Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for mifepristone/misoprostol

Proprietary Product Name: MS-2 Step

Sponsor: MS Health Pty Ltd

Date of CER: 14 October 2013

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 is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), 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 <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
µg	Microgram
AE	Adverse event
CI	Confidence interval
CSR	Clinical study report
D&C	Dilatation and curettage
DA	Days of amenorrhoea
GA	Gestational age
IUD	Intrauterine device
LMP	Last menstrual period
MF	Mifepristone
Msp	Misoprostol
PI	Product information
PR	Pregnancy rate
RCT	Randomised controlled trial
SAE	Serious Adverse Event
TOP	Termination of Pregnancy

1. Clinical rationale

Both mifepristone and misoprostol were originally developed by Laboratoire HRA Pharma, France, which licensed them to Linepharma Sarl, France, for registration and marketing worldwide. Marie Stopes International (Australia), an independent non-governmental organisation, licensed both products from Linepharma. MS Health Pty Ltd is a subsidiary of Marie Stopes International (London), which is a registered charity in the UK and a global partner with Marie Stopes International (Australia) (MSIA).

The current product information (PI) for mifepristone states that it is to be used in sequential combination with a prostaglandin analogue. Likewise, the PI for GyMiso (misoprostol) also states that it is to be used in sequential combination with a mifepristone 200 mg tablet.

The rationale for the composite pack presentation is therefore logical and according to the Sponsor *'will allow a simplification in the use of the mifepristone – misoprostol method for*

termination of pregnancy and will ensure a better compliance (less risk that a woman omits to take the misoprostol tablets after having taken the mifepristone tablets).'

The extended indication for the combination proposes use for medical termination of pregnancy out to 63 days of gestation (from 49 days). This provides an alternative to surgical termination of pregnancy for this gestational age. The sponsor stated that there is no intention to alter the indications for the individual components.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission contained the following clinical information:

- One clinical pharmacology study (MCPK12001J1).
- One Phase III study (Study 1.1.4).
- A summary of authorised prescriber experience at MSIA clinics in 2012.
- Protocol for a Phase IV post-registration study (HREC2012001).
- PSUR for GyMiso (20 October 2012 to 28 April 2013) and PSUR for mifepristone Linepharma (29 June 2012 to 28 December 2012).
- Literature references.
- The sponsor's Clinical Overview, Summary of Clinical Pharmacology, Summary of Clinical Efficacy, Summary of Clinical Safety, individual study synopses and listing of literature references.

2.2. Paediatric data

The submission did not include paediatric data. The product is for use in women of child bearing age.

There have been no clinical trials in adolescent girls and the sponsor states that no such studies are planned.

The sponsor also stated that there was no requirement in the EU to submit a Paediatric Investigational Plan. It was stated however that Linepharma is planning to seek future marketing authorisation in the EU (under Decentralised Procedure) for the combination product of Mifepristone Linepharma + GyMiso, [information redacted].

The proposed PIP will relate to continuing collection of data from use of the two products for medical abortion in women under 18 years, as a post-marketing prospective follow-up investigation.

2.3. Good clinical practice

The sponsor stated that both clinical trials submitted in the dossier were conducted according to Good Clinical Practice guidelines as well as local ethical and regulatory requirements.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

The dossier included one pharmacokinetic study which has been summarised.

The sponsor stated that since 2003, medical practices have changed and currently prescribers are often using misoprostol tablets by buccal or sublingual routes, and thus a comparative study aiming to compare the pharmacokinetic properties of misoprostol by oral/buccal/sublingual administration was undertaken.

3.2. Summary of pharmacokinetics

The following information is derived from the sponsor's summaries and the respective product informations.

- mifepristone is a synthetic steroid with an antiprogestational action as a result of competition with progesterone at the progesterone receptors. 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 uterine cervix.

  After oral administration of a single dose of 200 mg, mifepristone is rapidly absorbed with peak concentration reached after 0.75 hours. The PK is non-linear. 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. mifepristone is 98% bound to plasma proteins. Metabolism is hepatic (CYP3A4) and metabolites may contribute to the pharmacological effects of mifepristone.

- Misoprostol is a synthetic analogue of prostaglandin E1. It induces contractions of the smooth muscle fibres in the myometrium and relaxation of the uterine cervix. The uterotonic properties of misoprostol should facilitate cervical opening and evacuation of intrauterine debris.

  After a single oral dose, misoprostol is rapidly and almost completely absorbed from the gastrointestinal tract. It undergoes extensive and rapid first-pass metabolism (de-esterification) to form misoprostol acid, the principal active metabolite of the drug. 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. Elimination of misoprostol and its metabolites is also rapid with a plasma elimination half-life of 35 minutes.

