnancy since its first approval in France in 1989. In China, exposure to mifepristone is estimated at 13 to 39 million women (Professor Linan Cheng, Shanghai Institute of Planning Parenthood Research, personal communication).

SVI – ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for improper use

The MS-2 Step product is presented as a composite pack in a carton containing two cartons, each of which is different in appearance (as described below). The generic names of the two component medicines, i.e. mifepristone and misoprostol, appear beneath the name MS-2 Step on the composite pack carton.

The two component products contain different amounts of their respective medicines. The labelling on the component products clearly identifies the right order for taking the two products.

An instruction insert ~~will~~ is ~~be~~ placed in each MS-2 Step product carton to explain the right order for intake of the two products, the recommended time period between intake of the two products, and the importance of a follow-up appointment 14-21 days following the administration of Mifepristone Linepharma to confirm successful termination of pregnancy.

Commented s22 Editorial changes through out the RMP to change the text to t he current state

The correct way to take the two products is also described in the respective Consumer Medicine Information sheets that are placed inside each component product carton.

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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These component products are distinguished from each other in the following ways:

- The Mifepristone Linepharma 200 mg Tablet carton has a green colour on it, and it contains only one mifepristone tablet
- The GyMiso® carton has a purple colour on it, and it contains 4 misoprostol tablets
- Mifepristone Linepharma packaging ~~will include~~includes the statement Step 1, take this tablet first.
- GyMiso packaging ~~will include~~includes the statement Step 2 take these 36 to 48 hrs after Mifepristone Linepharma

Potential for misuse for illegal purpose

Mifepristone Linepharma and GyMiso® are components of MS-2 Step available by prescription only from ~~qualified~~ medical practitioners hereafter referred to as prescribers. The distribution of MS-2 Step and Mifepristone Linepharma (monopack) in Australia ~~will occur~~occurs using the secure distribution channels for prescription medicines that operate in this country. There is therefore very low potential for misuse.

Commented s22 17 Feb 2023 Update

Potential for off label use in adults

In some other countries, mifepristone is approved for softening and dilatation of the cervix prior to surgical termination of pregnancy during the first trimester and labour induction in foetal death in utero. Similarly, misoprostol is approved in other territories for cervical preparation before surgical abortion during first trimester, labour induction and treatment and prevention of post-partum haemorrhage.

To date, since Marketing Authorisation has been granted for both products, off label use of Mifepristone Linepharma and GyMiso® has been continuously evaluated: there has been no concern regarding off label use of these drugs.

Use of oral misoprostol beyond 49 days of gestation is associated with lower efficacy, and the acceptable regimen for dosing of GyMiso® by the buccal route only is stated in the MS-2 Step Product Information, in the Consumer Medicine Information Instruction Insert in the MS-2 Step -carton, as well as in the Consumer Medicine Information for each component product.

Uterine hyperstimulation and rupture have been reported beyond the first trimester when much lower dosage of misoprostol may be required.

Potential for off label use in children

Mifepristone Linepharma 200 mg Tablet and GyMiso® are recommended for use in females of childbearing age. There are limited data available in women below the age of 18 years. It is possible that the treating medical practitioner will use their discretion and may use the medical method of termination in child-bearing adolescents aged over 12 years of age. It would be expected that the medical practitioner would seek informed consent from a legal guardian before use of the medical method as per use of any method for termination of pregnancy. The sponsor is not aware of any available evidence at present that risks might arise from such off-label use beyond the risks documented herein.

The Sponsor has completed a report on use of mifepristone and misoprostol for termination of early pregnancy under the Authorised Prescriber ~~programme~~program for the period September 1, 2009 to the end of August 2011. During this time 13,345 clients were treated and of that number 939 were

aged between 14 and 19 years. No risks have been identified in that study specific to that patient group.(10)

Potential for overdose

The EU SPC for Mifegyne® and the current Mifepristone Linepharma Australian Product Information indicate that no overdose has been reported.

In the event of massive ingestion signs of adrenal failure might occur. Signs of acute intoxication may require specialist treatment including the administration of dexamethasone.

As a component of MS-2 Step, Mifepristone Linepharma 200 mg Tablet is only available by prescription as a single pack containing only one tablet. ~~MS-2 Step will be~~is ~~prescribed by qualified medical practitioners, who have completed all required training and have been certified by the sponsor as part of the Risk Management Plan associated with the registration of the product in Australia.~~ It ~~will be~~is distributed in Australia using the secure distribution channels for prescription medicines. Therefore, it would be unlikely for a person in the community to access large volumes of this product to enable an overdose to occur.

Commented s22 Proposed removal of mandatory training program and certification for prescribers

The Australian MIMS for Cytotec®(11) and the current GyMiso® Australian Product Information indicate that the toxic dose of misoprostol in humans has not been determined. Cumulative total daily doses of 1600 micrograms have been tolerated, with only symptoms of gastrointestinal discomfort reported.

Clinical signs that may indicate an overdose are sedation, tremor, convulsions, dyspnoea, abdominal pain, diarrhoea, fever, palpitations, hypotension or bradycardia. Hypertension and tachycardia have also been reported following overdoses. Overdose in pregnancy has resulted in uterine contractions with foetal death.

There is no specific antidote. Treatment should be symptomatic and supportive.

As a component of MS-2 Step, GyMiso® will be available as a single pack containing four tablets. MS-2 Step will be prescribed by ~~qualified~~ medical practitioners ~~who have completed all required training and have been certified by the sponsor as part of the Risk Management Plan associated with the registration of the product in Australia~~. It ~~will be~~is distributed in Australia using the secure distribution channels for prescription medicines. Therefore it would be unlikely for a person in the community to access large volumes of this product to enable an overdose to occur.

Commented s22 Proposed removal of mandatory training program and certification for prescribers

Potential for transmission infectious agents

Mifepristone as a substance is devoid of any risk of transmission of infectious agents since none of the components are of biological origin. There is no excipient of animal origin in Mifepristone Linepharma 200 mg Tablets.

GyMiso® as a substance is devoid of any risk of transmission of infectious agents since none of the components are of biological origin. There is no excipient of animal origin in GyMiso® tablets.

Medical Education Program, **Informed Consent, Compliance to the Method and Follow-~~up The~~up**

A number of education programs are available to support prescribers including from family planning organisations, RANZCOG, electronic therapeutic guidelines as well as the Sponsor's MS Health Medical Education Program (an education program that has been developed and implemented in Australia by the Sponsor) as a resource for prescribers of MS-2 Step. The Sponsor's Medical Education Program includes modules with:

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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~~The MS Health Medical Education Program is a comprehensive education program that has been developed and implemented in Australia by the Sponsor as part of the Risk Management Plan associated with the approval of the Mifepristone Linepharma and GyMiso® individual products~~MS-2 Step in Australia. ~~During the approval process the~~ The Medical Education Program ~~was revised to include new~~includes ~~modules with~~ :

- ~~information supporting the availability of MS-2 Step;~~
- clinical data supporting ~~its~~the use of MS-2 Step in terminations up to 63 days of gestation, in line with the approved Product Information for MS-2 Step~~, as well as information on the listing of MS-2 Step on the Pharmaceutical Benefits Scheme. An additional module was also developed for the purposes of re-certification.~~
- ~~Medical practitioners currently~~information on the listing of MS-2 Step on the Pharmaceutical Benefits Scheme.

Commented [s22]: Updated to remove the reference to the mandatory medical education program

Commented [s22]: MS Health propose to remove the need for recertification. This has been updated throughout the RMP document

~~Practitioners seeking to become registered and certified for the use of Mifepristone Linepharma and GyMiso® individual products by the Sponsor will be~~, ~~or MS-2 Step are required to complete relevant sections of the amended~~MS-2 Step ~~education program relating to MS-2 Step in order to maintain their certification, and~~in order to ~~gain access to MS-2 Step these products. Fellows and advanced diplomats of RANZCOG will be able to~~can ~~waive the requirement to complete relevant sections of the amended program in order to maintain their certification. Fellows and advanced diplomats of RANZCOG will be required to provide evidence of continuing qualifications in order to maintain their certification the program to achieve certification. The Medical Education Program is provided in Appendix 5. The existing training modules (PowerPoint based slide kit), and case studies were amended in accordance with the TGA and Pharmaceutical Benefits Advisory Committee approvals for MS-2 Step and have been revised as part of the current RMP update. Medical education will be~~1. ~~Medical education is offered by the Sponsor to all appropriately qualified prescribers to ensure that this information is delivered to women undergoing treatment.~~

~~The updated MS Health Medical Education Program includes references to the updated Information Sheet and Patient Agreement that is proposed~~used ~~with the use of MS-2 Step in Australia, to assist the informed consent process. In addition, the education program will provide~~ Education Program ~~provides:~~

- ~~information on the process for gaining informed consent;~~
- ~~the need for appropriate counselling ;~~
- ~~time for the patient to consider options and to ask questions. The program will provide, information on the critical importance of compliance to the Method and Follow-up. In addition, the Information Sheet and Patient Agreement has been updated to highlight ;~~
- ~~practitioner specified 24 hour emergency care (if and when required)); and~~
- ~~the ability for treating medical practitioner to record follow-up appointment details.~~

Commented [s22]: Proposed removal of mandatory training program and certification for prescribers

In addition to the Medical Education Program, the Sponsor makes available to prescribers an Information Sheet and Patient Agreement, the MS-2 Step Product Information and the Consumer Medicine Information documents for the MS-2 Step components. These documents all note the importance that patients are required to be informed about the administration of the medical method, compliance to the method, the importance of follow-up, side effects and associated risks. It is recommended that informed consent is obtained from the woman before use of the medical method as per use of any method for termination of pregnancy. The Information Sheet and Patient Agreement, Product Information and Consumer Medicine Information note the need for the woman to remain in

contact with the treating practitioner and or clinic and it is recommended that they do not travel during the episode of bleeding so that they can visit the clinic if necessary.

~~The MS-2 Step Product Information and Consumer Medicine Information and product labelling provides details of the 24 hour nurse after care telephone service provided by the Sponsor and staffed by qualified registered nurses. Patients may also give consent and elect to receive a follow up SMS text communication from the Sponsor 3 to 5 days following ingestion of mifepristone. This message will provideprovides the 24 hour nurse after care call centre contact telephone number and describes the symptoms that are of concern in relation to infection, incomplete abortion or therapeutic failure that require medical follow up.~~

Commented S22 roposed removal of 24 hour nurse after care program removed.

Training of Medical Practitioners

~~The MS Health Medical Education Program is a comprehensive education program that has been implemented in Australia by the Sponsor as part of the Risk Management Plan associated with the approval of the Mifepristone Linepharma and GyMiso® individual products in Australia. This Medical Education Program was revised to include information supporting the availability of MS-2 Step, clinical data supporting its use in terminations up to 63 days of gestation, and in line with the proposed Product Information for MS-2 Step, as well as information on the listing of MS-2 Step on the Pharmaceutical Benefits Scheme. An updated Medical Education Program training manual is provided in Appendix 5.~~

~~Medical education will be offered by the sponsor~~Medical education is offered by the Sponsor to ~~all appropriately qualified~~ treating practitioners~~, to ensure that this information is delivered to women undergoing treatment. The Sponsor has amended its existing medical education program, to include~~Medical Education Program includes~~ pre-assessment, post-assessment and case studies, supporting~~, the approval of MS-2 Step and all~~. ~~Any amendments will be~~to ~~the program are reviewed by a medical expert in the field. The Sponsor will also seek~~seeks ~~review and endorsement for the amended program~~of ~~any amendments from the~~ RANZCOG~~.~~

The Medical Education Program ~~will be~~is delivered online and ~~be made~~ freely available to all treating ~~practitioners. Prescribers currently registered and certified for the use of Mifepristone Linepharma and GyMiso® individual products by the Sponsor will be required to complete relevant sections of the amended program relating to MS-2 Step in order to maintain their certification, and gain access to MS-2 Step. Prescribers registering for the first time will be~~are required to complete the entire Medical Education Program in order to secure certification (approval to prescribe) for Mifepristone Linepharma and MS-2 Step packs. Medical practitioners, fellows~~. Once registered and certified no re-registration or re-certification is required. Fellows~~ and advanced diplomats of RANZCOG can ~~waive the requirement for additional training associated with the approval of MS-2 Step.~~

~~Effectiveness measures will be~~are ~~included in the amended Medical Education Programme, in line with the existing education programme for Mifepristone Linepharma and GyMiso® single packs.~~Program~~. which will detect the level of knowledge known by the participant, prior to completion of the module, and post-completion of the module. The participant scores will be~~are ~~monitored. A certificate of completion will~~is only be issued to participants who demonstrate ~~appropriate knowledge at the completion of the amended education programme~~program~~.~~ ~~The required level of knowledge will be~~is ~~determined during the review and endorsement process, which the Sponsor will embarkhas embarked upon with the RANZCOG.~~

Commented S22 roposed removal of mandatory training program and certification for prescribers

The ~~amended~~ Medical Education ~~plan~~Program has been prepared to ensure, to the extent practical, that the medical method of termination using ~~the Mifepristone Linepharma and GyMiso® products (i.e. the~~ MS-2 Step ~~Medical Method)~~ is used in Australia responsibly and appropriately. The plan has

been designed ~~to limit the availability of these medicines to appropriately qualified and resourced prescribers and~~ to ensure that prescribers and patients have access to appropriate information regarding the safe and effective administration of the Medical Method.

Elements of the Risk Management Program

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The elements of the ~~amended Medical Education Programme~~Risk Management Program include:

1. ~~Access and distribution – to~~ To ensure that only appropriately qualified prescribers have access to either the Mifepristone Linepharma single pack or MS-2 Step containing one pack each of Mifepristone Linepharma 200 mg and GyMiso® 200 µg tablets.

Commented S22 Updated to remove reference to qualified prescribers

2. ~~1.~~ Education ~~– provision~~ Provision of information regarding the appropriate use of the Medical Method including follow up offered to all prescribers and to patients. The education ~~programme~~program includes information on first trimester termination of pregnancy and for use of mifepristone in terminations beyond the first trimester.

3. ~~2.~~ Informed Consent ~~– provision~~ Provision of preprinted Information Sheet and Patient Agreement to ~~health care~~healthcare professionals to ensure that information for patients is available to assist the provision of informed consent by patients. Patient Information and Patient Consent forms are accessible to health care professionals as downloadable pdf files from the ~~health care~~healthcare professional secure website: www.ms2step.com.au.

4. ~~3.~~ Product labeling and packaging and Consumer Medicine Information ~~– inclusion of, which includes a toll –free telephone number for 24 –hour nurse after care advice from registered nurses provided by the Sponsor, and website URL – to provide,~~ which provides additional information to patients in an accessible and easy to understand format.

5. ~~4.~~ The inclusion of the Black Box warning ~~in the~~regarding follow-up, in the following documents, emphasises the need for special attention on the part of healthcare professionals: MS-2 Step Product Information, MS-2 Step Consumer Medicine Information Instruction Insert ~~and~~, the Mifepristone Linepharma ~~and~~ Consumer Medicine Information, and the GyMiso® Consumer Medicine Information ~~regarding follow up emphasises the need for special attention on the part of health care professionals.~~

Commented S22 Proposed removal of 24 hour after care service

6. ~~Follow up SMS text message to patients – Patients may also give consent and elect to receive a follow up SMS text communication from the Sponsor 3 to 5 days following ingestion of mifepristone. This message will provide~~provides the 24 ~~–~~hour nurse after ~~care call centre contact telephone number and describe symptoms that are of concern in relation to infection, incomplete abortion, or therapeutic failure that require medical follow up.~~

7. ~~5.~~ Monitoring ~~– to~~ To test that the objectives of the educational program are being met with ~~healthcare professionals and patients. –~~ Periodic review of the pharmacovigilance database maintained by ~~MSIA~~MS Health in Australia to ensure adverse event reporting is not ~~unusual for particular centres relative to Australia as a whole~~trending.

8. ~~6.~~ Adverse Event Monitoring in Australia and Ongoing Post Marketing Surveillance ~~–~~. The Sponsor holds a significant database from the use of mifepristone for termination of first trimester pregnancy under the Authorised Prescriber Program (APP) in the MSIA network. ~~The MSIA experience, gained from its suburban clinic network, now covers treatment of over 20,000 women under the APP since 2009. A report on the first 13,345 cases treated by MSIA was published by the Medical Journal of Australia in September~~

~~2012 (10) and provides a summary of the efficacy and safety of the treatment regimen, including data such as failure rate (3.48%) and complication rate (3.89%). This clinical dataset provides a comprehensive review of the Australian clinical experience with mifepristone under the APP. This article will be part of the materials provided during training~~The training modules will continue to be reviewed and updated to reflect the results of other peer-reviewed published studies e.g. ANZJOG 2017; 57: 366-371 as well as other large studies/meta-analyses.

Potential for medication errors

The brand name for the composite pack is ***MS-2 Step***. The product is presented as a composite pack in a carton containing two cartons, each of which is different in appearance (as described below). The generic names of the two component medicines, i.e. mifepristone and misoprostol, appear beneath the name ***MS-2 Step*** on the composite pack carton.

The component products contain different amounts of their respective medicines.

The labelling on the component products clearly identifies the right order for intake of the two products on the front panel of the packaging for each individual product. An instruction insert ~~will be~~is placed in each ***MS-2 Step*** product carton to explain the right order for intake of the two products. The correct way to take the two products is also described in the respective Consumer Medicines Information leaflets, which are placed inside each component product carton.

These products are distinguished from each other in the following ways:

- The Mifepristone Linepharma 200 mg Tablet carton has a green colour, and it contains only one mifepristone tablet
- The GyMiso® carton has a purple colour, and it contains 4 misoprostol tablets
- Mifepristone Linepharma packaging ~~will include~~includes the statement *Step 1, take this tablet first*.
- GyMiso packaging ~~will include~~includes the statement *Step 2, take these 36 to 48 hrs after Mifepristone Linepharma*

The brand name Mifepristone Linepharma 200 mg Tablet uses the INN mifepristone and this should minimise the risk of confusion.

Mifepristone Linepharma 200 mg Tablet is available in a single strength as 200 mg tablets, each pack contains one tablet sufficient for one single treatment. Each tablet is ~~embossed~~debossed on one side (with the letters "MF")~~ so as~~ to avoid confusion with other tablets.

Commented s22 Editorial: description of product corrected

The Consumer Medicine Information ~~will be~~is included in each Mifepristone Linepharma component package and this document includes information on indication, contraindications, precautions and dosing recommendations.

The brand GyMiso® refers only to misoprostol approved in combination with mifepristone in the ***MS-2 Step*** composite pack, and this should minimise the risk of confusion.

GyMiso® is available in a single strength as 200 microgram tablet, and each GyMiso® pack contains four tablets sufficient for one single treatment. Each tablet is engraved on one side with "ML" ~~on one side~~ and "200" on the other~~ so as~~ to avoid confusion with other tablets.

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

CTD Module 1, Section 1.8.2
Risk Management Plan Version 4.0~~0.34~~

The Consumer Medicine Information ~~will be~~is included in each GyMiso® component ~~package~~pack and this document includes information on indication, contraindications, precautions and dosing recommendations.

SVIII – IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

Since this is not initial RMP submission, this section is not applicable.

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.2 New Safety concerns and reclassifications with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

The description that follows provides details on the identified and potential risks that have been described for the product(s), based on the clinical trial data, literature and post-marketing experience data currently available for MS-2 Step.

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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SVII.3.1 Presentation of important identified risks and important potential risks

Table 4 Important Identified Risks

Commented s22 RFI 13 Dec 2022 - Q2

~~Identified risk~~	~~"Bleeding"~~
~~MedDRA terms~~	~~Vaginal bleeding (PT)~~
~~Seriousness~~	~~Yes~~ ~~Heavy bleeding occurs in about 5% of cases and may require haemostatic curettage in up to 1.4% of cases. A transfusion is required in 0.1-0.2% of cases.(19)~~
~~Severity and nature of risk~~	~~Vaginal bleeding is part of the method. Bleeding occurs in almost all cases and is not in any way proof of complete expulsion.~~ ~~Follow-up must take place within a period of 14 to 21 days after administration of mifepristone to verify by the appropriate means that expulsion has been completed and that vaginal bleeding has stopped. In case of persistent bleeding (even light) beyond follow-up, its disappearance should be checked within a few days.~~ ~~If continuing pregnancy is suspected, a further ultrasound scan may be required to evaluate its viability.~~ ~~Persistence of vaginal bleeding at this point could signify incomplete abortion, or an unnoticed extra-uterine pregnancy, and appropriate treatment should be considered.~~ ~~Heavy bleeding occurs in about 5% of cases and may require haemostatic curettage in up to 1.4% of cases.~~ ~~In the event of continuing pregnancy diagnosed after follow-up, termination by another method may be proposed to the woman.~~
~~Frequency~~	~~Bleeding occurs in almost all cases.~~ ~~Heavy bleeding occurs in about 5% of cases and may require haemostatic curettage in up to 1.4% of cases.~~
~~Background incidence/prevalence~~	~~Induced termination of pregnancy always induces vaginal bleeding, whatever the method.~~
~~Risk group or risk factors~~	~~Patients with haemostatic disorders, with known or suspected hypocoagulability or with anaemia, or taking anticoagulants.~~
~~Potential mechanism~~	~~Lack of uterine contractility, incomplete expulsion.~~
~~Preventability~~	~~Information about the potential occurrence of the event in Product Information (Precautions and Adverse Events) and Consumer Medicine Information. Warning about risk groups in Contraindications section of Product Information and Consumer Medicine Information.~~
~~Potential public health impact~~	~~Yes, hence the need for proper training of practitioners and adequate information of women.~~

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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Identified risk	**"Incomplete abortion (method failure) with severe bleeding"**
MedDRA terms	Induced abortion failed (PT) Vaginal bleeding (PT)
Seriousness	Yes. Method failure occurs in 1.3 to 7.5% of cases. Heavy bleeding occurs in about 5% of cases and may require haemostatic curettage in up to 1.4% of cases. A transfusion is required in 0.1-0.2% of cases.(19) Method failure may occur with severe bleeding and it may occur without severe bleeding. Severe bleeding may not be a symptom of method failure. As there is a risk of failure of the method follow up of women is mandatory to check that abortion is complete.
Severity and nature of risk	Vaginal bleeding is part of the method. Bleeding occurs in almost all cases and is not in any way proof of complete expulsion. Follow-up must take place within a period of 14 to 21 days after administration of mifepristone to verify by the appropriate means that expulsion has been completed and that vaginal bleeding has stopped. In case of persistent bleeding (even light) beyond follow up, its disappearance should be checked within a few days. If continuing pregnancy is suspected, a further ultrasound scan may be required to evaluate its viability. Persistence of vaginal bleeding at this point could signify incomplete abortion, or an unnoticed extra-uterine pregnancy, and appropriate treatment should be considered. Heavy bleeding occurs in about 5% of cases and may require haemostatic curettage in up to 1.4% of cases. In the event of continuing pregnancy diagnosed after follow up, termination by another method may be proposed to the woman. As there is a risk of failure, follow up of women is mandatory to check that abortion is complete.
Frequency	Failure occurs in 1.3 to 7.5 % of cases.
Background incidence/prevalence	Early vacuum aspiration leads to up to 5% failure rate.(20)
Risk group or risk factors	None identified
Potential mechanism	Incomplete detachment of conceptus from uterine wall, insufficient uterine contractility.
Preventability	Information about the potential occurrence of both method failure and severe bleeding respectively is in the Product Information and the Consumer Medicine Information. Education to be offered to Medical Practitioners.

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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Identified risk	**"Incomplete abortion (method failure) with severe bleeding"**
Potential public health impact	Yes, hence the need for educational resources to be available to practitioners and adequate information for women~~None~~

Commented [s22]: Updated to align with terminology used for other identified risks

Identified risk	**"Infection, toxic shock syndrome"**
MedDRA terms	Infection (PT), Toxic shock syndrome (PT)
Seriousness	Yes. Infection following termination occurs in less than 1% of cases regardless of the method. Infection in medical termination occurs in 0.3-0.9% of cases.(21) Fatal toxic shock syndrome is very rare.
Severity and nature of risk	Very rare cases of fatal toxic shock caused by *Clostridium sordellii* endometritis presenting without fever or other obvious symptoms of infection, have been reported after medical abortion with the use of 200 mg mifepristone following the non-approved vaginal administration of misoprostol tablets for oral use. In Australia a case of fatal probable toxic shock syndrome has been reported in a woman treated with mifepristone 200 mg followed by 800 mcg buccal misoprostol. Clinicians should be aware of this potentially fatal complication.
Frequency	Infection following termination occurs in less than 5% of cases regardless of the method. Very rare cases of fatal toxic shock syndrome.
Background incidence/prevalence	Infection following termination occurs in less than 5% of cases regardless of the method.
Risk group or risk factors	May be associated with vaginal administration of misoprostol oral tablets.
Potential mechanism	Unknown
Preventability	Information about the potential occurrence of the event in Product Information (Precautions) indicating that the vaginal administration route of misoprostol should not be used. Information about the possibility of infection occurring is included in the Consumer Medicine Information. Education to be offered to Medical Practitioners.
Potential public health impact	Yes, hence the need for educational resources to be available to practitioners and adequate information for women~~Yes, hence the need for proper training of practitioners and adequate information of women~~

MS-2 Step composite pack
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Identified risk	"Cardiac Disorders"
MedDRA terms	Adverse event reports of cardiovascular events are identified using a prespecified list of Standard MedDRA query: SOC Cardiac disorders
Seriousness	No cardiovascular event was reported during pivotal studies. Cardiovascular events reported with misoprostol use in a gynaecological indication, in literature studies and postmarketing experience, include myocardial infraction, myocardial ischemia, sudden death, stroke and transient ischemic accident. Most of these events have a favourable outcome, but event with sequel or fatal outcome has also been reported. If some occurred after a treatment including mifepristone and misoprostol, for most of them mifepristone administration was unknown
Severity and nature of risk	In a prospective study on 9 women evaluating cardio-vascular safety of 600 µg misoprostol administration via vaginal route, none of evaluated parameters (cardiac frequency, arterial pressure, cardiac index…) for 4 days after the take were significantly modified (Ramsey 2000). An investigation on cardiovascular effect of misoprostol was performed by the French National Agency in 2013. This evaluation based on international literature search, French and international post-marketing reports (from commercialisation to December 2012) concludes in the existence of coronary and cerebral adverse reaction with the use of misoprostol in medical termination of a pregnancy. Regarding mifepristone potential effect on cardiovascular system, non-clinical data, clinical data, post- marketing surveillance of adverse events and the drug's action mechanism on the adrenocortical pathway do not associate the product with typical proarrhythmic events that could indicate a QT/QTc interval prolongation.
Frequency	French National Agency estimated the incidence of cardiovascular events with the use of misoprostol at 2.7 cases [0.3 to 9.8] for 106 exposed women. In the Australian phase IV safety study, from cumulative data to 31st March 2016, incidence (%) of cardiovascular event by gestational ages is provided below:
Background incidence/prevalence	There are no specific studies that evaluate prevalence of cardiovascular risks of first trimester pregnant women.
Risk group or risk factors	Vascular risks factors such as tobacco use, hypertension and heredity as well as a sur-exposure to misoprostol.
Potential mechanism	Coronary manifestations observed during medical termination of pregnancy could be explained by the existence of vascular risks factors (tobacco use, hypertension, heredity) and a sur-exposition to misoprostol related to the high dose (double posology) and the vaginal administration, this way leading to a doubling of AUC.
Preventability	Information about the potential occurrence of the event in Product Information and Consumer Medicine Information.
Potential public health impact	Yes, hence the need for educational resources to be available to practitioners and adequate information for women.