3.2.1. Pharmacokinetics in healthy subjects

3.2.1.1. Bioavailability

A three-way crossover comparative pharmacokinetic study of misoprostol 200 µg tablet by oral, buccal and sublingual administration in 10 healthy female volunteers was conducted. The concentration time profile and summary PK parameters were reported.

The study found statistically significant differences ($p < 0.05$) between the 3 routes of administration for the log-transformed AUC_{0_t}, $AUC_{0\text{-}\infty}$ and C_{max}. Sublingual administration of misoprostol resulted in a higher exposure (AUC_{0_t}, $AUC_{0\text{-}\infty}$) compared to oral or buccal administration and the latter two had similar exposure ($AUC_{0\text{-}\infty}$: 3.21 versus 2.02 and 2.07 hr*ng/mL, respectively). The peak concentration (C_{max}) was higher following oral and sublingual than via buccal administration (2.68 and 2.44 versus 1.36 ng/mL). The time to peak

concentration (T_{max}) was shortest with oral compared to buccal or sublingual administration. No difference was found when comparing oral, sublingual and buccal half-lives ($p > 0.05$).

3.3. Evaluator's overall conclusions on pharmacokinetics

The dossier included one PK study comparing three routes of administration for misoprostol – oral, buccal and sublingual. It found significant differences between the routes with the highest exposure with sublingual administration and similar exposure between the buccal and oral routes. The sponsor stated that the higher bioavailability by sublingual route of administration may be explained by the absence of a first-pass effect by the liver. For buccal administration, some portions of the dose may be swallowed and metabolised by the liver before reaching the systemic circulation and so result in a lower exposure than the sublingual route. It is noted that sublingual misoprostol is not proposed for the route of administration in the PI while buccal administration is already approved for use and is proposed for the extended indication of 50-63 gestational age.]

4. Pharmacodynamics

There were no pharmacodynamic studies submitted.

5. Dosage selection for the pivotal studies

No dosage change is proposed and the registered dosage was used in the clinical trial.

6. Clinical efficacy

6.1. Medical termination of pregnancy

6.1.1. Efficacy studies

6.1.1.1. Study 1.1.4.

6.1.1.1.1. Study design, objectives, locations and dates

Study 1.1.4 was an open label, non-comparative multicentre study that was conducted between September 2010 and May 2011 at 3 sites in Mexico. The study sponsor was Gynuity Health Projects. The objective of the study was to assess the acceptability and efficacy of a combined regimen of mifepristone (200 mg oral) and misoprostol (800 microgram buccal) for abortion in women with pregnancies through 63 days of gestation in first and second level care units.

On day one subjects were screened, enrolled and received mifepristone. This was followed by misoprostol 24 to 48 hours later given at home. Follow-up at day 8 assessed abortion status. Women with a complete abortion finished the study, those with ongoing pregnancy had surgical intervention and those with an incomplete abortion had a second dose of misoprostol and were followed at day 15 to 36. At this stage, those with a complete abortion finished the study and those with an incomplete abortion underwent surgical intervention.

> Comment: It is not clear from the CSR if women had an ultrasound to confirm gestational age or if this was solely determined by the date of the last menstrual period. The sponsor has been asked a question to clarify this.

6.1.1.1.2. Inclusion and exclusion criteria

Inclusion criteria were women requesting an abortion with a pregnancy of gestational age less than or equal to 63 days since last menstrual period (LMP) and willing to undergo surgical intervention if necessary. Exclusion criteria were: gestational age >63 days since LMP; suspected ectopic pregnancy or undiagnosed adnexal mass; IUD user; current long term treatment with corticosteroids; allergic to mifepristone, misoprostol or other prostaglandins; bleeding disorder or on anticoagulants; and history of porphyria.

6.1.1.1.3. Study treatments

Treatment was with mifepristone 200 mg (mifepristone Linepharma 200 mg) orally followed by misoprostol 800 microgram (Cytotec Pfizer USA) bucally 24-48 hours after the mifepristone. Mifepristone was taken at the study site. Misoprostol was self-administered at home and women were instructed to hold the tablets in the cheek pouch for 30 minutes and then swallow remnants. Prohibited medications included long term corticosteroids and anticoagulants.

6.1.1.1.4. Efficacy variables and outcomes

The primary efficacy variable was abortion status. The outcome of complete abortion was defined as uterine evacuation with study drugs alone without recourse to surgical uterine evacuation for any reason. This was determined by history, clinical/pelvic examination and ultrasound one week post medication.

6.1.1.1.5. Randomisation and blinding methods

The study was open-label and non-randomised.

6.1.1.1.6. Analysis populations

The population analysed for efficacy included all women for whom outcome data were available (that is those who received the study drug treatment and were available for follow up).

6.1.1.1.7. Sample size

The CSR stated that a sample of 500 participants would be sufficient to demonstrate an estimated 95% efficacy with a 95% confidence interval of ±2%. A sample of 1000 was chosen to allow for subject variability.

6.1.1.1.8. Statistical methods

Statistical analysis was descriptive.

6.1.1.1.9. Participant flow

There were 1000 women enrolled, 1000 treated and 29 (2.9%) were lost to follow up which resulted in 971 (97.1%) analysed for efficacy.

6.1.1.1.10. Major protocol violations/deviations

There were two (0.2%) women enrolled with gestational age > 63 days since LMP (64 and 66 days). Both had successful abortions.

6.1.1.1.11. Baseline data

The mean age of women was 25.4 years, mean gravidity of 2.3, 9.6% reported a previous abortion and 7.4% a previous medical abortion. Most women (82.1%) presented with gestational age less than or equal to 56 days. The gestational age was less than or equal to 49 days, 50-56 days, 57-63 days and > 64 days in 56.9%, 25.2%, 17.7%, and 0.2% of the study population, respectively. There were 431 (43.1%) women with gestational age > 49 weeks.

6.1.1.1.12. Results for the primary efficacy outcome

The overall medical abortion efficacy was 97.3% with 94.9% achieving successful abortion with one dose of misoprostol.

The rate of surgical evacuation was 2.7% and these were required for bleeding (1.6%), ongoing pregnancy (0.6%), persistent sac (0.2%) and pain (0.2%).

The success rate by gestational age is shown in Table 1 (below) and shows similar rates in those with gestation of over 49 days compared to those with gestation of 49 days or less (96.4% versus 98.0%). Success rate for primigravidas was 97.2% (342/352) and for multigravidas was 97.4% (603/619).

Table 1. Study 1.1.4 Success by gestational age.

SUCCESS BY GESTATIONAL AGE			N=971		
	≤ 49d n (%)	50-56d n (%)	57-63d n (%)	>64d	Total n (%)
Success	540 (98)	239 (96.8)	164 (95.9)	2 (100)	945 (97.3)
Surgical evacuation	11 (2)	8 (3.2)	7 (4.1)	0 (0)	26 (2.7)

Comment: There was no formal statistical testing to compare efficacy by gestational age.

6.1.1.1.13. Results for other efficacy outcomes

Not applicable.

6.1.2. Authorised prescriber program

6.1.2.1. Methods

In Australia, the sponsor Marie Stopes International Australia (MSIA) has collected efficacy and safety data during the Authorised Prescriber Program in 2012. Medical terminations were performed using mifepristone 200 mg followed by misoprostol 800 microgram bucally. If no bleeding occurred within 24 hours of the misoprostol dose a second 800 microgram dose was given. Patients were followed up at 14-21 days post mifepristone dose. Gestational age was determined by ultrasound.

6.1.2.2. Results

In 2012, there were 7166 medical terminations performed, 4488 (62.6%) had a pregnancy of < 49 GA, 1951 (27.2%) of 49-55 GA, 705 (9.8%) of 56-62 GA and 22 (0.3%) of 63 GA.

The overall success rate was 96.6% (6920/7166) with 3.0% requiring surgical aspiration for incomplete abortion and continuing pregnancy reported in 0.4%. Efficacy was 97.4% at < 49 GA and was similar at older gestational age groups: 94.6%, 96.9% and 95.5% at 49-55 GA, 56-62 GA and 63 GA, respectively (Table 2 below). There was a small trend for increasing rate of continuing pregnancy with increasing gestation (0.3%, 0.6%, 0.9%, 0% for <49, 49-55, 56-62 and 63 GA, respectively).

Table 2. Outcomes of pregnancies in women included in the MSIA Authorised Prescriber Program: data collected in 2012

Pregnancy age (GA, days)	< 49		49 - 55		56 - 62		63		All Women	
	n	%	n	%	n	%	n	%	n	%
Total	4,488		1,951		705		22		7,166	
Success	4,370	97.4	1,846	94.6	683	96.9	21	95.5	6,920	96.6
Incomplete abortion requiring surgical aspiration	103	2.3	94	4.8	16	2.3	1	4.5	214	3.0
Continuing pregnancy	15	0.3	11	0.6	6	0.9	0	0	32	0.4

Comment: Data from the Authorised Prescriber Program has been presented using gestational age groups of < 49 days and 49-63 days. In contrast, data from Study 1.1.4 categorised data at less than or equal to 49 days and 50-63 days. It would have been preferable to have the data presented in the same gestational age groupings. Nonetheless, the evaluator does not believe that the one day difference would have resulted in any clinically significant change in the results and as such the sponsor has not been requested to submit reanalysed data.