≤ 35 days	36-42 days	43-49 days	50-56 days	57-63 days	Total
0	0.1	0.1	0.3	0.2	0.1

Commented s22 Editorial - added to align with summary tables (data as per PUSR)

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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~~Identified risk~~	~~"Method failure"~~
~~MedDRA terms~~	~~Induced abortion failed (PT)~~
~~Seriousness~~	~~Yes. Failure occurs in 1.3 to 7.5% of cases.~~
~~Severity and nature of risk~~	~~As there is a risk of failure, follow up of women is mandatory to check that abortion is complete.~~
~~Frequency~~	~~Failure occurs in 1.3 to 7.5 % of cases.~~
~~Background incidence/prevalence~~	~~Early vacuum aspiration leads to up to 5% failure rate.(20)~~
~~Risk group or risk factors~~	~~None identified~~
~~Potential mechanism~~	~~Incomplete detachment of conceptus from uterine wall, insufficient uterine contractility.~~
~~Preventability~~	~~Information about the potential occurrence of the event in Product Information and the Consumer Medicine Information. Education to be offered to Medical Practitioners.~~
~~Potential public health impact~~	~~None~~

Commented S22 included in the section above

~~Identified risk~~	~~"Uterine contractions / cramping"~~
~~MedDRA terms~~	~~Uterine spasm (PT)~~
~~Seriousness~~	~~No~~
~~Severity and nature of risk~~	~~Uterine contractions or cramping which may sometimes need prescription and short term use of opioid and other analgesics.~~
~~Frequency~~	~~Very common (10 to 45%) in the hours following prostaglandin intake.~~
~~Background incidence /prevalence~~	~~Uterine contractions / cramping are frequent unspecific symptoms after intrauterine procedures or prostaglandin analogue use.~~
~~Risk group or risk factors~~	~~None identified~~
~~Potential mechanism~~	~~Uterine hypercontractility after prostaglandin analogue administration.~~
~~Preventability~~	~~Information about the potential occurrence of the event in Product Information and Consumer Medicine Information.~~

Potential public health	None

Identified risk	**"Uterine infection (endometritis, pelvic inflammatory disease")**
MedDRA terms	Uterine infection (PT)
Seriousness	No
Severity and nature of risk	Infection following abortion: suspected or confirmed infections (endometritis, pelvic inflammatory disease) which can result from incomplete abortion.
Frequency	Infection following termination occurs in less than 1% of cases regardless of the method. Infection in medical termination occurs in 0.3–0.9% of cases.(21)
Background incidence/prevalence	Intrauterine procedure can lead to uterine infection, whatever the method used.
Risk group or risk factors	None identified
Potential mechanism	Incomplete abortion with debris remaining in the uterine cavity. Additional intrauterine procedure (D & C or vacuum aspiration) can increase the infectious risk.
Preventability	Follow up is recommended for all women using the medical method of termination to identify incomplete abortion. Information about the potential occurrence of the event in Product Information and Consumer Medicine Information.
Potential public health impact	None

Identified risk	**"Nausea, vomiting"**
MedDRA terms	Nausea (PT), Vomiting (PT)
Seriousness	No
Severity and nature of risk	These symptoms are frequently reported in the hours following prostaglandin analogue administration.
Frequency	Very common
Background incidence/prevalence	Not applicable
Risk group or risk factors	None identified

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~~**Identified risk**~~	~~**"Nausea, vomiting"**~~
~~**Potential mechanism**~~	~~Unknown (likely related to prostaglandin intake)~~
~~**Preventability**~~	~~Information about the potential occurrence of the event in Product Information and Consumer Medicine Information.~~
~~**Potential public health impact**~~	~~None~~

~~**Identified risk**~~	~~**"Diarrhoea"**~~
~~**MedDRA terms**~~	~~Diarrhoea (PT)~~
~~**Seriousness**~~	~~No~~
~~**Severity and nature of risk**~~	~~This symptom is frequently reported in the hours following prostaglandin analogue administration.~~
~~**Frequency**~~	~~Very common~~
~~**Background incidence/prevalence**~~	~~Not applicable~~
~~**Risk group or risk factors**~~	~~None identified~~
~~**Potential mechanism**~~	~~Unknown (likely related to prostaglandin analogue intake)~~
~~**Preventability**~~	~~Information about the potential occurrence of the event in Product Information and Consumer Medicine Information.~~
~~**Potential public health impact**~~	~~None~~

~~**Identified risk**~~	~~**"Hypotension"**~~
~~**MedDRA terms**~~	~~Hypotension (PT)~~
~~**Seriousness**~~	~~No~~
~~**Severity and nature of risk**~~	~~This symptom is frequently reported in the hours following prostaglandin analogue administration.~~
~~**Frequency**~~	~~Rare (0.25 %)~~
~~**Background incidence/prevalence**~~	~~Not applicable~~

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~~**Risk group or risk factors**~~	~~None identified~~
~~**Potential mechanism**~~	~~Unknown~~
~~**Preventability**~~	~~Information about the potential occurrence of the event in Product Information and Consumer Medicine Information.~~
~~**Potential public health impact**~~	~~None~~

~~**Identified risk**~~	~~**"Skin rashes, urticaria"**~~
~~**MedDRA terms**~~	~~Rash (PT), Urticaria (PT)~~
~~**Seriousness**~~	~~No~~
~~**Severity and nature of risk**~~	~~Skin eruption~~
~~**Frequency**~~	~~Uncommon for skin rashes~~ ~~Rare for urticarial reaction~~
~~**Background incidence/prevalence**~~	~~Not applicable~~
~~**Risk group or risk factors**~~	~~None identified~~
~~**Potential mechanism**~~	~~Unknown~~
~~**Preventability**~~	~~Information about the potential occurrence of the event in Product Information and Consumer Product Information.~~
~~**Potential public health impact**~~	~~None~~

Table 5 Important Potential risks

~~**Important Potential risks**~~ **Important Potential Risk - Unintended pregnancy exposure to mifepristone / misoprostol and risk of incomplete abortion with severe bleeding**
Evidence source: In approximately 3% of the cases (EU Summary of Product Characteristics (SPC) for Mifegyne® and for Mifepristone Linepharma, section 4.4) abortion can occur with mifepristone alone (with no prostaglandin intake). Follow-up is still required to ensure that complete abortion has occurred. In addition, as indicated in the EU SPC for Mifegyne® and for Mifepristone Linepharma (section 4.4) during clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses. Due to the long half-life of mifepristone, the possibility exists of exposure of a subsequent pregnancy to mifepristone.

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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To avoid potential exposure of a subsequent pregnancy to mifepristone, it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after mifepristone and misoprostol administration.

Important Potential risk / Unintended pregnancy exposure (risk of malformations)
Evidence source: In the EU SPC for both Mifegyne® and for Mifepristone Linepharma, it is stated in section 4.6, it is stated that "in animals the abortifacient effect of mifepristone precludes the proper assessment of any teratogenic effect of the molecule" and that "with sub abortive doses, isolated cases of malformations observed in rabbits, but not in rats or mice were too few to be considered significant, or attributable to mifepristone". In section 4.6 of the EU SPC for Mifegyne® and Mifepristone Linepharma, it is indicated that "in humans, the few reported cases of malformations do not allow a causality assessment for mifepristone alone or associated to prostaglandin. Therefore, data is too limited to determine whether the molecule is a human teratogen." The issue of the outcome of persisting pregnancy in case of failure of the method remains incompletely solved: although, up to date there does not seem to be clear-cut foetal malformations attributable to mifepristone or to prostaglandin analogues (19), such possibility cannot be definitively ruled out and women should be adequately counseled in such a situation. In addition, as indicated in Part II, Table 3 of this RMP, misoprostol, through its smooth muscle contracting activity, could have effects on the developing foetus and there are several reports in the literature on the occurrence of congenital defects in children born to mothers who had taken misoprostol to terminate pregnancy; this off-label use of misoprostol appears to have been a particular problem in Brazil, from where considerable evidence has accumulated on its possible teratogenic activity in humans (cited by Orioli *et al,* 2000; Paumgarten *et al*, 1995). Data would suggest a link between misoprostol and congenital malformations, based on a retrospective analysis of cases, and a prospective study based on Brazilian data suggested that misoprostol may increase the incidence of congenital anomalies, but that the magnitude of the increased risk is low (Schuler *et al*, 1999). As a consequence, the EU SPC for Mifegyne® and Mifepristone Linepharma proposes the following recommendations: - Women should be informed, that due to the risk of failure of the medical method of pregnancy termination and to the unknown risk to the foetus, follow-up is mandatory (see Section 4.4 special warnings and special precautions for use). - Should a failure of the method be diagnosed at follow-up (viable ongoing pregnancy), and should the patient still agree, pregnancy termination should be completed by another method. - Should the patient wish to continue with her pregnancy, the available data is too limited to justify a systematic termination of an exposed pregnancy. In that event, careful ultra-sonographic monitoring of the pregnancy should be carried out." In addition, as indicated in the EU SPC for Mifegyne® and Mifepristone Linepharma ~~-~~(section 4.4) during clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses. To avoid potential exposure of a subsequent pregnancy to mifepristone, it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after mifepristone / misoprostol administration.

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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Important Potential risk / ~~Severe asthma uncontrolled by treatment~~Induced Bronchial Asthma
Evidence source: Data to evaluate the inadvertent risk of induced bronchial asthma after the administration of mifepristone and misoprostol are derived from analyses conducted of extensive review of literature published in English and in Chinese as well as non Linepharma France sponsored trials and reports from post-marketing setting. ~~This is labelled as a contraindication in the EU SPC for Mifegyne® and Mifepristone Linepharma, whatever the indication.~~ Mifepristone binds to the glucocorticoid receptor. It may therefore interfere with the action of glucocorticoid treatments. This might be relevant in case of severe asthma inadequately controlled by oral or inhaled glucocorticoid. In addition, bronchospasm may occur with some prostaglandins and prostaglandin analogues. The possibility should be borne in mind in patients with a history of asthma. Severe asthma uncontrolled by treatment is labelled as a contraindication in the EU SPC for Mifegyne® and Mifepristone Linepharma, whatever the indication.

Commented S22 RFI 13 Dec

Table 6 Potential interaction with CYP3A4 inhibitors or inducers

Interacting substance/CYP3A4 inhibitors or inducers
Evidence source: EU Mifegyne® SPC, literature review No interaction studies have been performed. On the basis of this drug's metabolism by CYP3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum levels of mifepristone). Furthermore, rifampicin, dexamethasone, St. John's Wort and certain anticonvulsants (phenytoin, phenobarbitone, carbamazepine) may induce mifepristone metabolism (lowering serum levels of mifepristone). Based on in vitro inhibition information, co-administration of mifepristone may lead to an increase in serum levels of drugs that are CYP3A4 substrates. Due to the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP3A4 substrates and have narrow therapeutic range, including some agents used during general anaesthesia. For misoprostol, limited studies on effects of misoprostol on hepatic drug metabolism in the rat did not show any effect on aminopyrine metabolism (single oral dose of 0.1 mg/kg of misoprostol) or, after 0.1 mg/kg twice daily for four days, cytochrome P450 content or the activities in liver microsomes of hexobarbital hydroxylase, aniline hydrolase or p-nitroanisole O-demethylase. Based on this information, no drug interaction is expected after misoprostol administration.

Table 7 Potential interaction with products interacting with the glucocorticoid receptor

Interacting substance/ Products interacting with the glucocorticoid receptor
Evidence source: EU Mifegyne® and Mifepristone Linepharma SPC's, literature review Mifepristone binds to the glucocorticoid receptor. It may therefore interfere with the action of glucocorticoid treatments. This might be relevant in case of severe asthma inadequately controlled by oral or inhaled glucocorticoid.

SVII.3.2. Presentation of the missing information

Table 8 Presentation of the missing information

Missing Information/ Inherited porphyria
Evidence source: This is labelled as a contraindication in the EU SPC for Mifegyne® and Mifepristone Linepharma, whatever the indication. The reason for this contraindication is unclear. Literature search for "mifepristone and porphyria" yields only one abstract (15) indicating that in an *in vitro* model mifepristone and deferoxamine together produced significant accumulations of protoporphyrin. The authors concluded that "RU-486 may pose a risk in patients with known acute porphyria and should be used with caution".

Missing Information / Theoretical interaction with NSAIDs
Evidence source: This is a potential precaution in the EU SPC for Mifegyne® and Mifepristone Linepharma, whatever the indication. A decrease of the efficacy of the method can theoretically occur due to the antiprostaglandin properties of non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin (acetyl salicylic acid). Limited evidence suggests that co-administration of NSAIDs on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medical termination of pregnancy. The reason for this precaution is therefore unclear.(23,24)

Missing Information / Potential interaction with products interacting with the progesterone receptor
Evidence source: EU Mifegyne® and Mifepristone Linepharma SPC's, literature review Mifepristone is a progesterone receptor antagonist. Therefore, it may interfere with the action of progestin-only contraceptives.

Missing Information / use in adolescents
Evidence source: Literature review Mifepristone Linepharma 200 mg Tablet and GyMiso® are recommended for use in females of childbearing age. There are limited data available in women below the age of 18 years.

SVII.3.3. Presentation of the pharmacological class effect

Mifepristone belongs to the progesterone receptor antagonist class.
Mifepristone also displays anti-glucocorticoid activity. Such activity, evidenced by an ACTH elevation, has not been observed at the dose of 200 mg per dose for several years (157 months for treatment of meningioma in patients with normal adrenal function).(18) Therefore, use of a single

intake mifepristone is not expected to have anti-glucocorticoid activity. As indicated above, mifepristone may interfere with the action of glucocorticoid treatments. This might be relevant in case of severe asthma inadequately controlled by oral glucocorticoid.

For medical pregnancy termination, mifepristone treatment must be followed by the administration of the prostaglandin analogue, misoprostol (GyMiso®) which is the second component of ***MS-2 Step***. Therefore, risks inherent with this class of product must also be taken in consideration.

Pharmacological class effect / Risks related to the use of prostaglandin
Evidence source: Termination of pregnancy with mifepristone necessitates the use of prostaglandin analogues, such as misoprostol, which has its own potential risks. This is taken into account in the EU Mifegyne® SPC: In section 4.3, the method should not been used in case of contraindication to a prostaglandin analogue. In section 4.4, it is acknowledged that rare serious cardiovascular accidents have been reported following the intra muscular administration of prostaglandin E2 analogue, sulprostone. For this reason women with risk factors for cardiovascular disease or established cardiovascular disease should be treated with caution. This is taken into account in the current Mifepristone Linepharma Australian Product Information: In Contraindications, the product should not be prescribed in case of a contraindication to the prostaglandin analogue.

In Precautions, it is stated that rare serious cardiovascular accidents have been reported following administration of prostaglandins including misoprostol. For this ~~reason~~reason, women with risk factors for cardiovascular disease or established cardiovascular disease should be treated with caution.

PART II: MODULE SVIII – SUMMARY OF THE SAFETY CONCERNS

Table 9 ~~SVIII.1:~~ Summary- safety concerns

Commented [S22] RFI 13 Dec 2022 - Q2

Summary of safety concerns	
Important Identified Risks:	~~Bleeding~~ Infection, toxic shock syndrome Method failure ~~Uterine contractions / cramping~~ ~~Uterine infection (endometritis, pelvic inflammatory disease)~~ ~~Nausea, vomiting~~ ~~Diarrhoea~~ ~~Hypotension~~ ~~Skin rashes, urticarial~~

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Summary of safety concerns	
	Cardiac disorders
Important Potential Risks:	Inadvertent pregnancy exposure and risk of incomplete abortion with severe bleeding Inadvertent pregnancy exposure (risk of malformations) Potential interaction with CYP3A4 inhibitors or inducers Potential interaction with products interacting with the glucocorticoid receptor ~~Severe asthma uncontrolled by treatment~~Induced bronchial asthma Effects in lactating women Effects in women with impaired liver function Effects in women with impaired renal function Effects in women with malnutrition Incorrect determination of gestational age Potential for missed ectopic pregnancy Potential for postnatal developmental delay Potential for off-label use beyond the first trimester Potential for loss to follow-up Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up
Missing Information:	Inherited porphyria Theoretical interaction with NSAIDs Potential interaction with products interacting with the progesterone receptor Use in adolescents
Pharmacological class effect	Risks related to the use of prostaglandin

Commented [s22] RFI 13 Dec

Commented [s22] Additional important potential risk added (as per the Canadian RMP).

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Commented [s22] Status of PSUR commitments updated

~~The description of the routine~~Routine pharmacovigilance ~~system~~ activities including adverse event reporting and signal detection is conducted.

Periodic Safety Updates

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Periodic Safety Update Reports (PSURs) for Mifepristone Linepharma and GyMiso® will continue as ~~presented~~the safety reporting method for ***MS-2 Step***.

As agreed at the time of approval of the individual products, PSURs was submitted six monthly for the first 12 months from registration and then annually after that, with a data lock of no more than 60 days for Mifepristone Linepharma and GyMiso®, respectively. Use of mifepristone beyond the first trimester (including off-label use) is given separate consideration in the ~~European CTD Module~~PSURs.

PSURs would be aligned with international reporting in accordance with the international birth date (IBD) defined in ICH E2C(R1), which for:

- Mifepristone Linepharma is based on the EU-harmonised IBD of 31 May. MS Health have completed the PSUR submission commitments.
- The Mifepristone Linepharma product was launched in Australia on 4 February 2013.
- GyMiso® is based on an EU-harmonised IBD of 31 May. The GyMiso® product was launched in Australia on 1~~.8.1 is available upon request.~~ August 2013.
- MS 2 Step PSUR obligations have been met and no further submission are required.

The safety update reports for both Mifepristone Linepharma and GyMiso® will include the ongoing post marketing collection of the data in Australia.

III.2 Additional pharmacovigilance activities

Not applicable~~The Sponsor is conductinghas conducted a post marketing surveillance study of use of Mifepristone Linepharma and GyMiso® for early medical abortion within MSIA clinics. *MS-2 Step* will bewas added to the protocol following its launch into the Australian market by the Sponsor.~~

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~~This study will involveinvolved a sufficient sample of patients that have completed treatment, and that sample size will bewas adequately powered to detect adverse events of bleeding, retained products of conception and infection. The adverse event rate in this 'trial' canwas then be compared to use in the Authorised Prescriber setting. Key endpoints arewere follow up rates, failure rate, and adverse event rates. With respect to the sample size, the objective of this study iswas to estimate adverse event rates related to administration of the early medical procedure in Australia including retained products of conception / failure rate, heavy bleeding, and infection, and these events are reported in the literature to occur at rates of up to 7%, 12% and 0.1 – 1%, respectively. Then, at most, a sample size of 15,351 patients will bewas required. (Calculation: if the adverse event rate was 0.1% then to achieve a width of 0.05% for the 95% CI requires a sample size of 15,351 patients).~~

~~To potentially acquire data on outcomes and risk of adverse events in women considered to belong to vulnerable groups (including women in regional and remote areas of Australia), the postcodes will bewere added to the information required with patient adverse event reporting.~~

~~A copy of the current amended protocol for the post marketing surveillance study is providedwas provided and on completion, the complete phase IV study results were submitted to the TGA.~~

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III.3 Summary Table of Additional Pharmacovigilance Activities

Table 10 ~~Part III.1~~ On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not Applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not Applicable				
Category 3 - Required additional pharmacovigilance activities				
Not Applicable				

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Routine risk minimisation measures include the Product information and Consumer Medicine Information. Details are outlined in Table 6 below.

Table 11 ~~Part V.1~~ Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
~~Important identified risk:~~ ~~Bleeding~~	~~Routine:~~ ~~Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS.~~ ~~Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.~~
Important identified risk: Infection, toxic shock syndrome	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.

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Safety concern	Routine risk minimisation activities
Important identified risk: Method failure	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.
~~Important identified risk:~~ ~~Uterine contractions / cramping~~	~~Routine:~~ ~~Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS.~~ ~~Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.~~
~~Important identified risk:~~ ~~Uterine infection (endometritis, pelvic inflammatory disease)~~	~~Routine:~~ ~~Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS.~~ ~~Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.~~
~~Important identified risk:~~ ~~Nausea, vomiting~~	~~Routine:~~ ~~Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS.~~ ~~Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.~~
~~Important identified risk:~~ ~~Diarrhoea~~	~~Routine:~~ ~~Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS.~~ ~~Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.~~
~~Important identified risk:~~ ~~Hypotension~~	~~Routine:~~ ~~Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS.~~ ~~Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.~~
~~Important identified risk:~~ ~~Skin rashes, urticarial~~	~~Routine:~~ ~~Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS.~~ ~~Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.~~

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Safety concern	Routine risk minimisation activities
Important identified risk: Cardiac disorders	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.
Important potential risk: Inadvertent pregnancy exposure (risk of malformations)	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.
Important potential risk: Inadvertent pregnancy exposure and risk of incomplete abortion with severe bleeding	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.
Important potential risk: Potential interaction with CYP3A4 inhibitors or inducers	Routine: Mentioned in the Product Information in INTERACTIONS WITH OTHER MEDICINES. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Physician education.
Important potential risk: Potential interaction with products interacting with the glucocorticoid receptor	Routine: Mentioned in the Product Information in PHARMACOLOGY and PRECAUTIONS. Physician education.

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Safety concern	Routine risk minimisation activities
Important potential risk: ~~Severe asthma uncontrolled by treatment~~Induced bronchial asthma	Routine: Mentioned in the Product Information in CONTRAINDICATIONS and PRECAUTIONS Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Physician education.
Important potential risk: Incorrect determination of gestational age	Routine: Mentioned in the Product Information in CONTRAINDICATIONS Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Physician education.
Important potential risk: Effects in lactating women	Routine: Mentioned in the Product Information in Use during lactation. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.
Important potential risk: Effects in women with impaired liver function	Routine: Mentioned in the Product Information in SPECIAL WARNINGS AND PRECAUTIONS FOR USE and in INTERACTIONS WITH OTHER MEDICINES. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.
Important potential risk: Effects in women with impaired renal function	Routine: Mentioned in the Product Information in SPECIAL WARNINGS AND PRECAUTIONS FOR USE and in INTERACTIONS WITH OTHER MEDICINES. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.

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Safety concern	Routine risk minimisation activities
Important potential risk: Effects in women with malnutrition	Routine: Mentioned in the Product Information in SPECIAL WARNINGS AND PRECAUTIONS FOR USE. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.
Important potential risk: Potential for missed ectopic pregnancy	Routine: Mentioned in the Product Information in SPECIAL WARNINGS AND PRECAUTIONS FOR USE and in ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.
Important potential risk: Potential for postnatal developmental delay	Routine: Mentioned in the Product Information in Use in pregnancy
Important potential risk: Potential for loss to follow up	Routine: Mentioned in the Product Information in SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Missing information: Inherited porphyria	Not mentioned in Product Information and the Consumer Medicine Information as there is limited evidence of this being a safety concern with administration of mifepristone.(22)
Missing information: Potential interaction with products interacting with the progesterone receptor	This potential risk has not been confirmed and no information is deemed necessary in the Product Information.
Missing information: Theoretical interaction with non-steroidal anti-inflammatory drugs	This potential risk has not been confirmed and no information is deemed necessary in the Product Information.

Commented s22 RFI 13 Dec

Safety concern	Routine risk minimisation activities
Missing information: Use in adolescents	Product Information and Consumer Medicine Information mention that use is limited in this population. The Product Information mentions, there is no relevant use of MS-2 Step in the prepubertal paediatric population in the indication. Administration to adolescents less than 18 years of age should be undertaken with caution.
Pharmacological class effect: Risks related to the use of prostaglandin	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.

V.2 Additional Risk Minimisation Measures

There are six specific risk minimisation tools planned, as detailed below, in addition to the routine measures for the identified risks, potential risks, missing information and pharmacological class effects, outlined below.

Black Box Warnings

A black box warning is included in the ***MS-2 Step*** Product Information:

> It is very important that all patients receiving these medications are followed up by a medical practitioner, preferably the prescriber, to ensure that the medication has been effective. Even if no adverse events have occurred all patients must receive follow-up 14 to 21 days after taking mifepristone. Read the ***SPECIAL WARNINGS AND PRECAUTIONS FOR USE*** carefully.

A black box warning is included in the Mifepristone Linepharma Consumer Medicine Information:

> It is very important that all patients receiving this medication are followed up by a medical practitioner, preferably the prescriber, to ensure that the medication has been effective. Even if no adverse events have occurred all patients must receive follow-up 14 to 21 days after taking mifepristone.

A black box warning is included in the GyMiso® Consumer Medicine Information:

> It is very important that all patients receiving this medication are followed up by a medical practitioner, preferably the prescriber, to ensure that the medication has been effective. Even if no adverse events have occurred all patients must receive follow-up 14 to 21 days after taking mifepristone.

Inclusion of Consumer Medicine Information

The Consumer Medicine Information ~~will be~~is included in every pack of Mifepristone Linepharma.

The Consumer Medicine Information ~~will~~is also be included in every pack of GyMiso®.

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Inclusion of Instruction Insert in Composite Pack Carton

An Instruction Insert ~~will be~~is included in every pack of ***MS-2 Step***, to clearly indicate the identity of the components, the order in which the component medicines should be taken, and the importance of a follow-up appointment 14-21 days following the administration of Mifepristone Linepharma to confirm successful termination of pregnancy.

~~Restricted Access to MS-2 Step [Mifepristone Linepharma and GyMiso®]~~

~~The Sponsor restricts the access to *MS-2 Step* to ensure that only eligible and registered prescribers can prescribe *MS-2 Step* and Mifepristone Linepharma (monopack). The Sponsor will distribute *MS-2 Step* to registered pharmacies, with supply to occur via the Sponsor's sole distributor Symbion. Supply from Symbion will only occur following confirmation received from the Sponsor by Symbion that the Pharmacy has registered with MS Health.~~

~~The programme will helpprogram helps to ensure that:~~

- ~~Distribution of *MS-2 Step* is controlled and monitored.~~
- ~~Only Prescribers registered with the Sponsor as having completed the Prescriber Education (or can waive the Prescriber Education asif they are current TGA Authorised Prescribers, FRANZCOG or advanced diplomates of RANZCOG) can prescribe *MS-2 Step*.~~
- ~~Only pharmacies registered with the Sponsor can dispense *MS-2 Step*, and will have access to a list of registered prescribers.~~
- ~~Participating prescribers are informed of the need to inform patients of the effectiveness of the method, how to manage potential risks and the importance of follow-up as well as the need to gain informed consent.~~
- ~~Participating prescribers will have access to a list of registered pharmacies, and be able to identify pharmacies that have registered with the Sponsor.~~

These arrangements ~~will be~~are set up and ~~will be~~are accessible via the Sponsor's secure healthcare professional website www.ms2step.com.au, or by calling the company directly. The Sponsor may change the restrictions on supply if in the future an effective control mechanism on prescriber access becomes possible via the PBS.

Informed Consent, Compliance with the Method and Follow-up

The Sponsor ~~will provide~~provides ~~all registered~~ prescribers with access to reprinted Information Sheet and Patient Consent Agreements Forms to ensure that information in relation to the medical method of pregnancy termination is available to assist the provision of informed consent by patients.

Information Sheets and Patient Consent Forms ~~will~~ also highlight symptoms patients will experience, along with symptoms requiring immediate follow up, and enable the prescriber to nominate the details of a 24-hour emergency facility for immediate follow-up if required, and details in relation to the patients scheduled follow up appointment 14-21 days after administration of the Mifepristone Linepharma tablet.

~~The Information Sheet will also containcontains contact details for the 24 hour after care nursing toll-free telephone service provided to all patients by MS Health. Patients may also give consent and elect to receive a follow up SMS text communication from the Sponsor 3 to 5 days following ingestion of mifepristone. This message will provideprovides the 24 hour nurse after care call centre contact telephone number and describe symptoms that are of concern in relation to infection, incomplete abortion or therapeutic failure that require medical follow up.~~

Commented [s22]: Proposed removal of mandatory training program and certification for prescribers

Commented [s22]: roposed removal of 24 hour after care service

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The Information Sheet and Patient Consent Agreements Forms ~~will be~~are provided without charge by MS Health, and can be downloaded from the secure health care professional website www.ms2step.com.au as pdf files, or can be requested by contacting MS Health directly as reprinted documents.

~~The 24-hour nursing aftercare and SMS text messaging service will also be~~is ~~provided by the Sponsor free of charge.~~

The medical method of pregnancy termination and requirement for patient follow-up appointment ~~will~~is also ~~be~~ documented in the ***MS-2 Step*** Product Information.

Prescriber Training

To support the education of Prescribers, ~~The Sponsor will provide~~the Sponsor provides access to Prescriber training through the provision of a comprehensive Medical Education ~~Programme~~Program, and ~~will ensure~~ensures, to the extent practical, that the medical method of termination using the Mifepristone Linepharma and GyMiso® products (i.e. the MS-2 Step Medical Method) is used in Australia responsibly and appropriately.

The Medical Education Program ~~will be~~is delivered online and ~~be~~is made freely available by the Sponsor to all prescribers. ~~All other prescribers~~

~~Prescribers registering with the Sponsor for the first time following TGA approval of *MS-2 Step* and the market launch by the Sponsor will be~~are ~~required to complete the entire amended Medical Education Programme~~Program ~~in order to secure certification (approval to prescribe) for Mifepristone Linepharma and *MS-2 Step* packs. In line with the existing Risk Management Plan for Mifepristone Linepharma and GyMiso®, medical~~Medical ~~practitioners who hold current Authorised Prescriber status along with medical practitioners holding Fellowship (FRANZCOG) or Advanced Diploma (DRANZCOG Advanced) of the RANZCOG qualifications will be able to can waive the requirement for additional training associated with~~to complete ~~the approval of *MS-2 Step*. program to achieve certification~~

~~Effectiveness measures will be~~are ~~included in the amended Medical Education Program, in line with the existing education program for Mifepristone Linepharma and GyMiso® single packs, which will detect (1) the level of knowledge known by the participant prior to completion of the module, and (2) the level of knowledge known by the participant post completion of the module. The participant scores will~~are ~~be monitored.~~

~~A certificate of completion will~~is ~~only be issued to participants who demonstrate appropriate knowledge at the completion of the amended education program. The required level of knowledge will be~~was ~~determined during the review and endorsement process.~~

~~Prescribers currently registered and certified for the use of Mifepristone Linepharma and GyMiso® individual products by the Sponsor will be required to complete new modules in the amended program relating to *MS-2 Step* in order to maintain their certification, and gain access to *MS-2 Step*. Fellows and advanced diplomats of RANZCOG will be able to waive the requirement to complete relevant sections of the amended program in order to maintain their certification. Fellows and advanced diplomats of RANZCOG will be required to provide evidence of continuing qualifications in order to maintain their certification.~~

Commented s22 roposed removal of mandatory training program and certification for prescribers

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V.3 Summary of risk minimization measures

Safety concern	Pharmacovigilance activities	Risk minimisation measures
Important identified risk:		
~~Bleeding~~	~~Routine:~~ ~~- Routine pharmacovigilance~~ ~~Additional:~~ ~~- Post-marketing surveillance study~~ ~~- Special attention in PSURs~~	~~Routine:~~ ~~Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS.~~ ~~Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.~~ ~~Additional:~~ ~~Black box warning on follow-up in ***MS-2 Step*** Product Information, and in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.~~ ~~Patient Information and Consent Agreement with emphasis on compliance and follow-up.~~ ~~Optional follow-up SMS text message communication.~~ ~~24-hour nurse after-care call service.~~ ~~Physician education.~~
Infection, toxic shock syndrome	Routine: - Routine pharmacovigilance ~~Additional:~~ ~~- Post-marketing surveillance study~~ - Special attention in PSURs	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Black box warning on follow-up in ***MS-2 Step*** Product Information, and in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Patient Information and Consent Agreement with emphasis on compliance and follow-up. ~~Optional follow-up SMS text message communication.~~ ~~24-hour nurse after-care telephone service.~~ Physician education.
Method failure	Routine: -Routine pharmacovigilance	Routine:

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Safety concern	Pharmacovigilance activities	Risk minimisation measures
	~~Additional:~~ ~~- Post-marketing surveillance study~~ - Special attention in PSURs	Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Black box warning on follow-up in ***MS-2 Step*** Product Information, and in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Patient Information and Consent Agreement with emphasis on compliance and follow-up. ~~Optional follow-up SMS text message communication.~~ ~~24-hour nurse after-care telephone service.~~ Physician education.
~~Identified risk:~~		
~~Uterine contractions / cramping~~	~~Routine:~~ ~~- Routine pharmacovigilance~~ ~~Additional:~~ ~~- Post-marketing surveillance study~~ ~~- Special attention in PSURs~~	~~Routine:~~ ~~Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS.~~ ~~Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.~~ ~~Additional:~~ ~~Patient Information and Consent Agreement with emphasis on compliance and follow-up.~~ ~~24-hour nurse after-care telephone service.~~ ~~Physician education.~~
~~Uterine infection (endometritis, pelvic inflammatory disease)~~	~~Routine:~~ ~~- Routine pharmacovigilance~~ ~~Additional:~~ ~~- Post-marketing surveillance study~~ ~~- Special attention in PSURs~~	~~Routine:~~ ~~Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS.~~ ~~Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.~~ ~~Additional:~~ ~~Patient Information and Consent Agreement with emphasis on compliance and follow-up.~~ ~~24-hour nurse after-care telephone service.~~

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Safety concern	Pharmacovigilance activities	Risk minimisation measures
		~~Physician education.~~
~~**Identified risk:**~~		
~~Nausea, vomiting~~	~~Routine:~~ ~~Routine pharmacovigilance~~ ~~Additional:~~ ~~Post-marketing surveillance study~~ ~~Special attention in PSURs~~	~~Routine:~~ ~~Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS.~~ ~~Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.~~ ~~Additional:~~ ~~Patient Information and Consent Agreement with emphasis on compliance and follow-up.~~ ~~24-hour nurse after-care telephone service.~~ ~~Physician education.~~
~~Diarrhoea~~	~~Routine:~~ ~~Routine pharmacovigilance~~ ~~Additional:~~ ~~Post-marketing surveillance study~~ ~~Special attention in PSURs~~	~~Routine:~~ ~~Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS.~~ ~~Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.~~ ~~Additional:~~ ~~Patient Information and Consent Agreement with emphasis on compliance and follow-up.~~ ~~24-hour nurse after-care telephone service.~~ ~~Physician education.~~
~~**Identified risk:**~~		
~~Hypotension~~	~~Routine:~~ ~~Routine pharmacovigilance~~ ~~Additional:~~ ~~Post-marketing surveillance study~~ ~~Special attention in PSURs~~	~~Routine:~~ ~~Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS.~~ ~~Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.~~ ~~Additional:~~ ~~Patient Information and Consent Agreement with emphasis on compliance and follow-up.~~ ~~24-hour nurse after-care telephone service.~~

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Safety concern	Pharmacovigilance activities	Risk minimisation measures
		~~Physician education.~~
~~Skin rashes, urticaria~~	~~Routine:~~ ~~- Routine pharmacovigilance~~ ~~Additional:~~ ~~- Post-marketing surveillance study~~ ~~- Special attention in PSURs~~	~~Routine:~~ ~~Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS.~~ ~~Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.~~ ~~Additional:~~ ~~Patient Information and Consent Agreement with emphasis on compliance and follow-up.~~ ~~24-hour nurse after-care telephone service.~~ ~~Physician education.~~
Potential risk:		
Inadvertent pregnancy exposure and risk of incomplete abortion with severe bleeding	Routine: - Routine pharmacovigilance ~~Additional:~~ - Special attention in PSURs	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Patient Information and Consent Agreement with emphasis on compliance and follow-up. ~~24-hour nurse after-care telephone service.~~ Physician education.
Inadvertent pregnancy exposure (risk of malformations)	Routine: - Routine pharmacovigilance ~~Additional:~~ - Special attention in PSURs	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Patient Information and Consent Agreement with emphasis on compliance and follow-up. ~~24-hour nurse after-care telephone service.~~ Physician education.

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[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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Safety concern	Pharmacovigilance activities	Risk minimisation measures
Potential risk:		
Potential interaction with CYP3A4 inhibitors or inducers	Routine: - Routine pharmacovigilance ~~Additional:~~ - Special attention in PSURs	Routine: Mentioned in the Product Information in INTERACTIONS WITH OTHER MEDICINES. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Physician education.
Potential interaction with products interacting with the glucocorticoid receptor	Routine: - Routine pharmacovigilance ~~Additional:~~ - Special attention in PSURs	Routine: Mentioned in the Product Information in PHARMACOLOGY and PRECAUTIONS. Additional: Physician education.
~~Severe asthma uncontrolled by treatment~~Induced bronchial asthma	Routine: - Routine pharmacovigilance ~~Additional:~~ - Special attention in PSURs	Routine: Mentioned in the Product Information in CONTRAINDICATIONS and PRECAUTIONS Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Physician education.
Effect in lactating women	Routine: - Routine pharmacovigilance	Routine: Mentioned in the Product Information in Use during lactation. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Physician education.
Potential risk:		
Effect in women with impaired liver function	Routine: - Routine pharmacovigilance	Routine: Mentioned in the Product Information in SPECIAL WARNINGS AND PRECAUTIONS

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Safety concern	Pharmacovigilance activities	Risk minimisation measures
		FOR USE and in INTERACTIONS WITH OTHER MEDICINES. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Physician education.
Effect in women with impaired renal function	Routine: - Routine pharmacovigilance	Routine: Mentioned in the Product Information in SPECIAL WARNINGS AND PRECAUTIONS FOR USE. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Physician education.
Effect in women with malnutrition	Routine: - Routine pharmacovigilance	Routine: Mentioned in the Product Information in SPECIAL WARNINGS AND PRECAUTIONS FOR USE. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Physician education.
Potential risk:		
Missed ectopic pregnancy	Routine: - Routine pharmacovigilance	Routine: Mentioned in the Product Information in SPECIAL WARNINGS AND PRECAUTIONS FOR USE and in ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Patient Information and Consent Agreement with emphasis on compliance and follow-up. ~~24 hour nurse after care telephone service.~~ Physician education.

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Safety concern	Pharmacovigilance activities	Risk minimisation measures
Postnatal development delay	Routine: - Routine pharmacovigilance ~~Additional:~~ - Special attention in PSURs	Routine: Mentioned in the Product Information in Use in pregnancy
Potential for off-label use beyond the first trimester	Routine: - Routine pharmacovigilance	Additional: Physician education.
Potential safety risks in vulnerable groups including women in rural and remote areas of Australia, particularly the risk of being lost to follow-up	Routine: - Routine pharmacovigilance	Additional: Physician education.
Missing information		
Inherited porphyria	Routine: - Routine pharmacovigilance ~~Additional:~~ - Special attention in PSURs	Not mentioned in Product Information and the Consumer Medicine Information as there is limited evidence of this being a safety concern with administration of mifepristone (6).
Potential interaction with products interacting with the progesterone receptor	Routine: - Routine pharmacovigilance ~~Additional:~~ - Special attention in PSURs	This potential risk has not been confirmed and no information is deemed necessary in the Product Information.
Theoretical interaction with non-steroidal anti-inflammatory drugs	Routine: - Routine pharmacovigilance ~~Additional:~~	This potential risk has not been confirmed and no information is deemed necessary in the Product Information.

Safety concern	Pharmacovigilance activities	Risk minimisation measures
	- Special attention in PSURs	
Use in adolescents	Routine: - Routine pharmacovigilance ~~Additional:~~ - Special attention in PSURs	Product Information and Consumer Medicine Information mention that use is limited in this population.
Pharmacological class effects		
Risks related to the use of prostaglandin	Routine: - Routine pharmacovigilance ~~Additional:~~ - Special attention in PSURs	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Patient Information and Consent Agreement with emphasis on compliance and follow-up. ~~24-hour nurse after-care telephone service.~~ Physician education.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Not applicable.

PART VII: ANNEXES

~~**Annex 1 Product Information for *MS-2 Step***~~
~~**Annex 2 Consumer Medicine Information of Mifepristone Linepharma 200 mg Tablet and Consumer Medicine Information of GyMiso® 200 microgram misoprostol tablets**~~
~~**Annex 3 EU Summary of Product Characteristics and Patient Leaflet of Mifepristone Linepharma 200 mg tablet**~~
~~**Annex 4 EU Summary of Product Characteristics and Patient Leaflet of Mifegyne® 200 mg tablet**~~
~~**Annex 5 MS Health Proposed Australian Medical Education Program**~~
~~**Annex 6 Copies of the Cited Literature**~~

~~**Periodic Safety Updates**~~

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~~Periodic Safety Update Reports (PSURs) for Mifepristone Linepharma and GyMiso® will continue as the safety reporting method for ***MS-2 Step***.~~

~~As agreed at the time of approval of the individual products, PSURs will be submitted six monthly for the first 12 months from registration and then annually after that, with a data lock of no more than 60 days for Mifepristone Linepharma and GyMiso®, respectively. Use of mifepristone beyond the first trimester (including off-label use) will be given separate consideration in the PSURs.~~

~~PSURs would be aligned with international reporting in accordance with the international birth date (IBD) defined in ICH E2C(R1), which for:~~

- ~~Mifepristone Linepharma is based on the EU harmonised IBD of 31 May. PSUR 5 dated 28 August 2013, covering the period 29 December 2012 to 28 June 2013, is the most recent report submitted to TGA (as of October 2013). PSUR 4 was included in the *MS-2 Step* dossier in June 2013.~~
- ~~The Mifepristone Linepharma product was launched in Australia on 4 February 2013.~~
- ~~GyMiso® is based on an EU harmonised IBD of 31 May. The first 6-monthly update report in Australia, PSUR GyMiso Australia #1 (covering the period of 29 October 2012 to 28 April 2013) was submitted in the *MS-2 Step* dossier in June 2013, and PSUR GyMiso® Australia #4 will be submitted to TGA in January 2015.~~
- ~~The GyMiso® product was launched in Australia on 1 August 2013.~~

~~The safety update reports for both Mifepristone Linepharma and GyMiso® will include the ongoing post-marketing collection of the data in Australia.~~

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~~Annex 1 MS Health Australian Medical Education Program~~

~~Annex 1.1 MS 2 Step Training Manual~~

~~Annex 1.2 MS 2 Step Training Slides~~

~~Annex 1.3 Patient Information Sheet – Consent Form~~

~~Annex 1.4 MS 2 Step Training – Case Studies~~

~~Annex 1.5 Pre and Post course assessment~~

~~Annex 1.6 MS Health Traning Manual – PBS Listing~~

Commented s22 roposed removal of mandatory training program and certification for prescribers

Not applicable

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Module 1.8.2 Risk Management Plan

MS-2 Step

Composite pack containing:

MIFEPRISTONE LINEPHARMA 200 mg Tablet mifepristone 200 mg

and

GyMiso® misoprostol 200 µg tablets

RMP version to be assessed as part of this application:	
RMP version number:	~~4.0~~4.0
Data lock point for this RMP:	31 May 2022
Date of final sign off:	~~14 January~~17 February 2023
Rationale for submitting an updated RMP	This RMP has been updated as follows: ~~To include the revised Education Program material included as Appendix 1, the format of the RMP has also been updated.~~ ~~To remove the need for pharmacists to be registered to be able to dispense the product.~~ ~~To remove the requirement for recertification training.~~ ~~Updated summary concerns and additional risk minimisation activities.~~ To remove the need for prescribers to complete mandatory training and receive ~~qualification~~certification to be able to prescribe the product. To remove the requirement for a Sponsor provided 24 hours aftercare service
Summary of significant changes in this RMP:	Revised into current EU-RMP template
Other RMP versions under evaluation:	~~NA~~Version 4.0, 14 January 2023
Details of the currently approved RMP:	
Version number:	Version 3.0; Data lock point 28 April 2013
Approved with procedure:	Version 3.0 was submitted on 14 November 2014 and provides documentation as agreed with the Office of Product Review and revised information, following the registration of MS-2 Step in May 2014. (Submission ID: PM-2013-01037-1-5)

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Date of approval:	28 May 2013

QPPV name: s22

Date: ~~14 January~~17 February 2023

QPPV signature:

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PART I: PRODUCT(S) OVERVIEW

Table 1 Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	MS-2 Step is a composite pack consisting of one pack of Mifepristone Linepharma (one mifepristone 200 mg tablet) and one pack of GyMiso® (four misoprostol 200 microgram tablets).
Pharmacotherapeutic group(s) (ATC Code)	**Component:** mifepristone G03XB51, mifepristone, combinations **Component:** misoprostol G02AD06, misoprostol
Name of Sponsor	MS Health Pty Ltd
Medicinal products to which this RMP refers	MS-2 Step (containing Mifepristone Linepharma and GyMiso®)
Invented name(s) in Australia	MS-2 Step (containing Mifepristone Linepharma and GyMiso®)
Brief description of the product	Chemical class **Component:** Mifepristone Linepharma Mifepristone is a synthetic competitive progesterone receptor and cortisol receptor antagonist **Component: GyMiso®** Misoprostol is a synthetic analogue of prostaglandin E1.
	Summary of mode of action **Component:** Mifepristone Linepharma. Mifepristone acts via high-affinity reversible binding to the human progesterone and cortisol receptors. **Component: GyMiso®** At the recommended dosages, misoprostol induces contractions of the smooth muscle fibers in the myometrium and relaxation of the uterine cervix. The uterotonic properties of misoprostol should facilitate cervical opening and evacuation of intrauterine debris. In the event of an early termination of pregnancy, the combination of GyMiso® used in a sequential regimen after mifepristone leads to an increase in the success rate and accelerates the expulsion of the conceptus.
	Important information about its composition N/A
Hyperlink to the Product Information	Module 1.3.1

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Indication(s) in AU	***MS-2 Step*** is indicated in females of childbearing age for the medical termination of an intrauterine pregnancy, up to 63 days of gestation. It is recommended that the duration of pregnancy (i.e., up to 63 days gestation) be confirmed by ultrasound. In the event that an ultrasound is not possible, extra caution should be exercised. Ultrasound is also useful to exclude ectopic pregnancy
Dosage in AU	Mifepristone Linepharma: 200 mg of mifepristone (1 tablet containing 200 mg) orally, followed 36 to 48 hours later by the administration of GyMiso®. GyMiso®: 800 micrograms of misoprostol (4 tablets, each tablet containing 200 micrograms) buccally, i.e: kept between the cheek and the gum for 30 minutes before any fragments being swallowed with water.
Pharmaceutical form(s) and strengths	**Component:** Mifepristone Linepharma Tablet Mifepristone 200 mg **Component: GyMiso®** Tablet Misoprostol 200 micrograms
Is/will the product be subject to additional monitoring in AU?	No

PART II: SAFETY SPECIFICATION

SI – EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

Indication

MS-2 Step is indicated in females of childbearing age for the medical termination of an intrauterine pregnancy, up to 63 days of gestation.

It is recommended that the duration of pregnancy (i.e., up to 63 days gestation) be confirmed by ultrasound. In the event that an ultrasound is not possible, extra caution should be exercised.

Ultrasound is also useful to exclude ectopic pregnancy.

Incidence:

Data from a number of Australian states on pregnancy termination rates applied to the Australian female population aged 15 to 44 years as at June 2009 indicates that between approximately 82,000 to 95,000 surgical terminations may occur in Australia each year. (1,2) Assuming that 30 percent of terminations of pregnancies are eligible for the medical method with mifepristone followed by misoprostol, then approximately 24,600 to 28,500 terminations could be performed with the medical method each year.

To this figure should be added the number of cases in which mifepristone will have been used for cervical priming prior to D & C for second trimester termination. The incidence of second term pregnancy termination is very low (approximately 8 / 1,000 births (3), thus may involve 2,000 cases per annum in Australia.

Prevalence:

Not applicable – refer to Incidence.

Demographic profile of target population:

Women of reproductive age, no specific profile.

The main treatment options:

In general, where pregnancy termination is legal (as is the case in most EU countries), D&C or vacuum aspiration, which are the standard surgical procedures for first trimester pregnancy termination are very safe: in a study of more than 14,000 subjects (4), the following complications were reported after suction curettage (SC):

Complication	SC only, *n* (%)	SC with dilatation, *n* (%)
Retention of fetoplacental material	228 (2.7)	129 (2)
Excessive bleeding	168 (2)	128 (2)
Infection	81 (< 1)	60 (< 1)
Perforation	None	7 (0.05)
Persistant fever	None	None
Unintended major surgery	None	None
Hemorrhage requiring transfusion	None	None

As shown in the table, retention of foetoplacental material and excessive bleeding are the most frequent, albeit rare, complications. Death appears exceptional in this indication and is related to general anaesthesia whenever used.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Not applicable.

Important co-morbidities:

No significant co-morbid conditions have been identified in the target population of women of reproductive age.

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Potential health risk:

A review of the safety of mifepristone from first trimester termination of pregnancy in the USA (5) reported an overall complication rate of 2.2 per 1000, with infection (0.2 per 1000), bleeding requiring transfusion (0.5 per 1000) and deaths 1.1 per 100,000.

Improper use of medical termination of pregnancy could lead to potential health risk linked to excessive bleeding, incomplete foetal expulsion and infection. –Such risk can be minimized by ~~adequate training of medical practitioners~~ensuring medical practitioners have access to education and training resources.

Commented [s22]: roposed removal of mandatory training program for prescribers

Since the use of mifepristone and misoprostol cannot terminate a pregnancy in 100% of the cases, the background incidence of congenital anomalies is presented below.

Table 2 Epidemiology of congenital anomaly

Identified or potential risk	**Congenital anomaly**
Incidence of condition	Congenital anomalies are reported in some 2.2% of live births, with the most common anomalies being cardiac malformations (68/10,000 births), orofacial clefts (16/10,000 births) and genital malformations (16/10,000 births) (EUROCAT Central Registry, Report 2004-2005).
Prevalence of condition	Not applicable.
Mortality of condition	Not applicable.
Risk factors	Some congenital anomalies can be attributed to a mother's genetic predisposition. Other risk factors include age (over 35), use of certain drugs and alcohol, and smoking during pregnancy.

SII – NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

Table 3 Safety concerns and relevance to human usage

Mifepristone	
Safety concern	**Relevance to human usage**
Pharmacology: Antiprogesterone activity Mifepristone prevented pregnancy maintenance in rats, rabbits, guinea pigs and monkeys as a consequence of its anti-progesterone activity. Anticortisol activity Mifepristone exerts anticortisol activity (due to receptor antagonism) in a variety of in vitro and in vivo models. Studies in humans have confirmed the existence of anticortisol activity. However, such activity can be	These actions justify the clinical use of mifepristone in humans (pregnancy termination). None given the duration (single-dose administration) of treatment, given the reversibility of cortisol blockade.

Mifepristone	
Safety concern	**Relevance to human usage**
demonstrated after repeated use at daily doses of 200 mg or more, and can be reversed (1 mg dexamethasone reverses the cortisol blockade induced by 400 mg mifepristone). In addition, cortisol blockage results in an increase in ACTH and cortisol blood levels which in turn overcome the cortisol receptor blockade induced by mifepristone. Antiandrogenic, estrogenic and antiestrogenic, mineralocorticoid and antimineralocorticoid activities. At repeated doses, mifepristone exhibits partial androgen antagonism in animal models. It exhibits little estrogen estrogenic or anti-estrogenic activity in spayed and immature animals but caused an increase in ovarian weight and prolonged estrus in mature animals and displays no antimineralocorticoid activity against aldosterone nor any mineralocorticoid activity (see section 2.4.3 of dossier).	None (single-dose administration)
Safety pharmacology: Mifepristone was evaluated in a variety of standard pharmacological tests (see section 2.4.3.3 of dossier). CNS activity - Only effect noted was a potentiation of the hexobarbital sleeping time in rodents with oral doses of 10-100 mg/kg. Autonomous nervous system activity In vitro, mifepristone antagonized acetylcholine, histamine and serotonin in the isolated guinea pig ileum at a concentration of 10-4M. Cardiovascular/respiratory activity No effects were seen at doses up to 10 mg/kg. Gastrointestinal activity No effects at doses up to 100 mg/kg. Genitourinary activity Mifepristone decreased sodium excretion at doses of 10-100 mg/kg, potassium at 30-100 mg/kg and the sodium/potassium ratio. Urine volume was increased at the 100 mg/kg dose. Endocrine activity In fasted rats, mifepristone produced a slight hypoglycemic effect at doses of 30-100 mg/kg. Analgesic / anti-inflammatory activity No effects at doses up to 100 mg/kg.	There is no finding which would be relevant when used as a single administration with a dose of 200 mg.

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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Mifepristone	
Safety concern	**Relevance to human usage**
Haematological activity No significant effects.	
Pharmacokinetic interactions: Using in vitro studies, mmifepristone has been shown to be a potent mechanism-based inactivator of human CYP-3A4 (see section 2.4.4.4 of dossier).	The clinical significance of the inactivation of CYP-3A4 by mifepristone is that it would be expected to increase the bioavailability of several clinically used drugs metabolized by CYP-3A4 such as cyclosporine A, tacrolimus and dihydropyridines.
Repeated dose toxicity studies: (See section 2.4.5.2 of dossier) Pituitary, adrenals, mammary, ovary, uterus, vagina, fallopian tubes: The toxicological profile emerging from these studies appears to be a consequence of the anti-progesterone and anti-glucocorticoid properties of mifepristone. Liver and kidney: Increase weight associated with hepatocyte hypertrophy in rats and in monkeys. Thyroid: In a chronic toxicity study, a thyroid follicular adenoma was seen in one high-dose female rat.	The effects observed in the toxicity studies were seen after repeated daily dosing. They appeared unspecific and are unlikely to be of consequence in women after a single 200 mg dose of mifepristone. This effect was observed after repeated daily dosing. It is unlikely to be of consequence in women after a single 200 mg dose of mifepristone.
Reproductive and developmental toxicity: Fertility: Mifepristone was administered orally to groups of 12 female Sprague-Dawley rats for 3 weeks at doses of 0, 0.3 or 1.0 mg/kg/day. After the end of treatment rats were observed for 5 weeks after which they were mated with untreated males. Cycles were monitored by daily vaginal smears. Results: The oestrous cycle was disrupted at both doses within 10 days of treatment. Withdrawal of treatment resulted in gradual dose-dependent restoration of the cycle over 2 - 3 weeks. Reproductive endpoints of mating, gestation, parturition, litter size, morphology of offspring, bodyweight change and survival were not affected by drug treatment. Embryofoetal development: Mouse	These findings suggest that if a woman is exposed to a 200 mg dose of mifepristone early during her pregnancy, no deleterious effects on foetal development are necessarily expected if pregnancy is maintained. Reproductive function should not be altered.