6.1.3. Literature review

6.1.3.1. Methods

The sponsor conducted a literature search of English published articles up to January 2013. Only completed studies from the clinicaltrials.gov site were included. Articles were included if they related to use of mifepristone 200 mg with misoprostol (any dose or route of administration) in early pregnancy termination to 63 days gestation and had data on efficacy by gestational age for the dose regimen. Articles were excluded if there was no relation to early pregnancy termination, it was not an original clinical trial, other medications were studied, the data source was unreliable or there was evidence of redundancy. The databases searched were: Cochrane Central Register of Controlled Trials (CCTR); Cochrane Database of Systematic Reviews (CDSR); Embase; Medline; Medline Daily; and Medline In-Process.

6.1.3.2. Results

The sponsor stated that there were 23 articles selected for review. Most articles that were rejected did not include efficacy data by pregnancy gestational age. The sponsor identified 6 reported studies which evaluated, in at least one arm, the combination of mifepristone 200 mg orally and misoprostol 800 microgram buccally. These studies included 399 women with pregnancies of gestational age (GA) 50-56 days, 344 with pregnancies of GA 57-63 and 46 with GA of 56-59.

Comment: In Module 2, the sponsor tabulated 23 articles and stated that 17 were rejected, 2 were kept for safety analysis and 4 kept for efficacy analysis. These 4 articles included 2 of the 6 discussed for efficacy below. From what was presented it was unclear what the actual results of the literature search were and how articles have been included or excluded. A question has been raised.

6.1.3.2.1. Winikoff 2008 (Reference 528)

This was a randomised, controlled trial of oral versus buccal misoprostol 800 microgram after mifepristone 200 mg in termination of pregnancy to 63 GA conducted in 966 women at seven sites in the USA. It reported that with increasing gestational age the success rate declined with

oral route for misoprostol while it was maintained with buccal misoprostol (GA 50-56: 88.8% oral versus 95.7% buccal; GA 57-63: 85.1% versus 94.8%). The difference was statistically significant for the older GA group of 57-63 days ($p < 0.048$).

Comment: This study provided the most robust evidence of improved efficacy of buccal over oral misoprostol 800 microgram at GA 50-63 days.

6.1.3.2.2. Chong 2012 (Reference 945)

This was a randomised controlled trial of 800 microgram versus 400 microgram buccal misoprostol after mifepristone 200 mg in termination of pregnancy to 63 GA. It was conducted in 1122 women in Vietnam and Georgia (Russia). It reported a success rate with buccal administration of 800 microgram of misoprostol of 98.5% at 50-56 GA and 93.0% at 57-63 days. This was similar to rates at GA of less than or equal to 49 days (95.8%-96.2%). The 800 microgram dose had significantly improved success over the 400 microgram dose at 50-56 GA (98.5% versus 94.3%, $p < 0.05$).

Comment: This study provided evidence of superiority of 800 microgram over 400 microgram buccal misoprostol for the older GA of 50-56 days.

6.1.3.2.3. Fjerstad 2009 (Reference 908).

This was a retrospective survey of 10 centres in the USA where medical termination of pregnancy was undertaken using mifepristone 200 mg followed by 800 microgram of misoprostol. Buccal misoprostol was introduced in 2006 at these centres. The study reported a success rate with buccal misoprostol after mifepristone of 95.7% to 98.3% for GA greater than or equal to 49 days, which was similar to earlier GA (98.1%-99.3%).

Comment: the retrospective nature of this study make the data less reliable.

6.1.3.2.4. Boersma 2011 (Reference 947).

This was a single centre, open-label, non-comparative study conducted at a general practice in Curacao which assessed medical abortion efficacy of 800 microgram buccal misoprostol after mifepristone in 330 women with pregnancies to 70 GA. The study only presented failure rates. The rate of suction curettage was 1.1%, 34.2% and 3.8% at less than or equal to 49 GA, 50-63 GA and 64-70 GA, respectively. This extrapolates to a success rate of 95.8% for 50-63 GA.

Comment: the study did not report success rates and extrapolating makes it less reliable.

6.1.3.2.5. Ngoc 2011 (Reference 948).

This was a double-blind, randomised placebo-controlled study of 400 women with GA to 63 days at a single centre in Vietnam. It compared two doses 24 hours apart of 800 microgram buccal misoprostol to 200 mg mifepristone followed by 800 microgram buccal misoprostol. For the mifepristone plus buccal misoprostol 800 microgram regimen, a low success rate of 89.3% for GA 50-56 was found although the success rate at GA 57-63 was 100%. This compared to a success rate of 97.5% at GA less than or equal to 49 days. Success with misoprostol only was low (76.2%).

Comment: The sample size for the two older GA groups were noted to be small (28 and 11 respectively) which may have contributed to the variable results.