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Mifepristone	
Safety concern	**Relevance to human usage**
Groups of 25 Swiss CD 1 mice were gavaged with vehicle, 0.5, 1 or 2 mg/kg/day mifepristone from day 6 to 17 of gestation. Clinical signs: None Body weight: Almost complete suppression of body weight gain in the 2 mg/kg/day group. Moderate suppression in the 1 mg/kg/day group. Final body weights (day 18) were Controls - 62.8; Low-dose - 58.9; medium-dose - 48.0; high-dose - 34.8 grams. There was a marked dose-related increase in fetal loss. The mean rate was 21% in low-dose; 60% in medium-dose and 100% in high-dose. Foetal weights were normal in the survivors. Foetal examination: There were no treatment related increases in foetal anomalies or malformations. Rat Groups of 25 pregnant Sprague-Dawley rats were gavaged with vehicle, 0.25, 0.50 or 1.0 mg/kg/day mifepristone from day 6 to day 17 of gestation. Clinical signs: None Body weight: weight gain was comparable between groups except for the high-dose group where there was a retardation at the end of treatment. Six high-dose rats had no living foetuses at autopsy. The post-implantation loss was 34% compared to 5.7% in controls (statistically significant). Foetal weights were equal between groups and the sex ratio was the same. Foetal examination: There were no treatment related differences in foetal anomalies or malformations. Rabbit Groups of 15-20 HY rabbits were gavaged with vehicle, 0.25, 0.5,1, 2, or 4 mg/kg/day mifepristone from day 6 to 18 of gestation. The two highest doses increased foetal loss (31% and 67% cf. 6% for controls) and increased the incidence of incomplete ossification of the cranium, sternum and paws, without affecting maternal body weight or producing clinical signs. In a published study in rabbits, treatment with mifepristone on 0.5 or 1 mg/day s.c. for 1-5 days starting on day 11 of gestation was associated with foetal malformations (failure	These data suggest some potential for adverse effects on foetal development, including teratogenicity, with exposure to mifepristone where pregnancy is maintained. The abnormalities observed in animals most likely occurred as a consequence of the mifepristone's effect on the uterus rather than any direct effect of the drug on the foetus. These results indicate that in case a woman carries her pregnancy to term despite exposure to mifepristone during pregnancy, there is some potential for postnatal development to be delayed.

Mifepristone	
Safety concern	**Relevance to human usage**
of the cranium to close and haemorrhagic destruction of the upper part of the head and brain, no spinal column, no closure of eyelids) considered to be treatment-related. Monkey A case of holoprosencephaly in a fetus of a cynomolgus monkey that had been treated with mifepristone at 2.5 mg/kg/day i.m. from day 15 to 18 of gestation is reported in the literature. This was considered most likely to have occurred secondary to disturbed development of the gestational sac and placenta due to an incomplete abortion, reducing blood supply to the conceptus. Pre-/post natal development: Groups of 20-25 Sprague-Dawley rats were gavaged with vehicle or 0.25, 0.5 or 1 mg/kg/day mifepristone from day 15 of gestation to the end of the lactation period (postnatal day 21). Increase morality at birth (not statistically significant) and delayed development of the righting reflex and slight inhibition of locomotor development were observed at the high-dose level. Other developmental parameters and the reproductive performance of the offspring were unaffected. Male and female Sprague-Dawley pups from 15 litters were injected s.c. 1 day after birth with vehicle, 1, 10 or 100 mg/kg mifepristone. On day 4, the number of offspring in each litter was reduced to 8 (4 of each sex) using a random distribution table. The general condition and growth of the offspring was not affected by treatment. Descent of testes was normal but there was a slight delay in vaginal opening in the high-dose females (not significant). At the age of 11 or 15 weeks, histopathology revealed no effects on the testes and activity of the seminiferous tubules. Reproductive function, assessed by mating rate and fertilizing capacity, was not affected by treatment. Disruption of normal sexual development in neonatal Wistar rats given 1 mg mifepristone s.c. every second day from postnatal day 1 or 4 for 14 days is reported in the literature.	

Misoprostol	
Safety concern	**Relevance to human usage**
Misoprostol, 15-deoxy-16-hydroxy-16-methyl-PGE1, is a synthetic analogue of PGE1.	

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[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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Misoprostol	
Safety concern	**Relevance to human usage**
Prostaglandins contract or relax many smooth muscles. Strips of non-pregnant human uterus are relaxed by PGEs; strips from pregnant women are contracted by low concentrations of PGE2 and relaxed by high concentrations. Intraperitoneal and oral administration of misoprostol induced diarrhoea in mice and rats, respectively, with ED50 values in the rat after oral administration being in the range 366-1305 µg/kg, depending on when in the 8-hour observation period following dosing the effect was measured. Oral administration of 30 µg/kg of misoprostol to conscious dogs did not affect blood pressure, heart rate or the ECG. Misoprostol inhibited histamine-induced bronchoconstriction in the anaesthetized guinea-pig after intravenous administration of 10-1000 µg/kg, the effect depending on the intensity of the histamine challenge; effects against a PGF2α challenge were more variable.	These actions justify the clinical use of misoprostol in humans (pregnancy termination). None (single-dose administration)
Toxicological information Single dose toxicity Oral LD50 values in mice and rats were 27-138 and 81-100 mg/kg, respectively, with corresponding values after intraperitoneal dosing of 70-160 and 40-62 mg/kg. In an ascending dose study in dogs, no deaths were observed at 10 mg/kg, the maximum dose administered. The most prominent clinical signs were diarrhea and reduced motor activity in rodents and, in dogs, emesis, tremors, mydriasis and diarrhea. Most deaths occurred within 24 hours of dosing and surviving animals appeared normal within 3-4 days. Repeat dose toxicity The rat and dog were selected as the species for the repeated dose toxicity studies. Rats Studies in the rat were of 5, 13 and 52 weeks duration; the 52 week study incorporated a 13 week recovery period. Administration 0, 160, 320, 1200, 1600, 8000 and 9000 µg/kg/day. The major clinical signs were diarrhoea, salivation, vaginal dilation and discharge, decreased body weight (mainly males) and increased food consumption. There was no effect on rectal temperature in the 5 week. In the 52 week study, no abnormal clinical signs were observed at 160 µg/kg/day and all signs at the higher doses of 1200 and 9000 µg/kg/day were absent by the end of the 13 week recovery period.	The effects observed in the toxicity studies were seen after repeated daily dosing. They appeared unspecific and are unlikely to be of consequence in women after a single 800 µg dose of misoprostol.

Misoprostol	
Safety concern	**Relevance to human usage**
There were no deaths that were attributable to treatment. Principal clinical biochemistry changes were decreases in serum total protein and increases in serum iron, with any changes in other parameters remaining within normal limits and considered incidental. The decrease in protein levels may be a consequence of poor absorption of nutrients resulting from diarrhoea. Serum iron was significantly increased at 9000 µg/kg/day in the 52 week study and at 1600 and 8000 µg/kg/day in the 5 week study. Any changes in laboratory parameters seen at the end of the 52 week study were absent after the 13 week recovery period. Dogs Studies in the dog were of 5, 13 and 52 weeks duration. Doses for the 52 week study were 0, 30, 100 and 300 µg/kg/day. These studies included recovery periods of 4 and 13 weeks. The most important clinical signs in these studies were emesis, diarrhoea, soft and/or mucoid stools and increased rectal temperature; these were dose related and either decreased or were absent by the end of the 4 and 13 week recovery periods. There were two deaths in the 52 week study, both in animals receiving 300 µg/kg/day. Changes in clinical biochemistry parameters were incidental or within normal limits, with the exception of serum chloride, which increased slightly in the 52 week study; there were no abnormal clinical laboratory findings at the end of the recovery periods.	
Genotoxicity Misoprostol was negative in five in vitro tests of genotoxic potential – the Ames test in five strains of Salmonella typhimurium, the mouse lymphoma TK+/- assay, mitotic gene conversion in Saccharomyces cerevisiae, a sister chromatid exchange assay in CHO cells and a C3H/10T 1/2 cell transformation assay. The first four of these were performed in the absence and presence of metabolic activation. In addition to these tests, an abstract (6) cites a negative result in an in vivo mouse micronucleus test.	None

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Misoprostol	
Safety concern	**Relevance to human usage**
Carcinogenicity The potential carcinogenicity of misoprostol has been evaluated in both mice and rats. The study in mice was of 21 months duration and administered doses of 0, 160, 1600 and 16000 µg/kg/day by gavage. In the rat study, doses of 0, 24, 240 and 2400 µg/kg/day were administered for 24 months by gavage. There was no indication of a carcinogenic effect in either species. In both species, there were statistically significant increases in epithelial hyperplasia and hyperkeratosis of the gastric mucosa; these were non-neoplastic and expected as a consequence of the pharmacological activity of misoprostol. This was also observed in the 52-week study in rats where it was seen to be reversible on stopping treatment. In addition, hyperostosis of the marrow cavity of sternebrae and femurs was observed in mice. This has also been reported for PGE2 in rats, dogs and children. However, this was not seen in the 24-month carcinogenicity study in rats with misoprostol, nor in the 52-week repeated dose toxicity study in dogs. It thus appears to be a phenomenon restricted to mice for misoprostol.	Given the short duration of administration to women covered by the current application, its relevance to the intended use of misoprostol is doubtful.
Reproductive and developmental toxicity: Two fertility studies were performed in the rat. One was with doses of 0, 100, 1000 and 10000 µg/kg/day; males were treated from day 71 premating until mating and females from 15 days premating to parturition. The other used doses of 0, 100, 400 and 1600 µg/kg/day; males were treated from day 70 premating and females from 14 days premating to day 7 of gestation. The number of implantations was decreased at 1600 and 10000 µg/kg/day and an increase in resorptions occurred at 1000 and 10000 µg/kg/day in one study, but not at 1600 µg/kg/day in the other; resorptions were not increased in the rat teratology study at doses up to 10000 µg/kg/day. As a consequence of these events, there were a decreased number of live foetuses or pups at 10000 µg/kg/day and a decreased number of foetuses at 1600 µg/kg/day. Foetal and pup survival and development were not affected. Two teratology studies were performed in rats using the same doses as the fertility studies with dosing on days 6 to 15 or 7 to 17 of gestation; there was no evidence of embryotoxicity, foetotoxicity or teratogenicity. Two rabbit studies, at doses of 0, 100, 300 and 1000 µg/kg/day on days 6 to 18 of gestation also showed no evidence of foetotoxicity or teratogenicity, although there was an increased number of resorptions at 1000 µg/kg/day in one study.	On the basis of the studies summarized in this application, there would not seem to be cause for concern with respect to possible effect on the foetus of misoprostol in circumstances where termination of pregnancy in association with mifepristone was not successful and the pregnancy was allowed to continue. However, misoprostol, through its smooth muscle contracting activity, could have effects on the developing foetus and there are several reports in the literature on the occurrence of congenital defects in children born to mothers who had taken misoprostol to terminate pregnancy; this off-label use of misoprostol appears to have been a particular problem in Brazil, from where considerable evidence has accumulated on its possible teratogenic activity in humans (7,8). Data would suggest a link between misoprostol and congenital malformations, based on a retrospective analysis of cases, and a prospective study based on Brazilian data suggested that misoprostol may increase the incidence of congenital anomalies, but that the magnitude of the increased risk is low (9).

Misoprostol	
Safety concern	**Relevance to human usage**
A rat pre/postnatal study used doses of 100, 1000 and 10000 µg/kg/day administered from day 15 of gestation to day 20 postpartum. Pup survival was unaffected, though a decrease in pup weight gain was apparent at 10000 µg/kg/day. The studies summarised above showed effects of misoprostol in decreasing implantations and increasing resorptions in rats and rabbits, but did not show any indication of a teratogenic effect. Moreover, the doses at which effects on implantations and resorptions were observed were 1000 µg/kg/day and above, levels 75 times higher than the 800 µg dose recommended in this application for use in the termination of pregnancy. In a more targeted embryotoxicity / teratogenicity study in the mouse, pregnant Han:NMRI mice were treated with single doses of 20 or 30 mg/kg of misoprostol on day 10 of pregnancy. A slight and reversible decrease in maternal weight gain was seen at both doses. Whereas there was no evidence of embryotoxicity at the 20 mg/kg dose, resorptions were increased at 30 mg/kg and an increased occurrence of cleft palate as well as other skeletal abnormalities was observed in surviving foetuses at this dose level. Embryotoxic effects of other prostaglandins have been reported, including PGE2 and PGF2α and rioprostil, a synthetic PGE1 analogue; these effects were attributed, at least in part, to the disturbances in blood supply to the foetus caused by these potent agents. Misoprostol will also reduce uterine blood flow and this could be the cause of the apparent malformations described in humans, although humans seem much more sensitive to misoprostol than mice, rats or rabbits.	

SIII – CLINICAL TRIAL EXPOSURE

Clinical efficacy of early medical abortion is defined as complete abortion without surgical intervention, regardless of the reason for the intervention, which may include continuing pregnancy, missed or incomplete abortion, prolonged or heavy vaginal bleeding or a woman's request.

The clinical trial exposure to MS-2 Step includes the following studies.

An open-label single-group prospective trial (Study 1.1.4) performed in Mexico by Gynuity Healthcare, USA, involving 971 women available for efficacy treated with 200 mg mifepristone followed by 800 micrograms misoprostol administered buccally indicated that efficacy was 98.0, 96.8 and 95.9% for women with gestational age 49 days and below, 50-56 days and 57-63 days, respectively. In these 3 gestational age groups, the rate of surgical evacuation was 2.0, 3.2 and 4.1% respectively. In this study 25 women received a second dose of misoprostol, in each case, a dose of 800 micrograms by the buccal route. Of those 25, 20 had a successful outcome with

medication alone, 4 had a surgical intervention and 1 woman did not return for follow up. In this study, bleeding occurred in all women independent of outcome, and was judged as more than expected in 27.1% of the women.

In an observational cohort study of 15 008 women attending one of 16 Marie Stopes International clinics in Australia for MTOP (gestational age ≤ 63 days) between 1 March 2013 and 30 September 2015, patients were administered 200 mg mifepristone orally in-clinic, followed 24-48 hours later by 800 micrograms of misoprostol buccally, self-administered at home. Method success was defined as complete abortion not requiring surgical intervention. Follow up information was available for 13,078 (87.2%) of the total cohort. Medical abortion was successful in 95.16% (12,445/13,078) of women with follow-up. Higher patient and gestational ages were associated (P < 0.001) with a slight increase in method failure. There were 674 serious adverse events (5.15%), mainly due to method failure. Infection (15; 0.11%) and haemorrhage (17; 0.13%) were rare. One death was recorded (<0.01%); however, an association between EMA and cause of death, necrotising pneumonia, was not established (26)

Studies published in the literature have reported mifepristone and oral or buccal misoprostol regimens. In one study of 966 patients(10) with pregnancies up to gestational age of 63 days, randomised to 200 mg mifepristone followed 24-36 hours later by 800 micrograms of misoprostol orally or buccally, reported efficacy rates were 91.3% for the oral and 96.2% for the buccal group (RR 0.95, 95% CI 0.92-0.98, p=0.003).

Studies published on the combination of mifepristone 200 mg and misoprostol 800 micrograms buccally, and reporting outcomes by gestational age, encompass 399 women with gestational ages 50 – 56 days and 344 women with gestational ages 57 – 63 days (10–16). Efficacy ranged from 86.5 to 98.5% in women with gestational age 50 – 56 days and from 93.0 to 100% in those with gestational age 57 – 63 days. In these studies, the rate of ongoing pregnancies ranged from 0 to 7.1% in women with gestational age 50 – 56 days and from 0 to 2.3% in those with gestational age 57 – 63 days.

Literature data provides information on the bleeding and expulsion pattern after termination of pregnancy with mifepristone and misoprostol: approximately half of women start to bleed before prostaglandin administration. Median bleeding time is 10 to 16 days. Bleeding is judged more or much more abundant than usual menses for 2 to 3 days after prostaglandin. In studies where it was measured, there was a slight but significant decrease in haemoglobin level after compared to baseline. In one study blood loss was quantified: the median blood loss was 83 mL and 5.4% of women had a blood loss above 200 mL. Expulsion usually takes place within 3 hours after misoprostol in approximately half of the women, and within 4 hours after misoprostol in approximately 50 to 90% of women.

SIV – POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Under the Authorised Prescribers Program in Australia in 2012, there were 7,166 medical terminations. Efficacy was 97.4% for women with gestational age <49 days, and 95.2% for women with gestational age of 49-63 days. The rate of incomplete termination requiring aspiration was: <49 days: 2.3%; 49-63 days: 4.8%. The rate of ongoing pregnancies was: <49 days: 0.3%; 49-63 days: 0.6%. Bleeding was considered as an adverse event in 0.24% of women, independent of pregnancy age.

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Not applicable.

SIV.2 Limitation to detect adverse reactions in clinical trial development programs

Not applicable.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programs

MS-2 Step is for use in women of childbearing age.

There is limited data available for use of ***MS-2 Step*** in women under 18 years of age. There is no relevant use of MS-2 Step in the prepubertal paediatric population in the indication. Administration to adolescents less than 18 years of age should be undertaken with caution.

SV – POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

Seventy nine thousand four hundred and three (79, 403) women have been exposed to Mifepristone Linepharma 200 mg tablet (Sweden, Norway, Finland, Kenya, United-Kingdom, Denmark and Australia).

For GyMiso®, since launch in 2004, one hundred and eighty seven thousand three hundred and thirty three (187,333) women have been exposed to GyMiso® (as per the most recent PSURs).

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Literature surveys indicate that in Western countries approximately 2 million women have been exposed to mifepristone and misoprostol for termination of pregnancy since its first approval in France in 1989. In China, exposure to mifepristone is estimated at 13 to 39 million women (Professor Linan Cheng, Shanghai Institute of Planning Parenthood Research, personal communication).

SVI – ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for improper use

The MS-2 Step product is presented as a composite pack in a carton containing two cartons, each of which is different in appearance (as described below). The generic names of the two component medicines, i.e. mifepristone and misoprostol, appear beneath the name MS-2 Step on the composite pack carton.

The two component products contain different amounts of their respective medicines. The labelling on the component products clearly identifies the right order for taking the two products.

An instruction insert is placed in each MS-2 Step product carton to explain the right order for intake of the two products, the recommended time period between intake of the two products, and the importance of a follow-up appointment 14-21 days following the administration of Mifepristone Linepharma to confirm successful termination of pregnancy.

The correct way to take the two products is also described in the respective Consumer Medicine Information sheets that are placed inside each component product carton.

These component products are distinguished from each other in the following ways:

- The Mifepristone Linepharma 200 mg Tablet carton has a green colour on it, and it contains only one mifepristone tablet
- The GyMiso® carton has a purple colour on it, and it contains 4 misoprostol tablets
- Mifepristone Linepharma packaging includes the statement Step 1, take this tablet first.
- GyMiso packaging includes the statement Step 2 take these 36 to 48 hrs after Mifepristone Linepharma

Potential for misuse for illegal purpose

Mifepristone Linepharma and GyMiso® are components of MS-2 Step available by prescription only from ~~qualified~~ medical practitioners hereafter referred to as prescribers. The distribution of MS-2 Step and Mifepristone Linepharma (monopack) in Australia occurs using the secure distribution channels for prescription medicines that operate in this country. There is therefore very low potential for misuse.

Potential for off label use in adults

In some other countries, mifepristone is approved for softening and dilatation of the cervix prior to surgical termination of pregnancy during the first trimester and labour induction in foetal death in utero. Similarly, misoprostol is approved in other territories for cervical preparation before surgical abortion during first trimester, labour induction and treatment and prevention of post-partum haemorrhage.

To date, since Marketing Authorisation has been granted for both products, off label use of Mifepristone Linepharma and GyMiso® has been continuously evaluated: there has been no concern regarding off label use of these drugs.

Use of oral misoprostol beyond 49 days of gestation is associated with lower efficacy, and the acceptable regimen for dosing of GyMiso® by the buccal route only is stated in the MS-2 Step Product Information, in the Consumer Medicine Information Instruction Insert in the MS-2 Step carton, as well as in the Consumer Medicine Information for each component product.

Uterine hyperstimulation and rupture have been reported beyond the first trimester when much lower dosage of misoprostol may be required.

Potential for off label use in children

Mifepristone Linepharma 200 mg Tablet and GyMiso® are recommended for use in females of childbearing age. There are limited data available in women below the age of 18 years. It is possible that the treating medical practitioner will use their discretion and may use the medical method of termination in child-bearing adolescents aged over 12 years of age. It would be expected that the medical practitioner would seek informed consent from a legal guardian before use of the medical method as per use of any method for termination of pregnancy. The sponsor is not aware of any available evidence at present that risks might arise from such off-label use beyond the risks documented herein.

The Sponsor has completed a report on use of mifepristone and misoprostol for termination of early pregnancy under the Authorised Prescriber program for the period September 1, 2009 to the end of August 2011. During this time 13,345 clients were treated and of that number 939 were aged between 14 and 19 years. No risks have been identified in that study specific to that patient group.(10)

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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Potential for overdose

The EU SPC for Mifegyne® and the current Mifepristone Linepharma Australian Product Information indicate that no overdose has been reported.

In the event of massive ingestion signs of adrenal failure might occur. Signs of acute intoxication may require specialist treatment including the administration of dexamethasone.

As a component of MS-2 Step, Mifepristone Linepharma 200 mg Tablet is only available by prescription as a single pack containing only one tablet. ~~MS-2 Step is prescribed by qualified medical practitioners, who have completed all required training and have been certified by the sponsor as part of the Risk Management Plan associated with the registration of the product in Australia~~. It is distributed in Australia using the secure distribution channels for prescription medicines. Therefore, it would be unlikely for a person in the community to access large volumes of this product to enable an overdose to occur.

Commented s22 Proposed removal of mandatory training program and certification for prescribers

The Australian MIMS for Cytotec®(11) and the current GyMiso® Australian Product Information indicate that the toxic dose of misoprostol in humans has not been determined. Cumulative total daily doses of 1600 micrograms have been tolerated, with only symptoms of gastrointestinal discomfort reported.

Clinical signs that may indicate an overdose are sedation, tremor, convulsions, dyspnoea, abdominal pain, diarrhoea, fever, palpitations, hypotension or bradycardia. Hypertension and tachycardia have also been reported following overdoses. Overdose in pregnancy has resulted in uterine contractions with foetal death.

There is no specific antidote. Treatment should be symptomatic and supportive.

As a component of MS-2 Step, GyMiso® will be available as a single pack containing four tablets. MS-2 Step will be prescribed by ~~qualified~~ medical practitioners ~~who have completed all required training and have been certified by the sponsor as part of the Risk Management Plan associated with the registration of the product in Australia~~. It is distributed in Australia using the secure distribution channels for prescription medicines. Therefore it would be unlikely for a person in the community to access large volumes of this product to enable an overdose to occur.

Commented s22 Proposed removal of mandatory training program and certification for prescribers

Potential for transmission infectious agents

Mifepristone as a substance is devoid of any risk of transmission of infectious agents since none of the components are of biological origin. There is no excipient of animal origin in Mifepristone Linepharma 200 mg Tablets.

GyMiso® as a substance is devoid of any risk of transmission of infectious agents since none of the components are of biological origin. There is no excipient of animal origin in GyMiso® tablets.

Medical Education Program, Informed Consent, Compliance to the Method and Follow-up

A number of education programs are available to support prescribers including from family planning organisations, RANZCOG, electronic therapeutic guidelines as well as ~~The~~ the Sponsor's MS Health Medical Education Program ~~is~~ (an ~~comprehensive~~ education program that has been developed and implemented in Australia by the Sponsor) ~~as part of the Risk Management Plan associated with the approval of the Mifepristone Linepharma and MS-2 Step in Australia~~which is available for use by as a resource for prescribers of MS-2 Step. The Sponsor's Medical Education Program includes modules with:

- ~~information supporting the availability of MS-2 Step,~~

- clinical data supporting the use of MS-2 Step in terminations up to 63 days of gestation, in line with the approved Product Information for MS-2 Step,
- information on the listing of MS-2 Step on the Pharmaceutical Benefits Scheme.

~~Practitioners seeking to become registered and certified for the use of Mifepristone Linepharma, or MS-2 Step are required to complete the MS-2 Step education program in order to gain access to these products. Fellows and advanced diplomats of RANZCOG can waive the requirement to complete the program to achieve certification. The Medical Education Program is provided in Appendix 1.~~

~~The updated MS Health Medical Education Program includes references to the Information Sheet and Patient Agreement that is used with MS-2 Step to assist the informed consent process. In addition, the Education Program provides:~~

- ~~information on the process for gaining informed consent,~~
- ~~the need for appropriate counselling,~~
- ~~time for the patient to consider options and to ask questions, information on the critical importance of compliance to the Method and Follow up,~~
- ~~practitioner specified 24 hour emergency care (if and when required), and~~
- ~~the ability for treating medical practitioner to record follow up appointment details.~~

Commented s22 Updated to remove the reference to the mandatory medical education program

Commented s22 Proposed removal of mandatory training program and certification for prescribers

In addition to the Medical Education Program, the Sponsor makes available to prescribers an Information Sheet and Patient Agreement, the MS-2 Step Product Information and the Consumer Medicine Information documents for the MS-2 Step components. These documents all note the importance that patients are required to be informed about the administration of the medical method, compliance to the method, the importance of follow-up, side effects and associated risks. It is recommended that informed consent is obtained from the woman before use of the medical method as per use of any method for termination of pregnancy. The Information Sheet and Patient Agreement, Product Information and Consumer Medicine Information note the need for the woman to remain in contact with the treating practitioner and or clinic and it is recommended that they do not travel during the episode of bleeding so that they can visit the clinic if necessary.

~~The MS-2 Step Product Information and Consumer Medicine Information and product labelling provides details of the 24 hour nurse after care telephone service provided by the Sponsor and staffed by qualified registered nurses. Patients may also give consent and elect to receive a follow up SMS text communication from the Sponsor 3 to 5 days following ingestion of mifepristone. This message provides the 24 hour nurse after care call centre contact telephone number and describes the symptoms that are of concern in relation to infection, incomplete abortion or therapeutic failure that require medical follow up.~~

Commented s22 Proposed removal of 24 hour nurse after care program removed.

Training of Medical Practitioners

Medical education is offered by the Sponsor to ~~all appropriately qualified~~ treating practitioners ~~to ensure that this information is delivered to women undergoing treatment~~. ~~The Medical Education Program, includes pre assessment, post assessment and case studies, supporting the approval of MS-2 Step. Any amendments to the program are reviewed by a medical expert in the field. The Sponsor also seeks review and endorsement of any amendments from the RANZCOG.~~

The Medical Education Program is delivered online and freely available to all treating. ~~Prescribers registering for the first time are required to complete the Medical Education Program to secure certification (approval to prescribe) for Mifepristone Linepharma and MS-2 Step. Once registered and certified no re-registration or re-certification is required. Fellows and advanced diplomats of~~

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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~~RANZCOG can waive the requirement for additional training associated with the approval of MS-2 Step.~~

~~Effectiveness measures are included in the amended Medical Education Program, which detect the level of knowledge known by the participant, prior to completion of the module, and post completion of the module. The participant scores are monitored. A certificate of completion is only issued to participants who demonstrate appropriate knowledge at the completion of the amended education program. The required level of knowledge is determined during the review and endorsement process, which the Sponsor has embarked upon with the RANZCOG.~~

Commented [s22]: roposed removal of mandatory training program and cer for prescribers

The Medical Education Program has been prepared to ensure, to the extent practical, that the medical method of termination using MS-2 Step is used in Australia responsibly and appropriately. The plan has been designed ~~to limit the availability of these medicines to appropriately qualified and resourced prescribers and~~ to ensure that prescribers and patients have access to appropriate information regarding the safe and effective administration of the Medical Method.

Elements of the Risk Management Program

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The elements of the Risk Management Program include:

~~1. Access and distribution. To ensure that only appropriately qualified prescribers have access to either the Mifepristone Linepharma single pack or MS-2 Step containing one pack each of Mifepristone Linepharma 200 mg and GyMiso® 200 µg tablets.~~

Commented [s22]: Updated to remove reference to qualified prescribers

~~2.~~1. Education. Provision of information regarding the appropriate use of the Medical Method including follow up offered to all prescribers and to patients. The education program includes information on first trimester termination of pregnancy and for use of mifepristone in terminations beyond the first trimester.

~~3.~~2. Informed Consent. Provision of preprinted Information Sheet and Patient Agreement to healthcare professionals to ensure that information for patients is available to assist the provision of informed consent by patients. Patient Information and Patient Consent forms are accessible to health care professionals as downloadable pdf files from the healthcare professional secure website: www.ms2step.com.au.

~~4.~~3. Product labeling and packaging and Consumer Medicine Information, ~~which includes a toll free telephone number for 24 hour nurse after care advice from registered nurses provided by the Sponsor, and website URL,~~ which provides additional information to patients in an accessible and easy to understand format.

~~5.~~4. The inclusion of the Black Box warning regarding follow-up, in the following documents, emphasises the need for special attention on the part of healthcare professionals: MS-2 Step Product Information, MS-2 Step Consumer Medicine Information Instruction Insert, the Mifepristone Linepharma Consumer Medicine Information, and the GyMiso® Consumer Medicine Information.

~~6. Follow-up SMS text message to patients. Patients may also give consent and elect to receive a follow-up SMS text communication from the Sponsor 3 to 5 days following ingestion of mifepristone. This message provides the 24 hour nurse after care call centre contact telephone number and describe symptoms that are of concern in relation to infection, incomplete abortion, or therapeutic failure that require medical follow up.~~

Commented [s22]: Proposed removal of 24 hour after care service

~~7.~~5. Monitoring. ~~To test that the objectives of the educational program are being met with healthcare professionals and patients.~~ Periodic review of the pharmacovigilance database maintained by MS Health in Australia to ensure adverse event reporting is not trending.

~~8.~~6. Adverse Event Monitoring in Australia and Ongoing Post Marketing Surveillance. The Sponsor holds a significant database from the use of mifepristone for termination of first trimester pregnancy under the Authorised Prescriber Program (APP) in the MSIA network. The training modules will continue to be reviewed and updated to reflect the results of other peer-reviewed published studies e.g. ANZJOG 2017; 57: 366-371 as well as other large studies/meta-analyses.

Potential for medication errors

The brand name for the composite pack is ***MS-2 Step.*** The product is presented as a composite pack in a carton containing two cartons, each of which is different in appearance (as described below). The generic names of the two component medicines, i.e. mifepristone and misoprostol, appear beneath the name ***MS-2 Step*** on the composite pack carton.

The component products contain different amounts of their respective medicines.

The labelling on the component products clearly identifies the right order for intake of the two products on the front panel of the packaging for each individual product. An instruction insert is placed in each ***MS-2 Step*** product carton to explain the right order for intake of the two products. The correct way to take the two products is also described in the respective Consumer Medicines Information leaflets, which are placed inside each component product carton.

These products are distinguished from each other in the following ways:

- The Mifepristone Linepharma 200 mg Tablet carton has a green colour, and it contains only one mifepristone tablet
- The GyMiso® carton has a purple colour, and it contains 4 misoprostol tablets
- Mifepristone Linepharma packaging includes the statement *Step 1, take this tablet first.*
- GyMiso packaging includes the statement *Step 2, take these 36 to 48 hrs after Mifepristone Linepharma*

The brand name Mifepristone Linepharma 200 mg Tablet uses the INN mifepristone and this should minimise the risk of confusion.

Mifepristone Linepharma 200 mg Tablet is available in a single strength as 200 mg tablets, each pack contains one tablet sufficient for one single treatment. Each tablet is debossed on one side (with the letters “MF”) to avoid confusion with other tablets.

The Consumer Medicine Information is included in each Mifepristone Linepharma component package and this document includes information on indication, contraindications, precautions and dosing recommendations.

The brand GyMiso® refers only to misoprostol approved in combination with mifepristone in the ***MS-2 Step*** composite pack, and this should minimise the risk of confusion.

GyMiso® is available in a single strength as 200 microgram tablet, and each GyMiso® pack contains four tablets sufficient for one single treatment. Each tablet is engraved on one side with “ML” and “200” on the other to avoid confusion with other tablets.

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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The Consumer Medicine Information is included in each GyMiso® component pack and this document includes information on indication, contraindications, precautions and dosing recommendations.

SVIII – IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

Since this is not initial RMP submission, this section is not applicable.

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.2 New Safety concerns and reclassifications with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

The description that follows provides details on the identified and potential risks that have been described for the product(s), based on the clinical trial data, literature and post-marketing experience data currently available for MS-2 Step.

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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SVII.3.1 Presentation of important identified risks and important potential risks

Table 4 Important Identified Risks

Identified risk	**"Incomplete abortion (method failure) with severe bleeding"**
MedDRA terms	Induced abortion failed (PT) Vaginal bleeding (PT)
Seriousness	Yes. Method failure occurs in 1.3 to 7.5% of cases. Heavy bleeding occurs in about 5% of cases and may require haemostatic curettage in up to 1.4% of cases. A transfusion is required in 0.1-0.2% of cases.(19) Method failure may occur with severe bleeding and it may occur without severe bleeding. Severe bleeding may not be a symptom of method failure. As there is a risk of failure of the method follow up of women is mandatory to check that abortion is complete.
Severity and nature of risk	Vaginal bleeding is part of the method. Bleeding occurs in almost all cases and is not in any way proof of complete expulsion. Follow-up must take place within a period of 14 to 21 days after administration of mifepristone to verify by the appropriate means that expulsion has been completed and that vaginal bleeding has stopped. In case of persistent bleeding (even light) beyond follow up, its disappearance should be checked within a few days. If continuing pregnancy is suspected, a further ultrasound scan may be required to evaluate its viability. Persistence of vaginal bleeding at this point could signify incomplete abortion, or an unnoticed extra-uterine pregnancy, and appropriate treatment should be considered. Heavy bleeding occurs in about 5% of cases and may require haemostatic curettage in up to 1.4% of cases. In the event of continuing pregnancy diagnosed after follow up, termination by another method may be proposed to the woman. As there is a risk of failure, follow up of women is mandatory to check that abortion is complete.
Frequency	Failure occurs in 1.3 to 7.5 % of cases.
Background incidence/prevalence	Early vacuum aspiration leads to up to 5% failure rate.(20)
Risk group or risk factors	None identified
Potential mechanism	Incomplete detachment of conceptus from uterine wall, insufficient uterine contractility.

MS-2 Step composite pack
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Identified risk	**"Incomplete abortion (method failure) with severe bleeding"**
Preventability	Information about the potential occurrence of both method failure and severe bleeding respectively is in the Product Information and the Consumer Medicine Information. Education to be offered to Medical Practitioners.
Potential public health impact	Yes, hence the need for educational resources to be available to practitioners and adequate information for women~~None~~

Commented [S22]: Updated to align with terminology used for other identified risks

Identified risk	**"Infection, toxic shock syndrome"**
MedDRA terms	Infection (PT), Toxic shock syndrome (PT)
Seriousness	Yes. Infection following termination occurs in less than 1% of cases regardless of the method. Infection in medical termination occurs in 0.3-0.9% of cases.(21) Fatal toxic shock syndrome is very rare.
Severity and nature of risk	Very rare cases of fatal toxic shock caused by *Clostridium sordellii* endometritis presenting without fever or other obvious symptoms of infection, have been reported after medical abortion with the use of 200 mg mifepristone following the non-approved vaginal administration of misoprostol tablets for oral use. In Australia a case of fatal probable toxic shock syndrome has been reported in a woman treated with mifepristone 200 mg followed by 800 mcg buccal misoprostol. Clinicians should be aware of this potentially fatal complication.
Frequency	Infection following termination occurs in less than 5% of cases regardless of the method. Very rare cases of fatal toxic shock syndrome.
Background incidence/prevalence	Infection following termination occurs in less than 5% of cases regardless of the method.
Risk group or risk factors	May be associated with vaginal administration of misoprostol oral tablets.
Potential mechanism	Unknown
Preventability	Information about the potential occurrence of the event in Product Information (Precautions) indicating that the vaginal administration route of misoprostol should not be used. Information about the possibility of infection occurring is included in the Consumer Medicine Information. Education to be offered to Medical Practitioners.
Potential public health impact	Yes, hence the need for ~~proper training~~ educational resources to be available to ~~of~~ practitioners and adequate information for~~of~~ women

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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<table>
<tr><td>Identified risk</td><td>“Cardiac Disorders”</td></tr>
<tr><td>MedDRA terms</td><td>Adverse event reports of cardiovascular events are identified using a prespecified list of Standard MedDRA query: SOC Cardiac disorders</td></tr>
<tr><td>Seriousness</td><td>No cardiovascular event was reported during pivotal studies.
Cardiovascular events reported with misoprostol use in a gynaecological indication, in literature studies and postmarketing experience, include myocardial infraction, myocardial ischemia, sudden death, stroke and transient ischemic accident. Most of these events have a favourable outcome, but event with sequel or fatal outcome has also been reported. If some occurred after a treatment including mifepristone and misoprostol, for most of them mifepristone administration was unknown</td></tr>
<tr><td>Severity and nature of risk</td><td>In a prospective study on 9 women evaluating cardio-vascular safety of 600 µg misoprostol administration via vaginal route, none of evaluated parameters (cardiac frequency, arterial pressure, cardiac index…) for 4 days after the take were significantly modified (Ramsey 2000).
An investigation on cardiovascular effect of misoprostol was performed by the French National Agency in 2013. This evaluation based on international literature search, French and international post-marketing reports (from commercialisation to December 2012) concludes in the existence of coronary and cerebral adverse reaction with the use of misoprostol in medical termination of a pregnancy.
Regarding mifepristone potential effect on cardiovascular system, non-clinical data, clinical data, post- marketing surveillance of adverse events and the drug’s action mechanism on the adrenocortical pathway do not associate the product with typical proarrhythmic events that could indicate a QT/QTc interval prolongation.</td></tr>
<tr><td>Frequency</td><td>French National Agency estimated the incidence of cardiovascular events with the use of misoprostol at 2.7 cases [0.3 to 9.8] for 106 exposed women.
In the Australian phase IV safety study, from cumulative data to 31st March 2016, incidence (%) of cardiovascular event by gestational ages is provided below:
<table>
<tr><td>≤ 35 days</td><td>36-42 days</td><td>43-49 days</td><td>50-56 days</td><td>57-63 days</td><td>Total</td></tr>
<tr><td>0</td><td>0.1</td><td>0.1</td><td>0.3</td><td>0.2</td><td>0.1</td></tr>
</table></td></tr>
<tr><td>Background incidence/prevalence</td><td>There are no specific studies that evaluate prevalence of cardiovascular risks of first trimester pregnant women.</td></tr>
<tr><td>Risk group or risk factors</td><td>Vascular risks factors such as tobacco use, hypertension and heredity as well as a sur-exposure to misoprostol.</td></tr>
<tr><td>Potential mechanism</td><td>Coronary manifestations observed during medical termination of pregnancy could be explained by the existence of vascular risks factors (tobacco use, hypertension, heredity) and a sur-exposition to misoprostol related to the high dose (double posology) and the vaginal administration, this way leading to a doubling of AUC.</td></tr>
<tr><td>Preventability</td><td>Information about the potential occurrence of the event in Product Information and Consumer Medicine Information.</td></tr>
<tr><td>Potential public health impact</td><td>~~Yes, hence the need for proper training of to be available to practitioners.~~ Yes, hence the need for educational resources to be available to practitioners and adequate information for women.</td></tr>
</table>

Table 5 Important Potential risks

Important Potential Risk - Unintended pregnancy exposure to mifepristone / misoprostol and risk of incomplete abortion with severe bleeding
Evidence source: In approximately 3% of the cases (EU Summary of Product Characteristics (SPC) for Mifegyne® and for Mifepristone Linepharma, section 4.4) abortion can occur with mifepristone alone (with no prostaglandin intake). Follow-up is still required to ensure that complete abortion has occurred. In addition, as indicated in the EU SPC for Mifegyne® and for Mifepristone Linepharma (section 4.4) during clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses. Due to the long half-life of mifepristone, the possibility exists of exposure of a subsequent pregnancy to mifepristone. To avoid potential exposure of a subsequent pregnancy to mifepristone, it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after mifepristone and misoprostol administration.

Important Potential risk / Unintended pregnancy exposure (risk of malformations)
Evidence source: In the EU SPC for both Mifegyne® and for Mifepristone Linepharma, it is stated in section 4.6, it is stated that "in animals the abortifacient effect of mifepristone precludes the proper assessment of any teratogenic effect of the molecule" and that "with sub abortive doses, isolated cases of malformations observed in rabbits, but not in rats or mice were too few to be considered significant, or attributable to mifepristone". In section 4.6 of the EU SPC for Mifegyne® and Mifepristone Linepharma, it is indicated that "in humans, the few reported cases of malformations do not allow a causality assessment for mifepristone alone or associated to prostaglandin. Therefore, data is too limited to determine whether the molecule is a human teratogen." The issue of the outcome of persisting pregnancy in case of failure of the method remains incompletely solved: although, up to date there does not seem to be clear-cut foetal malformations attributable to mifepristone or to prostaglandin analogues (19), such possibility cannot be definitively ruled out and women should be adequately counseled in such a situation. In addition, as indicated in Part II, Table 3 of this RMP, misoprostol, through its smooth muscle contracting activity, could have effects on the developing foetus and there are several reports in the literature on the occurrence of congenital defects in children born to mothers who had taken misoprostol to terminate pregnancy; this off-label use of misoprostol appears to have been a particular problem in Brazil, from where considerable evidence has accumulated on its possible teratogenic activity in humans (cited by Orioli *et al*, 2000; Paumgarten *et al*, 1995). Data would suggest a link between misoprostol and congenital malformations, based on a retrospective analysis of cases, and a prospective study based on Brazilian data suggested that misoprostol may increase the incidence of congenital anomalies, but that the magnitude of the increased risk is low (Schuler *et al*, 1999). As a consequence, the EU SPC for Mifegyne® and Mifepristone Linepharma proposes the following recommendations: - Women should be informed, that due to the risk of failure of the medical method of pregnancy termination and to the unknown risk to the foetus, follow-up is mandatory (see Section 4.4 special warnings and special precautions for use).

Important Potential risk / Unintended pregnancy exposure (risk of malformations)
- Should a failure of the method be diagnosed at follow-up (viable ongoing pregnancy), and should the patient still agree, pregnancy termination should be completed by another method. - Should the patient wish to continue with her pregnancy, the available data is too limited to justify a systematic termination of an exposed pregnancy. In that event, careful ultra-sonographic monitoring of the pregnancy should be carried out." In addition, as indicated in the EU SPC for Mifegyne® and Mifepristone Linepharma (section 4.4) during clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses. To avoid potential exposure of a subsequent pregnancy to mifepristone, it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after mifepristone / misoprostol administration.

Important Potential risk / Induced Bronchial Asthma
Evidence source: Data to evaluate the inadvertent risk of induced bronchial asthma after the administration of mifepristone and misoprostol are derived from analyses conducted of extensive review of literature published in English and in Chinese as well as non Linepharma France sponsored trials and reports from post-marketing setting. Mifepristone binds to the glucocorticoid receptor. It may therefore interfere with the action of glucocorticoid treatments. This might be relevant in case of severe asthma inadequately controlled by oral or inhaled glucocorticoid. In addition, bronchospasm may occur with some prostaglandins and prostaglandin analogues. The possibility should be borne in mind in patients with a history of asthma. Severe asthma uncontrolled by treatment is labelled as a contraindication in the EU SPC for Mifegyne® and Mifepristone Linepharma, whatever the indication.

Table 6 Potential interaction with CYP3A4 inhibitors or inducers

Interacting substance/CYP3A4 inhibitors or inducers
Evidence source: EU Mifegyne® SPC, literature review No interaction studies have been performed. On the basis of this drug's metabolism by CYP3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum levels of mifepristone). Furthermore, rifampicin, dexamethasone, St. John's Wort and certain anticonvulsants (phenytoin, phenobarbitone, carbamazepine) may induce mifepristone metabolism (lowering serum levels of mifepristone). Based on in vitro inhibition information, co-administration of mifepristone may lead to an increase in serum levels of drugs that are CYP3A4 substrates. Due to the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP3A4 substrates and have narrow therapeutic range, including some agents used during general anaesthesia. For misoprostol, limited studies on effects of misoprostol on hepatic drug metabolism in the rat did not show any effect on aminopyrine metabolism (single oral dose of 0.1 mg/kg of misoprostol) or, after 0.1 mg/kg twice daily for four days, cytochrome P450 content or the activities in liver microsomes of hexobarbital

Interacting substance/CYP3A4 inhibitors or inducers
hydroxylase, aniline hydrolase or p-nitroanisole O-demethylase. Based on this information, no drug interaction is expected after misoprostol administration.

Table 7 Potential interaction with products interacting with the glucocorticoid receptor

Interacting substance/ Products interacting with the glucocorticoid receptor
Evidence source: EU Mifegyne® and Mifepristone Linepharma SPC's, literature review Mifepristone binds to the glucocorticoid receptor. It may therefore interfere with the action of glucocorticoid treatments. This might be relevant in case of severe asthma inadequately controlled by oral or inhaled glucocorticoid.

SVII.3.2. Presentation of the missing information

Table 8 Presentation of the missing information

Missing Information/ Inherited porphyria
Evidence source: This is labelled as a contraindication in the EU SPC for Mifegyne® and Mifepristone Linepharma, whatever the indication. The reason for this contraindication is unclear. Literature search for "mifepristone and porphyria" yields only one abstract (15) indicating that in an *in vitro* model mifepristone and deferoxamine together produced significant accumulations of protoporphyrin. The authors concluded that "RU-486 may pose a risk in patients with known acute porphyria and should be used with caution".

Missing Information / Theoretical interaction with NSAIDs
Evidence source: This is a potential precaution in the EU SPC for Mifegyne® and Mifepristone Linepharma, whatever the indication. A decrease of the efficacy of the method can theoretically occur due to the antiprostaglandin properties of non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin (acetyl salicylic acid). Limited evidence suggests that co-administration of NSAIDs on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medical termination of pregnancy. The reason for this precaution is therefore unclear.(23,24)

Missing Information / Potential interaction with products interacting with the progesterone receptor
Evidence source: EU Mifegyne® and Mifepristone Linepharma SPC's, literature review Mifepristone is a progesterone receptor antagonist. Therefore, it may interfere with the action of progestin-only contraceptives.

Missing Information / use in adolescents
Evidence source: Literature review Mifepristone Linepharma 200 mg Tablet and GyMiso® are recommended for use in females of childbearing age. There are limited data available in women below the age of 18 years.

SVII.3.3. Presentation of the pharmacological class effect

Mifepristone belongs to the progesterone receptor antagonist class.
Mifepristone also displays anti-glucocorticoid activity. Such activity, evidenced by an ACTH elevation, has not been observed at the dose of 200 mg per dose for several years (157 months for treatment of meningioma in patients with normal adrenal function).(18) Therefore, use of a single intake mifepristone is not expected to have anti-glucocorticoid activity. As indicated above, mifepristone may interfere with the action of glucocorticoid treatments. This might be relevant in case of severe asthma inadequately controlled by oral glucocorticoid.

For medical pregnancy termination, mifepristone treatment must be followed by the administration of the prostaglandin analogue, misoprostol (GyMiso®) which is the second component of ***MS-2 Step***. Therefore, risks inherent with this class of product must also be taken in consideration.

Pharmacological class effect / Risks related to the use of prostaglandin
Evidence source: Termination of pregnancy with mifepristone necessitates the use of prostaglandin analogues, such as misoprostol, which has its own potential risks. This is taken into account in the EU Mifegyne® SPC: In section 4.3, the method should not been used in case of contraindication to a prostaglandin analogue. In section 4.4, it is acknowledged that rare serious cardiovascular accidents have been reported following the intra muscular administration of prostaglandin E2 analogue, sulprostone. For this reason women with risk factors for cardiovascular disease or established cardiovascular disease should be treated with caution. This is taken into account in the current Mifepristone Linepharma Australian Product Information: In Contraindications, the product should not be prescribed in case of a contraindication to the prostaglandin analogue.

In Precautions, it is stated that rare serious cardiovascular accidents have been reported following administration of prostaglandins including misoprostol. For this reason, women with risk factors for cardiovascular disease or established cardiovascular disease should be treated with caution.

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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PART II: MODULE SVIII – SUMMARY OF THE SAFETY CONCERNS

Table 9 Summary- safety concerns

Summary of safety concerns	
Important Identified Risks:	Infection, toxic shock syndrome Method failure Cardiac disorders
Important Potential Risks:	Inadvertent pregnancy exposure and risk of incomplete abortion with severe bleeding Inadvertent pregnancy exposure (risk of malformations) Potential interaction with CYP3A4 inhibitors or inducers Potential interaction with products interacting with the glucocorticoid receptor Induced bronchial asthma Effects in lactating women Effects in women with impaired liver function Effects in women with impaired renal function Effects in women with malnutrition Incorrect determination of gestational age Potential for missed ectopic pregnancy Potential for postnatal developmental delay Potential for off-label use beyond the first trimester Potential for loss to follow-up Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up
Missing Information:	Inherited porphyria Theoretical interaction with NSAIDs Potential interaction with products interacting with the progesterone receptor Use in adolescents
Pharmacological class effect	Risks related to the use of prostaglandin

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities including adverse event reporting and signal detection is conducted.

Periodic Safety Updates

Periodic Safety Update Reports (PSURs) for Mifepristone Linepharma and GyMiso® will continue as the safety reporting method for ***MS-2 Step***.

As agreed at the time of approval of the individual products, PSURs was submitted six monthly for the first 12 months from registration and then annually after that, with a data lock of no more than 60 days for Mifepristone Linepharma and GyMiso®, respectively. Use of mifepristone beyond the first trimester (including off-label use) is given separate consideration in the PSURs.

PSURs would be aligned with international reporting in accordance with the international birth date (IBD) defined in ICH E2C(R1), which for:

- Mifepristone Linepharma is based on the EU-harmonised IBD of 31 May. MS Health have completed the PSUR submission commitments.
- The Mifepristone Linepharma product was launched in Australia on 4 February 2013.
- GyMiso® is based on an EU-harmonised IBD of 31 May. The GyMiso® product was launched in Australia on 1 August 2013.
- MS 2 Step PSUR obligations have been met and no further submission are required.

The safety update reports for both Mifepristone Linepharma and GyMiso® will include the ongoing post marketing collection of the data in Australia.

III.2 Additional pharmacovigilance activities

Not applicable

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 10 On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not Applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not Applicable				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Not Applicable				

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Routine risk minimisation measures include the Product information and Consumer Medicine Information. Details are outlined in Table 6 below.

Table 11 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risk: Infection, toxic shock syndrome	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.
Important identified risk: Method failure	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.
Important identified risk: Cardiac disorders	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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Safety concern	**Routine risk minimisation activities**
Important potential risk: Inadvertent pregnancy exposure (risk of malformations)	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.
Important potential risk: Inadvertent pregnancy exposure and risk of incomplete abortion with severe bleeding	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.
Important potential risk: Potential interaction with CYP3A4 inhibitors or inducers	Routine: Mentioned in the Product Information in INTERACTIONS WITH OTHER MEDICINES. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Physician education.
Important potential risk: Potential interaction with products interacting with the glucocorticoid receptor	Routine: Mentioned in the Product Information in PHARMACOLOGY and PRECAUTIONS. Physician education.
Important potential risk: Induced bronchial asthma	Routine: Mentioned in the Product Information in CONTRAINDICATIONS and PRECAUTIONS Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Physician education.

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Safety concern	**Routine risk minimisation activities**
Important potential risk: Incorrect determination of gestational age	Routine: Mentioned in the Product Information in CONTRAINDICATIONS Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Physician education.
Important potential risk: Effects in lactating women	Routine: Mentioned in the Product Information in Use during lactation. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.
Important potential risk: Effects in women with impaired liver function	Routine: Mentioned in the Product Information in SPECIAL WARNINGS AND PRECAUTIONS FOR USE and in INTERACTIONS WITH OTHER MEDICINES. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.
Important potential risk: Effects in women with impaired renal function	Routine: Mentioned in the Product Information in SPECIAL WARNINGS AND PRECAUTIONS FOR USE and in INTERACTIONS WITH OTHER MEDICINES. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.
Important potential risk: Effects in women with malnutrition	Routine: Mentioned in the Product Information in SPECIAL WARNINGS AND PRECAUTIONS FOR USE. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.

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Safety concern	**Routine risk minimisation activities**
Important potential risk: Potential for missed ectopic pregnancy	Routine: Mentioned in the Product Information in SPECIAL WARNINGS AND PRECAUTIONS FOR USE and in ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.
Important potential risk: Potential for postnatal developmental delay	Routine: Mentioned in the Product Information in Use in pregnancy
Important potential risk: Potential for loss to follow up	Routine: Mentioned in the Product Information in SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Missing information: Inherited porphyria	Not mentioned in Product Information and the Consumer Medicine Information as there is limited evidence of this being a safety concern with administration of mifepristone.(22)
Missing information: Potential interaction with products interacting with the progesterone receptor	This potential risk has not been confirmed and no information is deemed necessary in the Product Information.
Missing information: Theoretical interaction with non-steroidal anti-inflammatory drugs	This potential risk has not been confirmed and no information is deemed necessary in the Product Information.
Missing information: Use in adolescents	Product Information and Consumer Medicine Information mention that use is limited in this population. The Product Information mentions, there is no relevant use of MS-2 Step in the prepubertal paediatric population in the indication. Administration to adolescents less than 18 years of age should be undertaken with caution.

Safety concern	Routine risk minimisation activities
Pharmacological class effect:	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS.
Risks related to the use of prostaglandin	Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.

Formatted: English (Australia)

V.2 Additional Risk Minimisation Measures

There are six specific risk minimisation tools planned, as detailed below, in addition to the routine measures for the identified risks, potential risks, missing information and pharmacological class effects, outlined below.

Black Box Warnings

A black box warning is included in the ***MS-2 Step*** Product Information:

> It is very important that all patients receiving these medications are followed up by a medical practitioner, preferably the prescriber, to ensure that the medication has been effective. Even if no adverse events have occurred all patients must receive follow-up 14 to 21 days after taking mifepristone. Read the ***SPECIAL WARNINGS AND PRECAUTIONS FOR USE*** carefully.

A black box warning is included in the Mifepristone Linepharma Consumer Medicine Information:

> It is very important that all patients receiving this medication are followed up by a medical practitioner, preferably the prescriber, to ensure that the medication has been effective. Even if no adverse events have occurred all patients must receive follow-up 14 to 21 days after taking mifepristone.