6.1.3.2.6. Blum 2012 (Reference 949).

This was double-blind, randomised placebo-controlled study of 441 women presenting for medical abortion up to 63 days GA. It was conducted in Tunisia and Vietnam at two sites. Treatment was with mifepristone 200 mg followed by 800 microgram buccal misoprostol or 1600 microgram buccal misoprostol given as 2 doses of 800 microgram 3 hours apart. With the combination treatment of mifepristone and misoprostol, this study also reported a lower

success at GA 50-56 days (86.5%) which was not seen at GA 57-63 days (96.5%). Success at GA less than or equal to 49 was 96.3%. Efficacy for the misoprostol-only regimen was low (78.0%).

Comment: the reason for low efficacy at 50-56 GA is unclear.

6.1.3.2.7. Summary

The efficacy in terms of medical abortion success from these studies for the proposed regimen ranged from 86.5% to 98.5% at GA 50-56 and 93.0% to 100% at GA of 57-63. The rate of ongoing pregnancies from these studies ranged from 0 to 7.1%. A high rate of ongoing pregnancy was noted in references 948 (7.1%) and 949 (2.7%) in women with pregnancies of 50-56 GA, however this did not carry through to the 57-63 GA group where there were no ongoing pregnancies.

A systematic review (Raymond 2012) assessing first trimester medical abortion with mifepristone 200 mg and misoprostol identified 87 trials with 47,283 treated women for whom outcome data were available for 96%. The medical abortion failure rate in the subgroup who received mifepristone with misoprostol greater than or equal to 800 microgram for the various routes of administration of misoprostol was 3.2% (71/2205) for buccal, 6.5%(158/2449) for oral, 5.2% (52/1003) for sublingual and 3.4% (653/19210) for vaginal. There was no breakdown by gestational age.

The sponsor also provided literature-based data showing an unacceptably low efficacy when lower doses of misoprostol (200-600 microgram) were used with mifepristone 200 mg for pregnancies above 49 days gestational age GA greater than or equal to 50 days.

6.1.4. Evaluator's conclusions on clinical efficacy for medical termination of pregnancy

The sponsor submitted three sources of efficacy data to support the composite pack and the proposed change to indication extending the gestational age limit from 49 days to 63 days.

Study 1.1.4 was an open label, non-comparative study of mifepristone (200 mg oral) and misoprostol (800 microgram buccal) for medical abortion in 1000 women with pregnancies through 63 days of gestation. The overall medical abortion efficacy was 97.3%, with 94.9% achieving successful abortion with one dose of misoprostol. Success rates were marginally lower at 50-56 GA (96.8%) and 57-63 GA (95.9%) compared to less than or equal to 49 GA (98.0%) although still felt to be acceptable.

Under the Authorised Prescriber Program in Australia in 2012, there were 7166 medical terminations, with 2678 for GA greater than or equal to 49, performed using mifepristone 200 mg followed by misoprostol 800 microgram bucally. The overall success rate was 96.6% and success rates for GA 49-63 (94.6% to 96.9%) were in line with gestational age < 49 (97.4%). The ongoing pregnancy rate was slightly higher 0.6%-0.9% at 49-62 days compared to 0.3% at < 49 days.

The literature review was conducted and, while the dossier adequately discussed how the searches were undertaken, the actual studies identified and then rejected were not well described. The review included 6 studies (4 were controlled trials, one a retrospective survey and one a non-comparative single centre study). These assessed, in at least one group, the efficacy of the mifepristone 200 mg and buccal misoprostol 800 microgram combination for medical termination of pregnancy to 63 days. The efficacy reported was similar in three trials and lower in two. The range reported was 86.5-98.5% and 93.0-100% in the 50-56 GA and the 57-63 GA groups, respectively.

A systematic review reported improved efficacy with buccal over oral misoprostol although failed to breakdown data by gestational age (Raymond 2012). A randomised controlled study (Winikoff 2008) provided evidence for superior efficacy of buccal over oral misoprostol administration for pregnancies at 57-63 GA.

Success was similar between primi- and multigravidas and efficacy data were available in both Caucasian and Asian populations although no direct comparisons were made.

Abortion success rates for pregnancies 50-56 GA and 57-63 GA from the three data sources overall, indicate comparable efficacy of the mifepristone 200 mg and buccal misoprostol 800 microgram regimen at 50-63 GA and less than or equal to 49 GA.