A black box warning is included in the GyMiso® Consumer Medicine Information:

> It is very important that all patients receiving this medication are followed up by a medical practitioner, preferably the prescriber, to ensure that the medication has been effective. Even if no adverse events have occurred all patients must receive follow-up 14 to 21 days after taking mifepristone.

Inclusion of Consumer Medicine Information

The Consumer Medicine Information is included in every pack of Mifepristone Linepharma.

The Consumer Medicine Information is also be included in every pack of GyMiso®.

Inclusion of Instruction Insert in Composite Pack Carton

An Instruction Insert is included in every pack of ***MS-2 Step***, to clearly indicate the identity of the components, the order in which the component medicines should be taken, and the importance of a follow-up appointment 14-21 days following the administration of Mifepristone Linepharma to confirm successful termination of pregnancy.

~~**Restricted Distribution to MS-2 Step [Mifepristone Linepharma and GyMiso®]**~~

~~The Sponsor restricts the access to *MS-2 Step* to ensure that only eligible and registered prescribers can prescribe *MS-2 Step* and Mifepristone Linepharma (monopack).~~

~~The program helps to ensure that:~~

- ~~Distribution of *MS-2 Step* is controlled and monitored.~~
- ~~Only Prescribers registered with the Sponsor as having completed the Prescriber Education (or can waive the Prescriber Education if they are current FRANZCOG or advanced diplomates of RANZCOG) can prescribe *MS-2 Step*.~~
- ~~Participating prescribers are informed of the need to inform patients of the effectiveness of the method, how to manage potential risks and the importance of follow-up as well as the need to gain informed consent.~~

~~These arrangements are set up and are accessible via the Sponsor's secure healthcare professional website www.ms2step.com.au, or by calling the company directly. The Sponsor may change the restrictions on supply if in the future an effective control mechanism on prescriber access becomes possible via the PBS.~~

Commented s22 Proposed removal of mandatory training program and certification for prescribers

Informed Consent, Compliance with the Method and Follow-up

The Sponsor provides all ~~registered~~ prescribers with access to reprinted Information Sheet and Patient Consent Agreements Forms to ensure that information in relation to the medical method of pregnancy termination is available to assist the provision of informed consent by patients.

Information Sheets and Patient Consent Forms also highlight symptoms patients will experience, along with symptoms requiring immediate follow up, and enable the prescriber to nominate the details of a 24-hour emergency facility for immediate follow-up if required, and details in relation to the patients scheduled follow up appointment 14-21 days after administration of the Mifepristone Linepharma tablet.

~~The Information Sheet also contains contact details for the 24 hour after care nursing toll free telephone service provided to all patients by MS Health. Patients may also give consent and elect to receive a follow up SMS text communication from the Sponsor 3 to 5 days following ingestion of mifepristone. This message provides the 24 hour nurse after care call centre contact telephone number and describe symptoms that are of concern in relation to infection, incomplete abortion or therapeutic failure that require medical follow up.~~

Commented s22 Proposed removal of 24 hour after care service

The Information Sheet and Patient Consent Agreements Forms are provided without charge by MS Health, and can be downloaded from the secure health care professional website www.ms2step.com.au as pdf files, or can be requested by contacting MS Health directly as reprinted documents.

~~The 24 hour nursing aftercare and SMS text messaging service is provided by the Sponsor free of charge.~~

The medical method of pregnancy termination and requirement for patient follow-up appointment is also documented in the ***MS-2 Step*** Product Information.

Prescriber Training

To support the education of Prescribers, ~~T~~the Sponsor provides access ~~(if needed)~~ to Prescriber training through the provision of a comprehensive Medical Education Program, and ensures, to the extent practical, that the medical method of termination using the Mifepristone Linepharma and GyMiso® products (i.e. the MS-2 Step Medical Method) is used in Australia responsibly and appropriately.

The Medical Education Program is delivered online and is made freely available by the Sponsor to all prescribers.

~~Prescribers registering with the Sponsor for the first time are required to complete the Medical Education Program in order to secure certification (approval to prescribe) for Mifepristone Linepharma and *MS-2 Step* packs. Medical practitioners who hold current Authorised Prescriber status along with medical practitioners holding Fellowship (FRANZCOG) or Advanced Diploma (DRANZCOG Advanced) of the RANZCOG qualifications can waive the requirement to complete the program to achieve certification~~

~~Effectiveness measures are included in the Medical Education Program, which detect (1) the level of knowledge known by the participant prior to completion of the module, and (2) the level of knowledge known by the participant post completion of the module. The participant scores are be monitored.~~

~~A certificate of completion is only be issued to participants who demonstrate appropriate knowledge at the completion of the amended education program. The required level of knowledge was determined during the review and endorsement process.~~

Commented s22 Proposed removal of mandatory training program and certification for prescribers

V.3 Summary of risk minimization measures

Safety concern	Pharmacovigilance activities	Risk minimisation measures
Important identified risk:		
Infection, toxic shock syndrome	Routine: - Routine pharmacovigilance - Special attention in PSURs	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Black box warning on follow-up in ***MS-2 Step*** Product Information, and in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Patient Information and Consent Agreement with emphasis on compliance and follow-up. ~~Optional follow-up SMS text message communication.~~ ~~24-hour nurse after-care telephone service.~~ Physician education.
Method failure	Routine: -Routine pharmacovigilance - Special attention in PSURs	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS.

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Safety concern	Pharmacovigilance activities	Risk minimisation measures
		Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Black box warning on follow-up in ***MS-2 Step*** Product Information, and in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Patient Information and Consent Agreement with emphasis on compliance and follow-up. ~~Optional follow-up SMS text message communication.~~ ~~24 hour nurse after-care telephone service.~~ Physician education.
Potential risk:		
Inadvertent pregnancy exposure and risk of incomplete abortion with severe bleeding	Routine: - Routine pharmacovigilance - Special attention in PSURs	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Patient Information and Consent Agreement with emphasis on compliance and follow-up. ~~24 hour nurse after-care telephone service.~~ Physician education.
Inadvertent pregnancy exposure (risk of malformations)	Routine: - Routine pharmacovigilance - Special attention in PSURs	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Patient Information and Consent Agreement with emphasis on compliance and follow-up. ~~24 hour nurse after-care telephone service.~~ Physician education.

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Safety concern	Pharmacovigilance activities	Risk minimisation measures
Potential risk:		
Potential interaction with CYP3A4 inhibitors or inducers	Routine: - Routine pharmacovigilance - Special attention in PSURs	Routine: Mentioned in the Product Information in INTERACTIONS WITH OTHER MEDICINES. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Physician education.
Potential interaction with products interacting with the glucocorticoid receptor	Routine: - Routine pharmacovigilance - Special attention in PSURs	Routine: Mentioned in the Product Information in PHARMACOLOGY and PRECAUTIONS. Additional: Physician education.
Induced bronchial asthma	Routine: - Routine pharmacovigilance - Special attention in PSURs	Routine: Mentioned in the Product Information in CONTRAINDICATIONS and PRECAUTIONS Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Physician education.
Effect in lactating women	Routine: - Routine pharmacovigilance	Routine: Mentioned in the Product Information in Use during lactation. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Physician education.
Potential risk:		
Effect in women with impaired liver function	Routine: - Routine pharmacovigilance	Routine: Mentioned in the Product Information in SPECIAL WARNINGS AND PRECAUTIONS FOR USE and in INTERACTIONS WITH OTHER MEDICINES.

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Safety concern	Pharmacovigilance activities	Risk minimisation measures
		Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Physician education.
Effect in women with impaired renal function	Routine: - Routine pharmacovigilance	Routine: Mentioned in the Product Information in SPECIAL WARNINGS AND PRECAUTIONS FOR USE. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Physician education.
Effect in women with malnutrition	Routine: - Routine pharmacovigilance	Routine: Mentioned in the Product Information in SPECIAL WARNINGS AND PRECAUTIONS FOR USE. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Physician education.
Potential risk:		
Missed ectopic pregnancy	Routine: - Routine pharmacovigilance	Routine: Mentioned in the Product Information in SPECIAL WARNINGS AND PRECAUTIONS FOR USE and in ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Patient Information and Consent Agreement with emphasis on compliance and follow-up. ~~24 hour nurse after care telephone service.~~ Physician education.

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Safety concern	Pharmacovigilance activities	Risk minimisation measures
Postnatal development delay	Routine: - Routine pharmacovigilance - Special attention in PSURs	Routine: Mentioned in the Product Information in Use in pregnancy
Potential for off-label use beyond the first trimester	Routine: - Routine pharmacovigilance	Additional: Physician education.
Potential safety risks in vulnerable groups including women in rural and remote areas of Australia, particularly the risk of being lost to follow-up	Routine: - Routine pharmacovigilance	Additional: Physician education.
Missing information		
Inherited porphyria	Routine: - Routine pharmacovigilance - Special attention in PSURs	Not mentioned in Product Information and the Consumer Medicine Information as there is limited evidence of this being a safety concern with administration of mifepristone (6).
Potential interaction with products interacting with the progesterone receptor	Routine: - Routine pharmacovigilance - Special attention in PSURs	This potential risk has not been confirmed and no information is deemed necessary in the Product Information.
Theoretical interaction with non-steroidal anti-inflammatory drugs	Routine: - Routine pharmacovigilance - Special attention in PSURs	This potential risk has not been confirmed and no information is deemed necessary in the Product Information.
Use in adolescents	Routine: - Routine pharmacovigilance - Special attention in PSURs	Product Information and Consumer Medicine Information mention that use is limited in this population.
Pharmacological class effects		

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Safety concern	Pharmacovigilance activities	Risk minimisation measures
Risks related to the use of prostaglandin	Routine: - Routine pharmacovigilance - Special attention in PSURs	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Patient Information and Consent Agreement with emphasis on compliance and follow-up. ~~24 hour nurse after care telephone service.~~ Physician education.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Not applicable.

PART VII: ANNEXES

~~Annex 1 MS Health Australian Medical Education Program~~

~~Annex 1.1 MS 2 Step Training Manual~~

~~Annex 1.2 MS 2 Step Training Slides~~

~~Annex 1.3 Patient Information Sheet – Consent Form~~

~~Annex 1.4 MS 2 Step Training – Case Studies~~

~~Annex 1.5 Pre and Post course assessment~~

~~Annex 1.6 MS Health Traning Manual – PBS Listing~~

Commented s22 Proposed removal of mandatory training program and certification for prescribers

Not applicable

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Module 1.8.2 Risk Management Plan

MS-2 Step

Composite pack containing:

MIFEPRISTONE LINEPHARMA 200 mg Tablet mifepristone 200 mg

and

GyMiso® misoprostol 200 µg tablets

RMP version to be assessed as part of this application:	
RMP version number:	4.0
Data lock point for this RMP:	31 May 2022
Date of final sign off:	17 February 2023
Rationale for submitting an updated RMP	This RMP has been updated as follows: To remove the need for pharmacists to be registered to be able to dispense the product. To remove the requirement for recertification training. Updated summary concerns and additional risk minimisation activities. To remove the need for prescribers to complete mandatory training and receive certification to be able to prescribe the product. To remove the requirement for a Sponsor provided 24 hours aftercare service
Summary of significant changes in this RMP:	Revised into current EU-RMP template
Other RMP versions under evaluation:	Version 4.0, 14 January 2023
Details of the currently approved RMP:	
Version number:	Version 3.0; Data lock point 28 April 2013
Approved with procedure:	Version 3.0 was submitted on 14 November 2014 and provides documentation as agreed with the Office of Product Review and revised information, following the registration of MS-2 Step in May 2014. (Submission ID: PM-2013-01037-1-5)
Date of approval:	28 May 2013

QPPV name: s22
Date: 17 February 2023
QPPV signature: s22

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PART I: PRODUCT(S) OVERVIEW

Table 1 Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	MS-2 Step is a composite pack consisting of one pack of Mifepristone Linepharma (one mifepristone 200 mg tablet) and one pack of GyMiso® (four misoprostol 200 microgram tablets).
Pharmacotherapeutic group(s) (ATC Code)	**Component:** mifepristone G03XB51, mifepristone, combinations **Component:** misoprostol G02AD06, misoprostol
Name of Sponsor	MS Health Pty Ltd
Medicinal products to which this RMP refers	MS-2 Step (containing Mifepristone Linepharma and GyMiso®)
Invented name(s) in Australia	MS-2 Step (containing Mifepristone Linepharma and GyMiso®)
Brief description of the product	Chemical class **Component:** Mifepristone Linepharma Mifepristone is a synthetic competitive progesterone receptor and cortisol receptor antagonist **Component: GyMiso®** Misoprostol is a synthetic analogue of prostaglandin E1.
	Summary of mode of action **Component:** Mifepristone Linepharma. Mifepristone acts via high-affinity reversible binding to the human progesterone and cortisol receptors. **Component: GyMiso®** At the recommended dosages, misoprostol induces contractions of the smooth muscle fibers in the myometrium and relaxation of the uterine cervix. The uterotonic properties of misoprostol should facilitate cervical opening and evacuation of intrauterine debris. In the event of an early termination of pregnancy, the combination of GyMiso® used in a sequential regimen after mifepristone leads to an increase in the success rate and accelerates the expulsion of the conceptus.
	Important information about its composition N/A
Hyperlink to the Product Information	Module 1.3.1

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Indication(s) in AU	***MS-2 Step*** is indicated in females of childbearing age for the medical termination of an intrauterine pregnancy, up to 63 days of gestation. It is recommended that the duration of pregnancy (i.e., up to 63 days gestation) be confirmed by ultrasound. In the event that an ultrasound is not possible, extra caution should be exercised. Ultrasound is also useful to exclude ectopic pregnancy
Dosage in AU	Mifepristone Linepharma: 200 mg of mifepristone (1 tablet containing 200 mg) orally, followed 36 to 48 hours later by the administration of GyMiso®. GyMiso®: 800 micrograms of misoprostol (4 tablets, each tablet containing 200 micrograms) buccally, i.e: kept between the cheek and the gum for 30 minutes before any fragments being swallowed with water.
Pharmaceutical form(s) and strengths	**Component:** Mifepristone Linepharma Tablet Mifepristone 200 mg **Component: GyMiso®** Tablet Misoprostol 200 micrograms
Is/will the product be subject to additional monitoring in AU?	No

PART II: SAFETY SPECIFICATION

SI – EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

Indication

MS-2 Step is indicated in females of childbearing age for the medical termination of an intrauterine pregnancy, up to 63 days of gestation.

It is recommended that the duration of pregnancy (i.e., up to 63 days gestation) be confirmed by ultrasound. In the event that an ultrasound is not possible, extra caution should be exercised.

Ultrasound is also useful to exclude ectopic pregnancy.

Incidence:

Data from a number of Australian states on pregnancy termination rates applied to the Australian female population aged 15 to 44 years as at June 2009 indicates that between approximately 82,000 to 95,000 surgical terminations may occur in Australia each year. (1,2) Assuming that 30 percent of terminations of pregnancies are eligible for the medical method with mifepristone followed by misoprostol, then approximately 24,600 to 28,500 terminations could be performed with the medical method each year.

To this figure should be added the number of cases in which mifepristone will have been used for cervical priming prior to D & C for second trimester termination. The incidence of second term pregnancy termination is very low (approximately 8 / 1,000 births (3), thus may involve 2,000 cases per annum in Australia.

Prevalence:

Not applicable – refer to Incidence.

Demographic profile of target population:

Women of reproductive age, no specific profile.

The main treatment options:

In general, where pregnancy termination is legal (as is the case in most EU countries), D&C or vacuum aspiration, which are the standard surgical procedures for first trimester pregnancy termination are very safe: in a study of more than 14,000 subjects (4), the following complications were reported after suction curettage (SC):

Complication	SC only, *n* (%)	SC with dilatation, *n* (%)
Retention of fetoplacental material	228 (2.7)	129 (2)
Excessive bleeding	168 (2)	128 (2)
Infection	81 (< 1)	60 (< 1)
Perforation	None	7 (0.05)
Persistant fever	None	None
Unintended major surgery	None	None
Hemorrhage requiring transfusion	None	None

As shown in the table, retention of foetoplacental material and excessive bleeding are the most frequent, albeit rare, complications. Death appears exceptional in this indication and is related to general anaesthesia whenever used.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Not applicable.

Important co-morbidities:

No significant co-morbid conditions have been identified in the target population of women of reproductive age.

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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Potential health risk:

A review of the safety of mifepristone from first trimester termination of pregnancy in the USA (5) reported an overall complication rate of 2.2 per 1000, with infection (0.2 per 1000), bleeding requiring transfusion (0.5 per 1000) and deaths 1.1 per 100,000.

Improper use of medical termination of pregnancy could lead to potential health risk linked to excessive bleeding, incomplete foetal expulsion and infection. Such risk can be minimized by ensuring medical practitioners have access to education and training resources.

Since the use of mifepristone and misoprostol cannot terminate a pregnancy in 100% of the cases, the background incidence of congenital anomalies is presented below.

Table 2 Epidemiology of congenital anomaly

Identified or potential risk	**Congenital anomaly**
Incidence of condition	Congenital anomalies are reported in some 2.2% of live births, with the most common anomalies being cardiac malformations (68/10,000 births), orofacial clefts (16/10,000 births) and genital malformations (16/10,000 births) (EUROCAT Central Registry, Report 2004-2005).
Prevalence of condition	Not applicable.
Mortality of condition	Not applicable.
Risk factors	Some congenital anomalies can be attributed to a mother's genetic predisposition. Other risk factors include age (over 35), use of certain drugs and alcohol, and smoking during pregnancy.

SII – NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

Table 3 Safety concerns and relevance to human usage

Mifepristone	
Safety concern	**Relevance to human usage**
Pharmacology: Antiprogesterone activity Mifepristone prevented pregnancy maintenance in rats, rabbits, guinea pigs and monkeys as a consequence of its anti-progesterone activity. Anticortisol activity Mifepristone exerts anticortisol activity (due to receptor antagonism) in a variety of in vitro and in vivo models. Studies in humans have confirmed the existence of anticortisol activity. However, such activity can be demonstrated after repeated use at daily doses of 200 mg or	These actions justify the clinical use of mifepristone in humans (pregnancy termination). None given the duration (single-dose administration) of treatment, given the reversibility of cortisol blockade.

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Mifepristone	
Safety concern	**Relevance to human usage**
more, and can be reversed (1 mg dexamethasone reverses the cortisol blockade induced by 400 mg mifepristone). In addition, cortisol blockage results in an increase in ACTH and cortisol blood levels which in turn overcome the cortisol receptor blockade induced by mifepristone. Antiandrogenic, estrogenic and antiestrogenic, mineralocorticoid and antimineralocorticoid activities. At repeated doses, mifepristone exhibits partial androgen antagonism in animal models. It exhibits little estrogen estrogenic or anti-estrogenic activity in spayed and immature animals but caused an increase in ovarian weight and prolonged estrus in mature animals and displays no antimineralocorticoid activity against aldosterone nor any mineralocorticoid activity (see section 2.4.3 of dossier).	None (single-dose administration)
Safety pharmacology: Mifepristone was evaluated in a variety of standard pharmacological tests (see section 2.4.3.3 of dossier). CNS activity - Only effect noted was a potentiation of the hexobarbital sleeping time in rodents with oral doses of 10-100 mg/kg. Autonomous nervous system activity In vitro, mifepristone antagonized acetylcholine, histamine and serotonin in the isolated guinea pig ileum at a concentration of 10-4M. Cardiovascular/respiratory activity No effects were seen at doses up to 10 mg/kg. Gastrointestinal activity No effects at doses up to 100 mg/kg. Genitourinary activity Mifepristone decreased sodium excretion at doses of 10-100 mg/kg, potassium at 30-100 mg/kg and the sodium/potassium ratio. Urine volume was increased at the 100 mg/kg dose. Endocrine activity In fasted rats, mifepristone produced a slight hypoglycemic effect at doses of 30-100 mg/kg. Analgesic / anti-inflammatory activity No effects at doses up to 100 mg/kg. Haematological activity	There is no finding which would be relevant when used as a single administration with a dose of 200 mg.

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Mifepristone	
Safety concern	**Relevance to human usage**
No significant effects.	
Pharmacokinetic interactions: Using in vitro studies, mmifepristone has been shown to be a potent mechanism-based inactivator of human CYP-3A4 (see section 2.4.4.4 of dossier).	The clinical significance of the inactivation of CYP-3A4 by mifepristone is that it would be expected to increase the bioavailability of several clinically used drugs metabolized by CYP-3A4 such as cyclosporine A, tacrolimus and dihydropyridines.
Repeated dose toxicity studies: (See section 2.4.5.2 of dossier) Pituitary, adrenals, mammary, ovary, uterus, vagina, fallopian tubes: The toxicological profile emerging from these studies appears to be a consequence of the anti-progesterone and anti-glucocorticoid properties of mifepristone. Liver and kidney: Increase weight associated with hepatocyte hypertrophy in rats and in monkeys. Thyroid: In a chronic toxicity study, a thyroid follicular adenoma was seen in one high-dose female rat.	The effects observed in the toxicity studies were seen after repeated daily dosing. They appeared unspecific and are unlikely to be of consequence in women after a single 200 mg dose of mifepristone. This effect was observed after repeated daily dosing. It is unlikely to be of consequence in women after a single 200 mg dose of mifepristone.
Reproductive and developmental toxicity: Fertility: Mifepristone was administered orally to groups of 12 female Sprague-Dawley rats for 3 weeks at doses of 0, 0.3 or 1.0 mg/kg/day. After the end of treatment rats were observed for 5 weeks after which they were mated with untreated males. Cycles were monitored by daily vaginal smears. Results: The oestrous cycle was disrupted at both doses within 10 days of treatment. Withdrawal of treatment resulted in gradual dose-dependent restoration of the cycle over 2 - 3 weeks. Reproductive endpoints of mating, gestation, parturition, litter size, morphology of offspring, bodyweight change and survival were not affected by drug treatment. Embryofoetal development: Mouse	These findings suggest that if a woman is exposed to a 200 mg dose of mifepristone early during her pregnancy, no deleterious effects on foetal development are necessarily expected if pregnancy is maintained. Reproductive function should not be altered.

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Mifepristone	
Safety concern	**Relevance to human usage**
Groups of 25 Swiss CD 1 mice were gavaged with vehicle, 0.5, 1 or 2 mg/kg/day mifepristone from day 6 to 17 of gestation. Clinical signs: None Body weight: Almost complete suppression of body weight gain in the 2 mg/kg/day group. Moderate suppression in the 1 mg/kg/day group. Final body weights (day 18) were Controls - 62.8; Low-dose - 58.9; medium-dose - 48.0; high-dose - 34.8 grams. There was a marked dose-related increase in fetal loss. The mean rate was 21% in low-dose; 60% in medium-dose and 100% in high-dose. Foetal weights were normal in the survivors. Foetal examination: There were no treatment related increases in foetal anomalies or malformations. Rat Groups of 25 pregnant Sprague-Dawley rats were gavaged with vehicle, 0.25, 0.50 or 1.0 mg/kg/day mifepristone from day 6 to day 17 of gestation. Clinical signs: None Body weight: weight gain was comparable between groups except for the high-dose group where there was a retardation at the end of treatment. Six high-dose rats had no living foetuses at autopsy. The post-implantation loss was 34% compared to 5.7% in controls (statistically significant). Foetal weights were equal between groups and the sex ratio was the same. Foetal examination: There were no treatment related differences in foetal anomalies or malformations. Rabbit Groups of 15-20 HY rabbits were gavaged with vehicle, 0.25, 0.5,1, 2, or 4 mg/kg/day mifepristone from day 6 to 18 of gestation. The two highest doses increased foetal loss (31% and 67% cf. 6% for controls) and increased the incidence of incomplete ossification of the cranium, sternum and paws, without affecting maternal body weight or producing clinical signs. In a published study in rabbits, treatment with mifepristone on 0.5 or 1 mg/day s.c. for 1-5 days starting on day 11 of gestation was associated with foetal malformations (failure	These data suggest some potential for adverse effects on foetal development, including teratogenicity, with exposure to mifepristone where pregnancy is maintained. The abnormalities observed in animals most likely occurred as a consequence of the mifepristone's effect on the uterus rather than any direct effect of the drug on the foetus. These results indicate that in case a woman carries her pregnancy to term despite exposure to mifepristone during pregnancy, there is some potential for postnatal development to be delayed.

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Mifepristone	
Safety concern	**Relevance to human usage**
of the cranium to close and haemorrhagic destruction of the upper part of the head and brain, no spinal column, no closure of eyelids) considered to be treatment-related. Monkey A case of holoprosencephaly in a fetus of a cynomolgus monkey that had been treated with mifepristone at 2.5 mg/kg/day i.m. from day 15 to 18 of gestation is reported in the literature. This was considered most likely to have occurred secondary to disturbed development of the gestational sac and placenta due to an incomplete abortion, reducing blood supply to the conceptus. Pre-/post natal development: Groups of 20-25 Sprague-Dawley rats were gavaged with vehicle or 0.25, 0.5 or 1 mg/kg/day mifepristone from day 15 of gestation to the end of the lactation period (postnatal day 21). Increase morality at birth (not statistically significant) and delayed development of the righting reflex and slight inhibition of locomotor development were observed at the high-dose level. Other developmental parameters and the reproductive performance of the offspring were unaffected. Male and female Sprague-Dawley pups from 15 litters were injected s.c. 1 day after birth with vehicle, 1, 10 or 100 mg/kg mifepristone. On day 4, the number of offspring in each litter was reduced to 8 (4 of each sex) using a random distribution table. The general condition and growth of the offspring was not affected by treatment. Descent of testes was normal but there was a slight delay in vaginal opening in the high-dose females (not significant). At the age of 11 or 15 weeks, histopathology revealed no effects on the testes and activity of the seminiferous tubules. Reproductive function, assessed by mating rate and fertilizing capacity, was not affected by treatment. Disruption of normal sexual development in neonatal Wistar rats given 1 mg mifepristone s.c. every second day from postnatal day 1 or 4 for 14 days is reported in the literature.	

Misoprostol	
Safety concern	**Relevance to human usage**
Misoprostol, 15-deoxy-16-hydroxy-16-methyl-PGE1, is a synthetic analogue of PGE1.	

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Misoprostol	
Safety concern	**Relevance to human usage**
Prostaglandins contract or relax many smooth muscles. Strips of non-pregnant human uterus are relaxed by PGEs; strips from pregnant women are contracted by low concentrations of PGE2 and relaxed by high concentrations. Intraperitoneal and oral administration of misoprostol induced diarrhoea in mice and rats, respectively, with ED50 values in the rat after oral administration being in the range 366-1305 µg/kg, depending on when in the 8-hour observation period following dosing the effect was measured. Oral administration of 30 µg/kg of misoprostol to conscious dogs did not affect blood pressure, heart rate or the ECG. Misoprostol inhibited histamine-induced bronchoconstriction in the anaesthetized guinea-pig after intravenous administration of 10-1000 µg/kg, the effect depending on the intensity of the histamine challenge; effects against a PGF2α challenge were more variable.	These actions justify the clinical use of misoprostol in humans (pregnancy termination). None (single-dose administration)
Toxicological information Single dose toxicity Oral LD50 values in mice and rats were 27-138 and 81-100 mg/kg, respectively, with corresponding values after intraperitoneal dosing of 70-160 and 40-62 mg/kg. In an ascending dose study in dogs, no deaths were observed at 10 mg/kg, the maximum dose administered. The most prominent clinical signs were diarrhea and reduced motor activity in rodents and, in dogs, emesis, tremors, mydriasis and diarrhea. Most deaths occurred within 24 hours of dosing and surviving animals appeared normal within 3-4 days. Repeat dose toxicity The rat and dog were selected as the species for the repeated dose toxicity studies. Rats Studies in the rat were of 5, 13 and 52 weeks duration; the 52 week study incorporated a 13 week recovery period. Administration 0, 160, 320, 1200, 1600, 8000 and 9000 µg/kg/day. The major clinical signs were diarrhoea, salivation, vaginal dilation and discharge, decreased body weight (mainly males) and increased food consumption. There was no effect on rectal temperature in the 5 week. In the 52 week study, no abnormal clinical signs were observed at 160 µg/kg/day and all signs at the higher doses of 1200 and 9000 µg/kg/day were absent by the end of the 13 week recovery period.	The effects observed in the toxicity studies were seen after repeated daily dosing. They appeared unspecific and are unlikely to be of consequence in women after a single 800 µg dose of misoprostol.