Table 3. Efficacy rate for Mifepristone (200 mg) followed by misoprostol (800 microgram buccally) as a function of gestational age: 50-56 Days GA

Study Reference	No. of Women	Success Rate	Rate of Ongoing Pregnancies
528	93	95.7	0
945	204	98.5	0.5
908*	46	95.7	0.4
948	28	89.3	7.1
949	74	86.5	2.7
Study 1.1.4	252**	96.8	0.6***
MSIA APP	1951	94.6	0.6

* 56 – 59 GA; ** 49 – 55 GA; *** no information on GA

Table 4. Efficacy rate for Mifepristone (200mg) followed by misoprostol (800 microgram buccally) as a function of gestational age: 57-63 Days GA

Study Reference	No. of Women	Success Rate	Rate of Ongoing Pregnancies
528	115	94.8	1.7
945	86	93.0	2.3
947**	105	95.8	0.6
948	11	100	0
949	27	96.3	0
Study 1.1.4	177	95.9	0.6***
MSIA APP.	705	96.9	0.9

* 50 – 63GA; ** 55 – 62 GA; *** non information on GA

7. Clinical safety

7.1. Studies providing evaluable safety data

In the efficacy study 1.1.4, general adverse events (AEs) were collected at the exit interview. Pain was scored on a 7 point scale. Safety data were also sourced from the literature review and the report of the Authorised Prescriber Program. Two of the six identified studies of mifepristone and buccal misoprostol did not report adverse events (Boersma 2011, reference 947 and Fjerstad 2009, reference 908). Safety data from the other four studies were available.

7.2. Pivotal studies that assessed safety as a primary outcome

None.

7.3. Patient exposure

Study 1.1.4 included 1000 women with safety data available from 969 (GA less than or equal to 63). The data from the Authorised Prescriber Program included 7166 women, of these 4488 had pregnancies of less than 49 GA and 2678 of 50-63 GA.

7.4. Adverse events

7.4.1. All adverse events (irrespective of relationship to study treatment)

7.4.1.1. Pivotal study

In study 1.1.4, the rate of AEs was 88.5%. Pain and bleeding were expected events. Pain during the abortion was reported as less than expected in 26.3%, as expected in 26.9%, more than expected in 46.0% and don't know in 0.7%. Bleeding was reported as less than expected in 30.6%, as expected in 41.6%, more than expected in 27.1% and don't know in 0.7%.

The most frequent AEs were diarrhoea (59.5%), fever/chills (45.3%), nausea (34.2%), vomiting (26.4%), weakness (20.9%), headache (13.9%) and dizziness (13.1%).

The rate of severe events was as follows: vomiting (20.0%), fever/chills (19.6%), headache (17.0%), weakness (14.3%), dizziness (14.2%), nausea (13.9%) and diarrhoea (13.2%).

Comment: safety data were not broken down by gestational age.

7.4.1.2. Literature

The study of Winikoff (2008, reference 528) was a randomised, controlled trial which compared oral to buccal misoprostol 800microgram (after mifepristone 200 mg) in termination of pregnancy to 63 days. There were 415 and 420 women included in the safety analysis of buccal and oral misoprostol groups, respectively. Adverse event rates were generally comparable between the two routes of administration except for a significantly higher rate of fever/chills with buccal than oral misoprostol (41.4% versus 33.3%, p = 0.02) reported at exit interview. The reported rates of other AEs in the buccal versus oral misoprostol groups were nausea (66.0% versus 63.6%), vomiting (40.2% versus 39.5%), diarrhoea (33.7% versus 35.0%), headache (34.0% versus 31.0%), dizziness (32.8% versus 29.8%) and weakness (45.1% versus 42.9%). Adverse events were reported to be acceptable in 71.3% and 76.4% of all women who received buccal and oral misoprostol, respectively. The reported amount of bleeding and pain compared to patient's expectations was similar between groups except for more women stating the amount of pain was less than expected with oral misoprostol (38.6% versus 29.6%, less than 0.05).

The Blum study (2012, reference 949) compared the combination of mifepristone-misoprostol (800 microgram buccal) with misoprostol alone (1600 microgram). It reported that in the mifepristone-misoprostol group (n = 209) the most frequent AEs were: diarrhoea (61.2%), nausea (45.9%), vomiting (37.8%), chills (30.6%) and fever (28.2%). The rates of AEs were similar between treatment groups apart from a higher rate of diarrhoea with misoprostol monotherapy (83.9% versus 61.2%, p less than 0.001). The overall experience with adverse events was acceptable or very acceptable in 96.1% of the dual therapy group.

The Ngoc study (2011, reference 948) also compared misoprostol-mifepristone (800 microgram buccal) to misoprostol monotherapy (1600 microgram buccal). It reported in the 200 women who received mifepristone-misoprostol the following similar AE rates: diarrhoea (58.5%), nausea (56.5%), vomiting (26.0%), chills (32.5%) and fever (24.5%). Again the main difference in AE rates between treatment groups was for diarrhoea (71% monotherapy versus 58.5% combination, p = 0.006). The overall experience was acceptable in 98.2% of the combination group.

In the larger study of Chong (2012)(reference 945) two doses of buccal misoprostol (400 microgram and 800 microgram) were compared when used in combination with mifepristone 200 mg. For the 563 women in the 800 microgram buccal misoprostol group, the reported AE rates were: pain/cramps (81%), nausea (47%), weakness (42%), fever/chills (33%), headache (33%), dizziness (24%) and vomiting (22%). Diarrhoea was not reported. Events of vomiting and fever/chills were significantly lower with the 400 microgram dose. The adverse effects were acceptable in 85% and 86% of the 800 microgram and 400 microgram groups, respectively.

Comment: safety data from the literature were not available broken down by gestational age.

7.4.1.3. Authorised prescriber program

In the 7166 subjects included in the MSIA Authorised Prescriber Program in 2012, there were 271 adverse events. The rate of AEs by gestation was 2.9%, 5.8%, 4.0% and 4.6% for less than 49 GA, 49-55 GA, 56-62 GA and 63 GA, respectively. Overall, the rate of haemorrhage (with or without transfusion) was 0.32%, infection (known or suspected) was 0.54% and drug reaction to misoprostol was 0.07%. There was a trend for increasing haemorrhage without transfusion with increasing GA (0.04%, 0.12%, 0.57% and 4.6% at less than 49 GA, 49-55 GA, 56-63 GA and 63 GA, respectively).

7.4.1.4. Other studies

All 18 subjects in the pharmacokinetic study MCPK12001J1 reported at least one AE. These included diarrhoea, abdominal pain, vaginal bleeding, nausea, vomiting, hand itch, needle phobia, chilliness and cheek swelling.

7.4.2. Treatment-related adverse events (adverse drug reactions)

7.4.2.1. Pivotal study

Treatment-related AEs were not reported separately in Study 1.1.4.

7.4.2.2. Other studies

Adverse event data in the literature were not separated by suspected causality.

7.4.3. Deaths and other serious adverse events

7.4.3.1. Pivotal study

There were no deaths reported in Study 1.1.4. The rate of SAEs was 1.1% (11/971) with all being hospitalisations for dilatation and curettage (D&C) due to “problematic bleeding”. One woman required a blood transfusion (0.1%) and one IV antibiotics (0.1%).

> Comment: no further details were provided and only very brief narratives were included in the CSR.

7.4.3.2. Other studies

There were no deaths in the Authorised Prescriber Program data analysed. The overall rate of incomplete abortion requiring surgical aspiration was 3.0%. The rate of haemorrhage requiring transfusion was 0.02%, 0.15%, 0.14% and 0% at less than 49 GA, 49-55 GA, 56-63 GA and 63 GA, respectively. There were no cases of pain requiring hospital treatment.

There were no deaths or SAEs in the PK study MCPK12001J1.

There were a number of significant adverse events reported from the literature search. These included:

- Acute necrotising pancreatitis following second trimester TOP with mifepristone 600 mg and gemeprost (reference 980, Hallberg 2004).

- Vasospastic angina pectoris with loss of consciousness, bradycardia and seizures following mifepristone 600 mg and gemeprost 1 mg (reference 981, Lindhardt 2000).
- Uterine rupture following termination of pregnancy at 12 weeks with mifepristone 200 mg and misoprostol 800 microgram vaginally and 400 microgram orally (reference 982, Willmott 2008).
- Birth of child with Mobius syndrome (facial palsy, microretrognathia, axial hypotonia) following foetal exposure to mifepristone 600 mg and misoprostol 400 microgram orally during 7th week of pregnancy (reference 983, Bos 2008).
- Congenital abnormalities (vascular abnormalities and early amniotic rupture with resultant limb deformities) were reported in two cases with exposure during pregnancy to misoprostol (reference 984, Rosa 2007 and reference 985, Genest 1999)
- A reported congenital malformation rate of 4.2% in a prospective review of 105 pregnancies exposed of mifepristone or mifepristone and misoprostol (reference 987, Bernard 2013).

7.4.4. D**iscontinuation due to adverse events**

7.4.4.1. Pivotal study

Not reported.

7.4.4.2. Other studies

In study MCPK12001J1, the discontinuation due to an AE was 6/18 (33.3%).

7.5. Laboratory tests and vital signs

Laboratory parameters and vital signs were not collected in Study 1.1.4. There were no reported abnormalities on laboratory parameters or vital signs in the pharmacokinetic study MCPK12001J1.

7.6. Post-marketing experience

The dossier included two PSURs. The mifepristone Linepharma 200 mg tablet PSUR number 4 covered the period from 29 June 2012 to 28 December 2012 during which 20,669 packs containing 1 tablet and 312 packs of 30 tablets were distributed worldwide. The total patient exposure during the period was 24,379 women. There was only one reported case with two events “feeling unwell” and “stomach flu” which were non-serious. There was a second case of disease progression and death in a compassionate use patient with Cushing syndrome and metastatic adrenal carcinoma.