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Misoprostol	
Safety concern	**Relevance to human usage**
There were no deaths that were attributable to treatment. Principal clinical biochemistry changes were decreases in serum total protein and increases in serum iron, with any changes in other parameters remaining within normal limits and considered incidental. The decrease in protein levels may be a consequence of poor absorption of nutrients resulting from diarrhoea. Serum iron was significantly increased at 9000 µg/kg/day in the 52 week study and at 1600 and 8000 µg/kg/day in the 5 week study. Any changes in laboratory parameters seen at the end of the 52 week study were absent after the 13 week recovery period. Dogs Studies in the dog were of 5, 13 and 52 weeks duration. Doses for the 52 week study were 0, 30, 100 and 300 µg/kg/day. These studies included recovery periods of 4 and 13 weeks. The most important clinical signs in these studies were emesis, diarrhoea, soft and/or mucoid stools and increased rectal temperature; these were dose related and either decreased or were absent by the end of the 4 and 13 week recovery periods. There were two deaths in the 52 week study, both in animals receiving 300 µg/kg/day. Changes in clinical biochemistry parameters were incidental or within normal limits, with the exception of serum chloride, which increased slightly in the 52 week study; there were no abnormal clinical laboratory findings at the end of the recovery periods.	
Genotoxicity Misoprostol was negative in five in vitro tests of genotoxic potential – the Ames test in five strains of Salmonella typhimurium, the mouse lymphoma TK+/- assay, mitotic gene conversion in Saccharomyces cerevisiae, a sister chromatid exchange assay in CHO cells and a C3H/10T 1/2 cell transformation assay. The first four of these were performed in the absence and presence of metabolic activation. In addition to these tests, an abstract (6) cites a negative result in an in vivo mouse micronucleus test.	None

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Misoprostol	
Safety concern	**Relevance to human usage**
Carcinogenicity The potential carcinogenicity of misoprostol has been evaluated in both mice and rats. The study in mice was of 21 months duration and administered doses of 0, 160, 1600 and 16000 µg/kg/day by gavage. In the rat study, doses of 0, 24, 240 and 2400 µg/kg/day were administered for 24 months by gavage. There was no indication of a carcinogenic effect in either species. In both species, there were statistically significant increases in epithelial hyperplasia and hyperkeratosis of the gastric mucosa; these were non-neoplastic and expected as a consequence of the pharmacological activity of misoprostol. This was also observed in the 52-week study in rats where it was seen to be reversible on stopping treatment. In addition, hyperostosis of the marrow cavity of sternebrae and femurs was observed in mice. This has also been reported for PGE2 in rats, dogs and children. However, this was not seen in the 24-month carcinogenicity study in rats with misoprostol, nor in the 52-week repeated dose toxicity study in dogs. It thus appears to be a phenomenon restricted to mice for misoprostol.	Given the short duration of administration to women covered by the current application, its relevance to the intended use of misoprostol is doubtful.
Reproductive and developmental toxicity: Two fertility studies were performed in the rat. One was with doses of 0, 100, 1000 and 10000 µg/kg/day; males were treated from day 71 premating until mating and females from 15 days premating to parturition. The other used doses of 0, 100, 400 and 1600 µg/kg/day; males were treated from day 70 premating and females from 14 days premating to day 7 of gestation. The number of implantations was decreased at 1600 and 10000 µg/kg/day and an increase in resorptions occurred at 1000 and 10000 µg/kg/day in one study, but not at 1600 µg/kg/day in the other; resorptions were not increased in the rat teratology study at doses up to 10000 µg/kg/day. As a consequence of these events, there were a decreased number of live foetuses or pups at 10000 µg/kg/day and a decreased number of foetuses at 1600 µg/kg/day. Foetal and pup survival and development were not affected. Two teratology studies were performed in rats using the same doses as the fertility studies with dosing on days 6 to 15 or 7 to 17 of gestation; there was no evidence of embryotoxicity, foetotoxicity or teratogenicity. Two rabbit studies, at doses of 0, 100, 300 and 1000 µg/kg/day on days 6 to 18 of gestation also showed no evidence of foetotoxicity or teratogenicity, although there was an increased number of resorptions at 1000 µg/kg/day in one study.	On the basis of the studies summarized in this application, there would not seem to be cause for concern with respect to possible effect on the foetus of misoprostol in circumstances where termination of pregnancy in association with mifepristone was not successful and the pregnancy was allowed to continue. However, misoprostol, through its smooth muscle contracting activity, could have effects on the developing foetus and there are several reports in the literature on the occurrence of congenital defects in children born to mothers who had taken misoprostol to terminate pregnancy; this off-label use of misoprostol appears to have been a particular problem in Brazil, from where considerable evidence has accumulated on its possible teratogenic activity in humans (7,8). Data would suggest a link between misoprostol and congenital malformations, based on a retrospective analysis of cases, and a prospective study based on Brazilian data suggested that misoprostol may increase the incidence of congenital anomalies, but that the magnitude of the increased risk is low (9).

Misoprostol	
Safety concern	**Relevance to human usage**
A rat pre/postnatal study used doses of 100, 1000 and 10000 µg/kg/day administered from day 15 of gestation to day 20 postpartum. Pup survival was unaffected, though a decrease in pup weight gain was apparent at 10000 µg/kg/day. The studies summarised above showed effects of misoprostol in decreasing implantations and increasing resorptions in rats and rabbits, but did not show any indication of a teratogenic effect. Moreover, the doses at which effects on implantations and resorptions were observed were 1000 µg/kg/day and above, levels 75 times higher than the 800 µg dose recommended in this application for use in the termination of pregnancy. In a more targeted embryotoxicity / teratogenicity study in the mouse, pregnant Han:NMRI mice were treated with single doses of 20 or 30 mg/kg of misoprostol on day 10 of pregnancy. A slight and reversible decrease in maternal weight gain was seen at both doses. Whereas there was no evidence of embryotoxicity at the 20 mg/kg dose, resorptions were increased at 30 mg/kg and an increased occurrence of cleft palate as well as other skeletal abnormalities was observed in surviving foetuses at this dose level. Embryotoxic effects of other prostaglandins have been reported, including PGE2 and PGF2α and rioprostil, a synthetic PGE1 analogue; these effects were attributed, at least in part, to the disturbances in blood supply to the foetus caused by these potent agents. Misoprostol will also reduce uterine blood flow and this could be the cause of the apparent malformations described in humans, although humans seem much more sensitive to misoprostol than mice, rats or rabbits.	

SIII – CLINICAL TRIAL EXPOSURE

Clinical efficacy of early medical abortion is defined as complete abortion without surgical intervention, regardless of the reason for the intervention, which may include continuing pregnancy, missed or incomplete abortion, prolonged or heavy vaginal bleeding or a woman's request.

The clinical trial exposure to MS-2 Step includes the following studies.

An open-label single-group prospective trial (Study 1.1.4) performed in Mexico by Gynuity Healthcare, USA, involving 971 women available for efficacy treated with 200 mg mifepristone followed by 800 micrograms misoprostol administered buccally indicated that efficacy was 98.0, 96.8 and 95.9% for women with gestational age 49 days and below, 50-56 days and 57-63 days, respectively. In these 3 gestational age groups, the rate of surgical evacuation was 2.0, 3.2 and 4.1% respectively. In this study 25 women received a second dose of misoprostol, in each case, a dose of 800 micrograms by the buccal route. Of those 25, 20 had a successful outcome with

medication alone, 4 had a surgical intervention and 1 woman did not return for follow up. In this study, bleeding occurred in all women independent of outcome, and was judged as more than expected in 27.1% of the women.

In an observational cohort study of 15 008 women attending one of 16 Marie Stopes International clinics in Australia for MTOP (gestational age ≤ 63 days) between 1 March 2013 and 30 September 2015, patients were administered 200 mg mifepristone orally in-clinic, followed 24-48 hours later by 800 micrograms of misoprostol buccally, self-administered at home. Method success was defined as complete abortion not requiring surgical intervention. Follow up information was available for 13,078 (87.2%) of the total cohort. Medical abortion was successful in 95.16% (12,445/13,078) of women with follow-up. Higher patient and gestational ages were associated (P < 0.001) with a slight increase in method failure. There were 674 serious adverse events (5.15%), mainly due to method failure. Infection (15; 0.11%) and haemorrhage (17; 0.13%) were rare. One death was recorded (<0.01%); however, an association between EMA and cause of death, necrotising pneumonia, was not established (26)

Studies published in the literature have reported mifepristone and oral or buccal misoprostol regimens. In one study of 966 patients(10) with pregnancies up to gestational age of 63 days, randomised to 200 mg mifepristone followed 24-36 hours later by 800 micrograms of misoprostol orally or buccally, reported efficacy rates were 91.3% for the oral and 96.2% for the buccal group (RR 0.95, 95% CI 0.92-0.98, p=0.003).

Studies published on the combination of mifepristone 200 mg and misoprostol 800 micrograms buccally, and reporting outcomes by gestational age, encompass 399 women with gestational ages 50 – 56 days and 344 women with gestational ages 57 – 63 days (10–16). Efficacy ranged from 86.5 to 98.5% in women with gestational age 50 – 56 days and from 93.0 to 100% in those with gestational age 57 – 63 days. In these studies, the rate of ongoing pregnancies ranged from 0 to 7.1% in women with gestational age 50 – 56 days and from 0 to 2.3% in those with gestational age 57 – 63 days.

Literature data provides information on the bleeding and expulsion pattern after termination of pregnancy with mifepristone and misoprostol: approximately half of women start to bleed before prostaglandin administration. Median bleeding time is 10 to 16 days. Bleeding is judged more or much more abundant than usual menses for 2 to 3 days after prostaglandin. In studies where it was measured, there was a slight but significant decrease in haemoglobin level after compared to baseline. In one study blood loss was quantified: the median blood loss was 83 mL and 5.4% of women had a blood loss above 200 mL. Expulsion usually takes place within 3 hours after misoprostol in approximately half of the women, and within 4 hours after misoprostol in approximately 50 to 90% of women.

SIV – POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Under the Authorised Prescribers Program in Australia in 2012, there were 7,166 medical terminations. Efficacy was 97.4% for women with gestational age <49 days, and 95.2% for women with gestational age of 49-63 days. The rate of incomplete termination requiring aspiration was: <49 days: 2.3%; 49-63 days: 4.8%. The rate of ongoing pregnancies was: <49 days: 0.3%; 49-63 days: 0.6%. Bleeding was considered as an adverse event in 0.24% of women, independent of pregnancy age.

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Not applicable.

SIV.2 Limitation to detect adverse reactions in clinical trial development programs

Not applicable.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programs

MS-2 Step is for use in women of childbearing age.

There is limited data available for use of ***MS-2 Step*** in women under 18 years of age. There is no relevant use of MS-2 Step in the prepubertal paediatric population in the indication. Administration to adolescents less than 18 years of age should be undertaken with caution.

SV – POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

Seventy nine thousand four hundred and three (79, 403) women have been exposed to Mifepristone Linepharma 200 mg tablet (Sweden, Norway, Finland, Kenya, United-Kingdom, Denmark and Australia).

For GyMiso®, since launch in 2004, one hundred and eighty seven thousand three hundred and thirty three (187,333) women have been exposed to GyMiso® (as per the most recent PSURs).

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Literature surveys indicate that in Western countries approximately 2 million women have been exposed to mifepristone and misoprostol for termination of pregnancy since its first approval in France in 1989. In China, exposure to mifepristone is estimated at 13 to 39 million women (Professor Linan Cheng, Shanghai Institute of Planning Parenthood Research, personal communication).

SVI – ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for improper use

The MS-2 Step product is presented as a composite pack in a carton containing two cartons, each of which is different in appearance (as described below). The generic names of the two component medicines, i.e. mifepristone and misoprostol, appear beneath the name MS-2 Step on the composite pack carton.

The two component products contain different amounts of their respective medicines. The labelling on the component products clearly identifies the right order for taking the two products.

An instruction insert is placed in each MS-2 Step product carton to explain the right order for intake of the two products, the recommended time period between intake of the two products, and the importance of a follow-up appointment 14-21 days following the administration of Mifepristone Linepharma to confirm successful termination of pregnancy.

The correct way to take the two products is also described in the respective Consumer Medicine Information sheets that are placed inside each component product carton.

These component products are distinguished from each other in the following ways:

- The Mifepristone Linepharma 200 mg Tablet carton has a green colour on it, and it contains only one mifepristone tablet
- The GyMiso® carton has a purple colour on it, and it contains 4 misoprostol tablets
- Mifepristone Linepharma packaging includes the statement Step 1, take this tablet first.
- GyMiso packaging includes the statement Step 2 take these 36 to 48 hrs after Mifepristone Linepharma

Potential for misuse for illegal purpose

Mifepristone Linepharma and GyMiso® are components of MS-2 Step available by prescription only from medical practitioners hereafter referred to as prescribers. The distribution of MS-2 Step and Mifepristone Linepharma (monopack) in Australia occurs using the secure distribution channels for prescription medicines that operate in this country. There is therefore very low potential for misuse.

Potential for off label use in adults

In some other countries, mifepristone is approved for softening and dilatation of the cervix prior to surgical termination of pregnancy during the first trimester and labour induction in foetal death in utero. Similarly, misoprostol is approved in other territories for cervical preparation before surgical abortion during first trimester, labour induction and treatment and prevention of post-partum haemorrhage.

To date, since Marketing Authorisation has been granted for both products, off label use of Mifepristone Linepharma and GyMiso® has been continuously evaluated: there has been no concern regarding off label use of these drugs.

Use of oral misoprostol beyond 49 days of gestation is associated with lower efficacy, and the acceptable regimen for dosing of GyMiso® by the buccal route only is stated in the MS-2 Step Product Information, in the Consumer Medicine Information Instruction Insert in the MS-2 Step carton, as well as in the Consumer Medicine Information for each component product.

Uterine hyperstimulation and rupture have been reported beyond the first trimester when much lower dosage of misoprostol may be required.

Potential for off label use in children

Mifepristone Linepharma 200 mg Tablet and GyMiso® are recommended for use in females of childbearing age. There are limited data available in women below the age of 18 years. It is possible that the treating medical practitioner will use their discretion and may use the medical method of termination in child-bearing adolescents aged over 12 years of age. It would be expected that the medical practitioner would seek informed consent from a legal guardian before use of the medical method as per use of any method for termination of pregnancy. The sponsor is not aware of any available evidence at present that risks might arise from such off-label use beyond the risks documented herein.

The Sponsor has completed a report on use of mifepristone and misoprostol for termination of early pregnancy under the Authorised Prescriber program for the period September 1, 2009 to the end of August 2011. During this time 13,345 clients were treated and of that number 939 were aged between 14 and 19 years. No risks have been identified in that study specific to that patient group.(10)

Potential for overdose

The EU SPC for Mifegyne® and the current Mifepristone Linepharma Australian Product Information indicate that no overdose has been reported.

In the event of massive ingestion signs of adrenal failure might occur. Signs of acute intoxication may require specialist treatment including the administration of dexamethasone.

As a component of MS-2 Step, Mifepristone Linepharma 200 mg Tablet is only available by prescription as a single pack containing only one tablet. It is distributed in Australia using the secure distribution channels for prescription medicines. Therefore, it would be unlikely for a person in the community to access large volumes of this product to enable an overdose to occur.

The Australian MIMS for Cytotec®(11) and the current GyMiso® Australian Product Information indicate that the toxic dose of misoprostol in humans has not been determined. Cumulative total daily doses of 1600 micrograms have been tolerated, with only symptoms of gastrointestinal discomfort reported.

Clinical signs that may indicate an overdose are sedation, tremor, convulsions, dyspnoea, abdominal pain, diarrhoea, fever, palpitations, hypotension or bradycardia. Hypertension and tachycardia have also been reported following overdoses. Overdose in pregnancy has resulted in uterine contractions with foetal death.

There is no specific antidote. Treatment should be symptomatic and supportive.

As a component of MS-2 Step, GyMiso® will be available as a single pack containing four tablets. MS-2 Step will be prescribed by medical practitioners. It is distributed in Australia using the secure distribution channels for prescription medicines. Therefore it would be unlikely for a person in the community to access large volumes of this product to enable an overdose to occur.

Potential for transmission infectious agents

Mifepristone as a substance is devoid of any risk of transmission of infectious agents since none of the components are of biological origin. There is no excipient of animal origin in Mifepristone Linepharma 200 mg Tablets.

GyMiso® as a substance is devoid of any risk of transmission of infectious agents since none of the components are of biological origin. There is no excipient of animal origin in GyMiso® tablets.

Medical Education Program, Informed Consent, Compliance to the Method and Follow-up

A number of education programs are available to support prescribers including from family planning organisations, RANZCOG, electronic therapeutic guidelines as well as the Sponsor's MS Health Medical Education Program (an education program that has been developed and implemented in Australia by the Sponsor) as a resource for prescribers of MS-2 Step. The Sponsor's Medical Education Program includes modules with:

- clinical data supporting the use of MS-2 Step in terminations up to 63 days of gestation, in line with the approved Product Information for MS-2 Step,
- information on the listing of MS-2 Step on the Pharmaceutical Benefits Scheme.

In addition to the Medical Education Program, the Sponsor makes available to prescribers an Information Sheet and Patient Agreement, the MS-2 Step Product Information and the Consumer Medicine Information documents for the MS-2 Step components. These documents all note the importance that patients are required to be informed about the administration of the medical method, compliance to the method, the importance of follow-up, side effects and associated risks. It is

recommended that informed consent is obtained from the woman before use of the medical method as per use of any method for termination of pregnancy. The Information Sheet and Patient Agreement, Product Information and Consumer Medicine Information note the need for the woman to remain in contact with the treating practitioner and or clinic and it is recommended that they do not travel during the episode of bleeding so that they can visit the clinic if necessary.

Training of Medical Practitioners

Medical education is offered by the Sponsor to treating practitioners.

The Medical Education Program is delivered online and freely available to all treating.

The Medical Education Program has been prepared to ensure, to the extent practical, that the medical method of termination using MS-2 Step is used in Australia responsibly and appropriately. The plan has been designed to ensure that prescribers and patients have access to appropriate information regarding the safe and effective administration of the Medical Method.

Elements of the Risk Management Program

The elements of the Risk Management Program include:

1. Education. Provision of information regarding the appropriate use of the Medical Method including follow up offered to all prescribers and to patients. The education program includes information on first trimester termination of pregnancy and for use of mifepristone in terminations beyond the first trimester.
2. Informed Consent. Provision of preprinted Information Sheet and Patient Agreement to healthcare professionals to ensure that information for patients is available to assist the provision of informed consent by patients. Patient Information and Patient Consent forms are accessible to health care professionals as downloadable pdf files from the healthcare professional secure website: www.ms2step.com.au.
3. Product labeling and packaging and Consumer Medicine Information, which provides additional information to patients in an accessible and easy to understand format.
4. The inclusion of the Black Box warning regarding follow-up, in the following documents, emphasises the need for special attention on the part of healthcare professionals: MS-2 Step Product Information, MS-2 Step Consumer Medicine Information Instruction Insert, the Mifepristone Linepharma Consumer Medicine Information, and the GyMiso® Consumer Medicine Information,
5. Monitoring. Periodic review of the pharmacovigilance database maintained by MS Health in Australia to ensure adverse event reporting is not trending.
6. Adverse Event Monitoring in Australia and Ongoing Post Marketing Surveillance. The Sponsor holds a significant database from the use of mifepristone for termination of first trimester pregnancy under the Authorised Prescriber Program (APP) in the MSIA network. The training modules will continue to be reviewed and updated to reflect the results of other peer-reviewed published studies e.g. ANZJOG 2017; 57: 366-371 as well as other large studies/meta-analyses.

Potential for medication errors

The brand name for the composite pack is ***MS-2 Step.*** The product is presented as a composite pack in a carton containing two cartons, each of which is different in appearance (as described below). The

generic names of the two component medicines, i.e. mifepristone and misoprostol, appear beneath the name ***MS-2 Step*** on the composite pack carton.

The component products contain different amounts of their respective medicines.

The labelling on the component products clearly identifies the right order for intake of the two products on the front panel of the packaging for each individual product. An instruction insert is placed in each ***MS-2 Step*** product carton to explain the right order for intake of the two products. The correct way to take the two products is also described in the respective Consumer Medicines Information leaflets, which are placed inside each component product carton.

These products are distinguished from each other in the following ways:

- The Mifepristone Linepharma 200 mg Tablet carton has a green colour, and it contains only one mifepristone tablet
- The GyMiso® carton has a purple colour, and it contains 4 misoprostol tablets
- Mifepristone Linepharma packaging includes the statement *Step 1, take this tablet first*.
- GyMiso packaging includes the statement *Step 2, take these 36 to 48 hrs after Mifepristone Linepharma*

The brand name Mifepristone Linepharma 200 mg Tablet uses the INN mifepristone and this should minimise the risk of confusion.

Mifepristone Linepharma 200 mg Tablet is available in a single strength as 200 mg tablets, each pack contains one tablet sufficient for one single treatment. Each tablet is debossed on one side (with the letters “MF”) to avoid confusion with other tablets.

The Consumer Medicine Information is included in each Mifepristone Linepharma component package and this document includes information on indication, contraindications, precautions and dosing recommendations.

The brand GyMiso® refers only to misoprostol approved in combination with mifepristone in the ***MS-2 Step*** composite pack, and this should minimise the risk of confusion.

GyMiso® is available in a single strength as 200 microgram tablet, and each GyMiso® pack contains four tablets sufficient for one single treatment. Each tablet is engraved on one side with “ML” and “200” on the other to avoid confusion with other tablets.

The Consumer Medicine Information is included in each GyMiso® component pack and this document includes information on indication, contraindications, precautions and dosing recommendations.

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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SVIII – IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

Since this is not initial RMP submission, this section is not applicable.

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.2 New Safety concerns and reclassifications with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

The description that follows provides details on the identified and potential risks that have been described for the product(s), based on the clinical trial data, literature and post-marketing experience data currently available for MS-2 Step.

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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SVII.3.1 Presentation of important identified risks and important potential risks

Table 4 Important Identified Risks

Identified risk	**"Incomplete abortion (method failure) with severe bleeding"**
MedDRA terms	Induced abortion failed (PT) Vaginal bleeding (PT)
Seriousness	Yes. Method failure occurs in 1.3 to 7.5% of cases. Heavy bleeding occurs in about 5% of cases and may require haemostatic curettage in up to 1.4% of cases. A transfusion is required in 0.1-0.2% of cases.(19) Method failure may occur with severe bleeding and it may occur without severe bleeding. Severe bleeding may not be a symptom of method failure. As there is a risk of failure of the method follow up of women is mandatory to check that abortion is complete.
Severity and nature of risk	Vaginal bleeding is part of the method. Bleeding occurs in almost all cases and is not in any way proof of complete expulsion. Follow-up must take place within a period of 14 to 21 days after administration of mifepristone to verify by the appropriate means that expulsion has been completed and that vaginal bleeding has stopped. In case of persistent bleeding (even light) beyond follow up, its disappearance should be checked within a few days. If continuing pregnancy is suspected, a further ultrasound scan may be required to evaluate its viability. Persistence of vaginal bleeding at this point could signify incomplete abortion, or an unnoticed extra-uterine pregnancy, and appropriate treatment should be considered. Heavy bleeding occurs in about 5% of cases and may require haemostatic curettage in up to 1.4% of cases. In the event of continuing pregnancy diagnosed after follow up, termination by another method may be proposed to the woman. As there is a risk of failure, follow up of women is mandatory to check that abortion is complete.
Frequency	Failure occurs in 1.3 to 7.5 % of cases.
Background incidence/prevalence	Early vacuum aspiration leads to up to 5% failure rate.(20)
Risk group or risk factors	None identified
Potential mechanism	Incomplete detachment of conceptus from uterine wall, insufficient uterine contractility.

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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Identified risk	**"Incomplete abortion (method failure) with severe bleeding"**
Preventability	Information about the potential occurrence of both method failure and severe bleeding respectively is in the Product Information and the Consumer Medicine Information. Education to be offered to Medical Practitioners.
Potential public health impact	Yes, hence the need for educational resources to be available to practitioners and adequate information for women

Identified risk	**"Infection, toxic shock syndrome"**
MedDRA terms	Infection (PT), Toxic shock syndrome (PT)
Seriousness	Yes. Infection following termination occurs in less than 1% of cases regardless of the method. Infection in medical termination occurs in 0.3-0.9% of cases.(21) Fatal toxic shock syndrome is very rare.
Severity and nature of risk	Very rare cases of fatal toxic shock caused by *Clostridium sordellii* endometritis presenting without fever or other obvious symptoms of infection, have been reported after medical abortion with the use of 200 mg mifepristone following the non-approved vaginal administration of misoprostol tablets for oral use. In Australia a case of fatal probable toxic shock syndrome has been reported in a woman treated with mifepristone 200 mg followed by 800 mcg buccal misoprostol. Clinicians should be aware of this potentially fatal complication.
Frequency	Infection following termination occurs in less than 5% of cases regardless of the method. Very rare cases of fatal toxic shock syndrome.
Background incidence/prevalence	Infection following termination occurs in less than 5% of cases regardless of the method.
Risk group or risk factors	May be associated with vaginal administration of misoprostol oral tablets.
Potential mechanism	Unknown
Preventability	Information about the potential occurrence of the event in Product Information (Precautions) indicating that the vaginal administration route of misoprostol should not be used. Information about the possibility of infection occurring is included in the Consumer Medicine Information. Education to be offered to Medical Practitioners.
Potential public health impact	Yes, hence the need for educational resources to be available to practitioners and adequate information for women

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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<table>
<tr><td>Identified risk</td><td>“Cardiac Disorders”</td></tr>
<tr><td>MedDRA terms</td><td>Adverse event reports of cardiovascular events are identified using a prespecified list of Standard MedDRA query: SOC Cardiac disorders</td></tr>
<tr><td>Seriousness</td><td>No cardiovascular event was reported during pivotal studies.
Cardiovascular events reported with misoprostol use in a gynaecological indication, in literature studies and postmarketing experience, include myocardial infraction, myocardial ischemia, sudden death, stroke and transient ischemic accident. Most of these events have a favourable outcome, but event with sequel or fatal outcome has also been reported. If some occurred after a treatment including mifepristone and misoprostol, for most of them mifepristone administration was unknown</td></tr>
<tr><td>Severity and nature of risk</td><td>In a prospective study on 9 women evaluating cardio-vascular safety of 600 µg misoprostol administration via vaginal route, none of evaluated parameters (cardiac frequency, arterial pressure, cardiac index…) for 4 days after the take were significantly modified (Ramsey 2000).
An investigation on cardiovascular effect of misoprostol was performed by the French National Agency in 2013. This evaluation based on international literature search, French and international post-marketing reports (from commercialisation to December 2012) concludes in the existence of coronary and cerebral adverse reaction with the use of misoprostol in medical termination of a pregnancy.
Regarding mifepristone potential effect on cardiovascular system, non-clinical data, clinical data, post- marketing surveillance of adverse events and the drug’s action mechanism on the adrenocortical pathway do not associate the product with typical proarrhythmic events that could indicate a QT/QTc interval prolongation.</td></tr>
<tr><td>Frequency</td><td>French National Agency estimated the incidence of cardiovascular events with the use of misoprostol at 2.7 cases [0.3 to 9.8] for 106 exposed women.
In the Australian phase IV safety study, from cumulative data to 31st March 2016, incidence (%) of cardiovascular event by gestational ages is provided below:
<table>
<tr><td>≤ 35 days</td><td>36-42 days</td><td>43-49 days</td><td>50-56 days</td><td>57-63 days</td><td>Total</td></tr>
<tr><td>0</td><td>0.1</td><td>0.1</td><td>0.3</td><td>0.2</td><td>0.1</td></tr>
</table></td></tr>
<tr><td>Background incidence/prevalence</td><td>There are no specific studies that evaluate prevalence of cardiovascular risks of first trimester pregnant women.</td></tr>
<tr><td>Risk group or risk factors</td><td>Vascular risks factors such as tobacco use, hypertension and heredity as well as a sur-exposure to misoprostol.</td></tr>
<tr><td>Potential mechanism</td><td>Coronary manifestations observed during medical termination of pregnancy could be explained by the existence of vascular risks factors (tobacco use, hypertension, heredity) and a sur-exposition to misoprostol related to the high dose (double posology) and the vaginal administration, this way leading to a doubling of AUC.</td></tr>
<tr><td>Preventability</td><td>Information about the potential occurrence of the event in Product Information and Consumer Medicine Information.</td></tr>
<tr><td>Potential public health impact</td><td>Yes, hence the need for educational resources to be available to practitioners and adequate information for women.</td></tr>
</table>

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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Table 5 Important Potential risks

Important Potential Risk - Unintended pregnancy exposure to mifepristone / misoprostol and risk of incomplete abortion with severe bleeding
Evidence source: In approximately 3% of the cases (EU Summary of Product Characteristics (SPC) for Mifegyne® and for Mifepristone Linepharma, section 4.4) abortion can occur with mifepristone alone (with no prostaglandin intake). Follow-up is still required to ensure that complete abortion has occurred. In addition, as indicated in the EU SPC for Mifegyne® and for Mifepristone Linepharma (section 4.4) during clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses. Due to the long half-life of mifepristone, the possibility exists of exposure of a subsequent pregnancy to mifepristone. To avoid potential exposure of a subsequent pregnancy to mifepristone, it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after mifepristone and misoprostol administration.

Important Potential risk / Unintended pregnancy exposure (risk of malformations)
Evidence source: In the EU SPC for both Mifegyne® and for Mifepristone Linepharma, it is stated in section 4.6, it is stated that "in animals the abortifacient effect of mifepristone precludes the proper assessment of any teratogenic effect of the molecule" and that "with sub abortive doses, isolated cases of malformations observed in rabbits, but not in rats or mice were too few to be considered significant, or attributable to mifepristone". In section 4.6 of the EU SPC for Mifegyne® and Mifepristone Linepharma, it is indicated that "in humans, the few reported cases of malformations do not allow a causality assessment for mifepristone alone or associated to prostaglandin. Therefore, data is too limited to determine whether the molecule is a human teratogen." The issue of the outcome of persisting pregnancy in case of failure of the method remains incompletely solved: although, up to date there does not seem to be clear-cut foetal malformations attributable to mifepristone or to prostaglandin analogues (19), such possibility cannot be definitively ruled out and women should be adequately counseled in such a situation. In addition, as indicated in Part II, Table 3 of this RMP, misoprostol, through its smooth muscle contracting activity, could have effects on the developing foetus and there are several reports in the literature on the occurrence of congenital defects in children born to mothers who had taken misoprostol to terminate pregnancy; this off-label use of misoprostol appears to have been a particular problem in Brazil, from where considerable evidence has accumulated on its possible teratogenic activity in humans (cited by Orioli *et al,* 2000; Paumgarten *et al*, 1995). Data would suggest a link between misoprostol and congenital malformations, based on a retrospective analysis of cases, and a prospective study based on Brazilian data suggested that misoprostol may increase the incidence of congenital anomalies, but that the magnitude of the increased risk is low (Schuler *et al*, 1999). As a consequence, the EU SPC for Mifegyne® and Mifepristone Linepharma proposes the following recommendations: - Women should be informed, that due to the risk of failure of the medical method of pregnancy termination and to the unknown risk to the foetus, follow-up is mandatory (see Section 4.4 special warnings and special precautions for use).

Important Potential risk / Unintended pregnancy exposure (risk of malformations)
- Should a failure of the method be diagnosed at follow-up (viable ongoing pregnancy), and should the patient still agree, pregnancy termination should be completed by another method. - Should the patient wish to continue with her pregnancy, the available data is too limited to justify a systematic termination of an exposed pregnancy. In that event, careful ultra-sonographic monitoring of the pregnancy should be carried out." In addition, as indicated in the EU SPC for Mifegyne® and Mifepristone Linepharma (section 4.4) during clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses. To avoid potential exposure of a subsequent pregnancy to mifepristone, it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after mifepristone / misoprostol administration.

Important Potential risk / Induced Bronchial Asthma
Evidence source: Data to evaluate the inadvertent risk of induced bronchial asthma after the administration of mifepristone and misoprostol are derived from analyses conducted of extensive review of literature published in English and in Chinese as well as non Linepharma France sponsored trials and reports from post-marketing setting. Mifepristone binds to the glucocorticoid receptor. It may therefore interfere with the action of glucocorticoid treatments. This might be relevant in case of severe asthma inadequately controlled by oral or inhaled glucocorticoid. In addition, bronchospasm may occur with some prostaglandins and prostaglandin analogues. The possibility should be borne in mind in patients with a history of asthma. Severe asthma uncontrolled by treatment is labelled as a contraindication in the EU SPC for Mifegyne® and Mifepristone Linepharma, whatever the indication.

Table 6 Potential interaction with CYP3A4 inhibitors or inducers

Interacting substance/CYP3A4 inhibitors or inducers
Evidence source: EU Mifegyne® SPC, literature review No interaction studies have been performed. On the basis of this drug's metabolism by CYP3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum levels of mifepristone). Furthermore, rifampicin, dexamethasone, St. John's Wort and certain anticonvulsants (phenytoin, phenobarbitone, carbamazepine) may induce mifepristone metabolism (lowering serum levels of mifepristone). Based on in vitro inhibition information, co-administration of mifepristone may lead to an increase in serum levels of drugs that are CYP3A4 substrates. Due to the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP3A4 substrates and have narrow therapeutic range, including some agents used during general anaesthesia. For misoprostol, limited studies on effects of misoprostol on hepatic drug metabolism in the rat did not show any effect on aminopyrine metabolism (single oral dose of 0.1 mg/kg of misoprostol) or, after 0.1 mg/kg twice daily for four days, cytochrome P450 content or the activities in liver microsomes of hexobarbital

Interacting substance/CYP3A4 inhibitors or inducers
hydroxylase, aniline hydrolase or p-nitroanisole O-demethylase. Based on this information, no drug interaction is expected after misoprostol administration.

Table 7 Potential interaction with products interacting with the glucocorticoid receptor

Interacting substance/ Products interacting with the glucocorticoid receptor
Evidence source: EU Mifegyne® and Mifepristone Linepharma SPC's, literature review Mifepristone binds to the glucocorticoid receptor. It may therefore interfere with the action of glucocorticoid treatments. This might be relevant in case of severe asthma inadequately controlled by oral or inhaled glucocorticoid.

SVII.3.2. Presentation of the missing information

Table 8 Presentation of the missing information

Missing Information/ Inherited porphyria
Evidence source: This is labelled as a contraindication in the EU SPC for Mifegyne® and Mifepristone Linepharma, whatever the indication. The reason for this contraindication is unclear. Literature search for "mifepristone and porphyria" yields only one abstract (15) indicating that in an *in vitro* model mifepristone and deferoxamine together produced significant accumulations of protoporphyrin. The authors concluded that "RU-486 may pose a risk in patients with known acute porphyria and should be used with caution".

Missing Information / Theoretical interaction with NSAIDs
Evidence source: This is a potential precaution in the EU SPC for Mifegyne® and Mifepristone Linepharma, whatever the indication. A decrease of the efficacy of the method can theoretically occur due to the antiprostaglandin properties of non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin (acetyl salicylic acid). Limited evidence suggests that co-administration of NSAIDs on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medical termination of pregnancy. The reason for this precaution is therefore unclear.(23,24)

Missing Information / Potential interaction with products interacting with the progesterone receptor
Evidence source: EU Mifegyne® and Mifepristone Linepharma SPC's, literature review Mifepristone is a progesterone receptor antagonist. Therefore, it may interfere with the action of progestin-only contraceptives.

Missing Information / use in adolescents
Evidence source: Literature review Mifepristone Linepharma 200 mg Tablet and GyMiso® are recommended for use in females of childbearing age. There are limited data available in women below the age of 18 years.

SVII.3.3. Presentation of the pharmacological class effect

Mifepristone belongs to the progesterone receptor antagonist class.
Mifepristone also displays anti-glucocorticoid activity. Such activity, evidenced by an ACTH elevation, has not been observed at the dose of 200 mg per dose for several years (157 months for treatment of meningioma in patients with normal adrenal function).(18) Therefore, use of a single intake mifepristone is not expected to have anti-glucocorticoid activity. As indicated above, mifepristone may interfere with the action of glucocorticoid treatments. This might be relevant in case of severe asthma inadequately controlled by oral glucocorticoid.

For medical pregnancy termination, mifepristone treatment must be followed by the administration of the prostaglandin analogue, misoprostol (GyMiso®) which is the second component of ***MS-2 Step***. Therefore, risks inherent with this class of product must also be taken in consideration.

Pharmacological class effect / Risks related to the use of prostaglandin
Evidence source: Termination of pregnancy with mifepristone necessitates the use of prostaglandin analogues, such as misoprostol, which has its own potential risks. This is taken into account in the EU Mifegyne® SPC: In section 4.3, the method should not been used in case of contraindication to a prostaglandin analogue. In section 4.4, it is acknowledged that rare serious cardiovascular accidents have been reported following the intra muscular administration of prostaglandin E2 analogue, sulprostone. For this reason women with risk factors for cardiovascular disease or established cardiovascular disease should be treated with caution. This is taken into account in the current Mifepristone Linepharma Australian Product Information: In Contraindications, the product should not be prescribed in case of a contraindication to the prostaglandin analogue.

In Precautions, it is stated that rare serious cardiovascular accidents have been reported following administration of prostaglandins including misoprostol. For this reason, women with risk factors for cardiovascular disease or established cardiovascular disease should be treated with caution.

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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PART II: MODULE SVIII – SUMMARY OF THE SAFETY CONCERNS

Table 9 Summary- safety concerns

Summary of safety concerns	
Important Identified Risks:	Infection, toxic shock syndrome Method failure Cardiac disorders
Important Potential Risks:	Inadvertent pregnancy exposure and risk of incomplete abortion with severe bleeding Inadvertent pregnancy exposure (risk of malformations) Potential interaction with CYP3A4 inhibitors or inducers Potential interaction with products interacting with the glucocorticoid receptor Induced bronchial asthma Effects in lactating women Effects in women with impaired liver function Effects in women with impaired renal function Effects in women with malnutrition Incorrect determination of gestational age Potential for missed ectopic pregnancy Potential for postnatal developmental delay Potential for off-label use beyond the first trimester Potential for loss to follow-up Potential safety risks in vulnerable groups including women in regional and remote areas of Australia, who may be particularly at risk of being lost to follow-up
Missing Information:	Inherited porphyria Theoretical interaction with NSAIDs Potential interaction with products interacting with the progesterone receptor Use in adolescents
Pharmacological class effect	Risks related to the use of prostaglandin

MS-2 Step composite pack
[MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet/GyMiso® misoprostol 200 µm tablet blister]

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PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities including adverse event reporting and signal detection is conducted.

Periodic Safety Updates

Periodic Safety Update Reports (PSURs) for Mifepristone Linepharma and GyMiso® will continue as the safety reporting method for ***MS-2 Step***.

As agreed at the time of approval of the individual products, PSURs was submitted six monthly for the first 12 months from registration and then annually after that, with a data lock of no more than 60 days for Mifepristone Linepharma and GyMiso®, respectively. Use of mifepristone beyond the first trimester (including off-label use) is given separate consideration in the PSURs.

PSURs would be aligned with international reporting in accordance with the international birth date (IBD) defined in ICH E2C(R1), which for:

- Mifepristone Linepharma is based on the EU-harmonised IBD of 31 May. MS Health have completed the PSUR submission commitments.
- The Mifepristone Linepharma product was launched in Australia on 4 February 2013.
- GyMiso® is based on an EU-harmonised IBD of 31 May. The GyMiso® product was launched in Australia on 1 August 2013.
- MS 2 Step PSUR obligations have been met and no further submission are required.

The safety update reports for both Mifepristone Linepharma and GyMiso® will include the ongoing post marketing collection of the data in Australia.

III.2 Additional pharmacovigilance activities

Not applicable

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 10 On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not Applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not Applicable				

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Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Not Applicable				

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Routine risk minimisation measures include the Product information and Consumer Medicine Information. Details are outlined in Table 6 below.

Table 11 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risk: Infection, toxic shock syndrome	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.
Important identified risk: Method failure	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.
Important identified risk: Cardiac disorders	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.

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Safety concern	**Routine risk minimisation activities**
Important potential risk: Inadvertent pregnancy exposure (risk of malformations)	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.
Important potential risk: Inadvertent pregnancy exposure and risk of incomplete abortion with severe bleeding	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.
Important potential risk: Potential interaction with CYP3A4 inhibitors or inducers	Routine: Mentioned in the Product Information in INTERACTIONS WITH OTHER MEDICINES. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Physician education.
Important potential risk: Potential interaction with products interacting with the glucocorticoid receptor	Routine: Mentioned in the Product Information in PHARMACOLOGY and PRECAUTIONS. Physician education.
Important potential risk: Induced bronchial asthma	Routine: Mentioned in the Product Information in CONTRAINDICATIONS and PRECAUTIONS Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Physician education.

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Safety concern	**Routine risk minimisation activities**
Important potential risk: Incorrect determination of gestational age	Routine: Mentioned in the Product Information in CONTRAINDICATIONS Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Physician education.
Important potential risk: Effects in lactating women	Routine: Mentioned in the Product Information in Use during lactation. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.
Important potential risk: Effects in women with impaired liver function	Routine: Mentioned in the Product Information in SPECIAL WARNINGS AND PRECAUTIONS FOR USE and in INTERACTIONS WITH OTHER MEDICINES. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.
Important potential risk: Effects in women with impaired renal function	Routine: Mentioned in the Product Information in SPECIAL WARNINGS AND PRECAUTIONS FOR USE and in INTERACTIONS WITH OTHER MEDICINES. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.
Important potential risk: Effects in women with malnutrition	Routine: Mentioned in the Product Information in SPECIAL WARNINGS AND PRECAUTIONS FOR USE. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.

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Safety concern	Routine risk minimisation activities
Important potential risk: Potential for missed ectopic pregnancy	Routine: Mentioned in the Product Information in SPECIAL WARNINGS AND PRECAUTIONS FOR USE and in ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.
Important potential risk: Potential for postnatal developmental delay	Routine: Mentioned in the Product Information in Use in pregnancy
Important potential risk: Potential for loss to follow up	Routine: Mentioned in the Product Information in SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Missing information: Inherited porphyria	Not mentioned in Product Information and the Consumer Medicine Information as there is limited evidence of this being a safety concern with administration of mifepristone.(22)
Missing information: Potential interaction with products interacting with the progesterone receptor	This potential risk has not been confirmed and no information is deemed necessary in the Product Information.
Missing information: Theoretical interaction with non-steroidal anti-inflammatory drugs	This potential risk has not been confirmed and no information is deemed necessary in the Product Information.
Missing information: Use in adolescents	Product Information and Consumer Medicine Information mention that use is limited in this population. The Product Information mentions, there is no relevant use of MS-2 Step in the prepubertal paediatric population in the indication. Administration to adolescents less than 18 years of age should be undertaken with caution.

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Safety concern	Routine risk minimisation activities
Pharmacological class effect:	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS.
Risks related to the use of prostaglandin	Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information.

V.2 Additional Risk Minimisation Measures

There are six specific risk minimisation tools planned, as detailed below, in addition to the routine measures for the identified risks, potential risks, missing information and pharmacological class effects, outlined below.

Black Box Warnings

A black box warning is included in the ***MS-2 Step*** Product Information:

> It is very important that all patients receiving these medications are followed up by a medical practitioner, preferably the prescriber, to ensure that the medication has been effective. Even if no adverse events have occurred all patients must receive follow-up 14 to 21 days after taking mifepristone. Read the ***SPECIAL WARNINGS AND PRECAUTIONS FOR USE*** carefully.

A black box warning is included in the Mifepristone Linepharma Consumer Medicine Information:

> It is very important that all patients receiving this medication are followed up by a medical practitioner, preferably the prescriber, to ensure that the medication has been effective. Even if no adverse events have occurred all patients must receive follow-up 14 to 21 days after taking mifepristone.

A black box warning is included in the GyMiso® Consumer Medicine Information:

> It is very important that all patients receiving this medication are followed up by a medical practitioner, preferably the prescriber, to ensure that the medication has been effective. Even if no adverse events have occurred all patients must receive follow-up 14 to 21 days after taking mifepristone.

Inclusion of Consumer Medicine Information

The Consumer Medicine Information is included in every pack of Mifepristone Linepharma.

The Consumer Medicine Information is also be included in every pack of GyMiso®.

Inclusion of Instruction Insert in Composite Pack Carton

An Instruction Insert is included in every pack of ***MS-2 Step***, to clearly indicate the identity of the components, the order in which the component medicines should be taken, and the importance of a follow-up appointment 14-21 days following the administration of Mifepristone Linepharma to confirm successful termination of pregnancy.

Informed Consent, Compliance with the Method and Follow-up

The Sponsor provides all prescribers with access to reprinted Information Sheet and Patient Consent Agreements Forms to ensure that information in relation to the medical method of pregnancy termination is available to assist the provision of informed consent by patients.

Information Sheets and Patient Consent Forms also highlight symptoms patients will experience, along with symptoms requiring immediate follow up, and enable the prescriber to nominate the details of a 24-hour emergency facility for immediate follow-up if required, and details in relation to the patients scheduled follow up appointment 14-21 days after administration of the Mifepristone Linepharma tablet.

The Information Sheet and Patient Consent Agreements Forms are provided without charge by MS Health, and can be downloaded from the secure health care professional website www.ms2step.com.au as pdf files, or can be requested by contacting MS Health directly as reprinted documents.

The medical method of pregnancy termination and requirement for patient follow-up appointment is also documented in the ***MS-2 Step*** Product Information.

Prescriber Training

To support the education of Prescribers, the Sponsor provides access to Prescriber training through the provision of a comprehensive Medical Education Program, and ensures, to the extent practical, that the medical method of termination using the Mifepristone Linepharma and GyMiso® products (i.e. the MS-2 Step Medical Method) is used in Australia responsibly and appropriately.

The Medical Education Program is delivered online and is made freely available by the Sponsor to all prescribers.

V.3 Summary of risk minimization measures

Safety concern	Pharmacovigilance activities	Risk minimisation measures
Important identified risk:		
Infection, toxic shock syndrome	Routine: - Routine pharmacovigilance - Special attention in PSURs	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Black box warning on follow-up in ***MS-2 Step*** Product Information, and in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Patient Information and Consent Agreement with emphasis on compliance and follow-up. Physician education.
Method failure	Routine:	Routine:

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Safety concern	Pharmacovigilance activities	Risk minimisation measures
	-Routine pharmacovigilance - Special attention in PSURs	Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Black box warning on follow-up in ***MS-2 Step*** Product Information, and in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Patient Information and Consent Agreement with emphasis on compliance and follow-up. Physician education.
Potential risk:		
Inadvertent pregnancy exposure and risk of incomplete abortion with severe bleeding	Routine: - Routine pharmacovigilance - Special attention in PSURs	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Patient Information and Consent Agreement with emphasis on compliance and follow-up. Physician education.
Inadvertent pregnancy exposure (risk of malformations)	Routine: - Routine pharmacovigilance - Special attention in PSURs	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Patient Information and Consent Agreement with emphasis on compliance and follow-up. Physician education.
Potential risk:		

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Safety concern	Pharmacovigilance activities	Risk minimisation measures
Potential interaction with CYP3A4 inhibitors or inducers	Routine: - Routine pharmacovigilance - Special attention in PSURs	Routine: Mentioned in the Product Information in INTERACTIONS WITH OTHER MEDICINES. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Physician education.
Potential interaction with products interacting with the glucocorticoid receptor	Routine: - Routine pharmacovigilance - Special attention in PSURs	Routine: Mentioned in the Product Information in PHARMACOLOGY and PRECAUTIONS. Additional: Physician education.
Induced bronchial asthma	Routine: - Routine pharmacovigilance - Special attention in PSURs	Routine: Mentioned in the Product Information in CONTRAINDICATIONS and PRECAUTIONS Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Physician education.
Effect in lactating women	Routine: - Routine pharmacovigilance	Routine: Mentioned in the Product Information in Use during lactation. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Physician education.
Potential risk:		
Effect in women with impaired liver function	Routine: - Routine pharmacovigilance	Routine: Mentioned in the Product Information in SPECIAL WARNINGS AND PRECAUTIONS FOR USE and in INTERACTIONS WITH OTHER MEDICINES.

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Safety concern	Pharmacovigilance activities	Risk minimisation measures
		Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Physician education.
Effect in women with impaired renal function	Routine: - Routine pharmacovigilance	Routine: Mentioned in the Product Information in SPECIAL WARNINGS AND PRECAUTIONS FOR USE. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Physician education.
Effect in women with malnutrition	Routine: - Routine pharmacovigilance	Routine: Mentioned in the Product Information in SPECIAL WARNINGS AND PRECAUTIONS FOR USE. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Physician education.
Potential risk:		
Missed ectopic pregnancy	Routine: - Routine pharmacovigilance	Routine: Mentioned in the Product Information in SPECIAL WARNINGS AND PRECAUTIONS FOR USE and in ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Patient Information and Consent Agreement with emphasis on compliance and follow-up. Physician education.
Postnatal development delay	Routine: - Routine pharmacovigilance	Routine:

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Safety concern	Pharmacovigilance activities	Risk minimisation measures
	- Special attention in PSURs	Mentioned in the Product Information in Use in pregnancy
Potential for off-label use beyond the first trimester	Routine: - Routine pharmacovigilance	Additional: Physician education.
Potential safety risks in vulnerable groups including women in rural and remote areas of Australia, particularly the risk of being lost to follow-up	Routine: - Routine pharmacovigilance	Additional: Physician education.
Missing information		
Inherited porphyria	Routine: - Routine pharmacovigilance - Special attention in PSURs	Not mentioned in Product Information and the Consumer Medicine Information as there is limited evidence of this being a safety concern with administration of mifepristone (6).
Potential interaction with products interacting with the progesterone receptor	Routine: - Routine pharmacovigilance - Special attention in PSURs	This potential risk has not been confirmed and no information is deemed necessary in the Product Information.
Theoretical interaction with non-steroidal anti-inflammatory drugs	Routine: - Routine pharmacovigilance - Special attention in PSURs	This potential risk has not been confirmed and no information is deemed necessary in the Product Information.
Use in adolescents	Routine: - Routine pharmacovigilance - Special attention in PSURs	Product Information and Consumer Medicine Information mention that use is limited in this population.
Pharmacological class effects		

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Safety concern	Pharmacovigilance activities	Risk minimisation measures
Risks related to the use of prostaglandin	Routine: - Routine pharmacovigilance - Special attention in PSURs	Routine: Mentioned in the Product Information in PRECAUTIONS and ADVERSE EFFECTS. Mentioned in the Mifepristone Consumer Medicine Information and the GyMiso® Consumer Medicine Information. Additional: Patient Information and Consent Agreement with emphasis on compliance and follow-up. Physician education.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Not applicable.

PART VII: ANNEXES

Not applicable

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From: LANGHAM, Robyn
To: ACM
Cc: TGA Committees Inbox; s22
Subject: RE: ACM - seeking specialist advisors [SEC=OFFICIAL]
Date: Tuesday, 9 May 2023 2:17:00 PM

I should add that all suggested speakers are likely to have conflicts due to participation in clinical trials – all manageable.
Robyn

From: ACM s22 @health.gov.au>
Sent: Tuesday, 9 May 2023 12:29 PM
To: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Cc: s22 @health.gov.au>; s22
s22 @health.gov.au>
Subject: ACM - seeking specialist advisors [SEC=OFFICIAL]
Good afternoon Robyn,
Grateful for your input on potential speakers for two items at ACM 39 on 1 and 2 June 2023 (face to face meeting in Canberra) please.

s22

Mifepristone and misoprostol (MS-2 Step composite pack)
Seeking expertise in the use of this medicine
The proposed change is:
Section 4.2 of the current PI advises MS-2 Step can only be prescribed by doctors with the appropriate qualifications and certified training. The Sponsor proposes to amend 'medical practitioner' in the boxed warning and 'doctors' in Section 4.2 of the PI to 'healthcare practitioners'
Any suggestions would be very much appreciated.
Many thanks.
Kind regards,

s22
ACM Secretariat and Prescription Medicine Expert Advice Service
Prescription Medicines Authorisation Branch

Phone: s22
Email: s22 @health.gov.au

Therapeutic Goods Administration
Department of Health and Aged Care

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From: LANGHAM, Robyn
To: ACM
Cc: TGA Committees Inbox; s22
Subject: RE: ACM - seeking specialist advisors [SEC=OFFICIAL]
Date: Tuesday, 9 May 2023 12:33:00 PM

Hi s22
s22

For MS2-Step, I would suggest s22 – this is largely a GP prescribing issue, so the ACM's GP could also help. (s22 @monash.edu)
Let me know if you need more names,
Robyn

From: ACM s22 @health.gov.au>
Sent: Tuesday, 9 May 2023 12:29 PM
To: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Cc: TGA Committees Inbox <Committees@health.gov.au>; s22
s22 @health.gov.au>
Subject: ACM - seeking specialist advisors [SEC=OFFICIAL]
Good afternoon Robyn,
Grateful for your input on potential speakers for two items at ACM 39 on 1 and 2 June 2023 (face to face meeting in Canberra) please.
s22

Mifepristone and misoprostol (MS-2 Step composite pack)
Seeking expertise in the use of this medicine
The proposed change is:
Section 4.2 of the current PI advises MS-2 Step can only be prescribed by doctors with the appropriate qualifications and certified training. The Sponsor proposes to amend 'medical practitioner' in the boxed warning and 'doctors' in Section 4.2 of the PI to 'healthcare practitioners'
Any suggestions would be very much appreciated.
Many thanks.
Kind regards,

s22
s22
ACM Secretariat and Prescription Medicine Expert Advice Service
Prescription Medicines Authorisation Branch

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