The GyMiso (misoprostol) 200 microgram tablet PSUR covered the period from 29 October 2012 to 28 April 2013. This was the first Australian PSUR for GyMiso following approval on 29 August 2012. During the period a total of 13138 packs (containing 2 x 200 microgram tablets) were distributed in France. There was no distribution in Australia. (It is noted that the pack size in Australia is 4x 200 microgram). A further 1960 packs were distributed for Gynuity Health Projects leading to a total patient exposure of 15,098 women. There were no reported adverse events during the period. There was however a report in May 2013 of a death of a 42 year old woman who took mifepristone Linepharma 200 mg followed by misoprostol 800 microgram (different brand) a day later at 47 days of gestation. The patient developed sepsis with acute renal failure and died 12 days after taking the medication.

7.7. Evaluator's overall conclusions on clinical safety

The three safety data sources in the dossier were the Phase III Study 1.1.4, the Authorised Prescriber Program in Australia and a literature review. Study 1.1.4 included 1000 women with safety data available from 969 and provided non-comparative safety data on the proposed regimen of mifepristone and buccal misoprostol 800 microgram, but did not break down AEs by gestational age. The Authorised Prescriber Program data included 7166 women, of these 4488 had pregnancies of gestational age less than 49 days and 2678 of 50-63 days. This provided safety data on the regimen by gestational age. One study from the literature provided randomised comparative data for buccal and oral routes of administration of misoprostol 800 microgram.

The Phase III study reported frequent adverse events with the treatment regimen, in particular diarrhoea, fever/chills, nausea, vomiting and weakness, although the events were mainly mild to moderate in severity. Four studies in the literature review which assessed 800 microgram buccal misoprostol with mifepristone reported a similar profile and frequency of adverse events to the sponsor's Phase III trial. In addition, the overall experience with adverse events was deemed acceptable or very acceptable in the majority of women (70-98%).

A randomised controlled trial (Winikoff 2008) found the rate of AEs was similar between buccal and oral misoprostol administration except for a significantly higher rate of fever/chills with the buccal route (41% versus 33%). Adverse events were reported as acceptable in at least 70% of women with no apparent difference between the routes of administration.

From the Australian Authorised Prescriber Program, the rate of AEs was slightly higher for gestational age of greater than or equal to 49 days than less than 49 days (2.9%, 5.8%, 4.0% and 4.6% for less than 49 GA, 49-55 GA, 56-62 GA and 63 GA, respectively), although the number of abortions at greater than or equal to 56 GA were low. There appeared to be a small but increasing risk of haemorrhage with increasing GA. The numbers, however, were low and so it is difficult to draw definitive conclusions on this potential risk.

There were no deaths reported in the clinical trials or Authorised Prescriber Program data analysed. There was one death from sepsis 12 days post treatment reported in post-marketing surveillance. The subject had received mifepristone and a different brand of misoprostol at 47 GA. Serious adverse events occurred in 1.1% of the study 1.1.4 population. All were related to hospitalisation for D&C to manage bleeding. There was one reported case requiring transfusion and one IV antibiotics (0.1% each). In the Authorised Prescriber Program the rate of rate of incomplete abortion requiring surgical aspiration was 3.0%, haemorrhage requiring transfusion 0.07%, haemorrhage not requiring transfusion 0.25% and infection (known or suspected) 0.54%.

Other risks identified from the literature included acute necrotising pancreatitis, vasospastic angina pectoris and uterine rupture.

> Comment: The sponsor stated that pancreatitis would be added to the product information.

Congenital abnormalities following foetal exposure were reported (Mobius syndrome, vascular abnormalities and limb deformities following to amniotic membrane rupture). A prospective study of 105 pregnancies exposed to mifepristone with or without misoprostol found a congenital malformation rate of 4.2%.

Post-marketing data from the two most recent PSURs were unremarkable apart from the death discussed above.

8. First round benefit-risk assessment

8.1. First round benefit-risk assessment

8.1.1. First round assessment of benefits

The benefits of mifepristone/misoprostol in the proposed usage are:

- Efficacy demonstrated to 63 GA with similar efficacy at ≤49 GA and 50-63 GA.
- The buccal route of misoprostol administration was efficacious and, from the literature, had greater efficacy than the oral route for GA >57-63.
- Physician and patient convenience of a combination pack supplying the two medications in the correct dosage.
- An alternative to surgical abortion for GA 50-63.

8.1.2. First round assessment of risks

The risks of mifepristone/misoprostol in the proposed usage are:

- Frequent adverse events of nausea, vomiting, diarrhoea, fevers/chills and weakness. The rate of fever/chills was higher with buccal than oral misoprostol, however patient acceptability was similar.
- Haemorrhage and the potential need for transfusion.
- Infection including endometritis and septic shock which may be fatal.
- Method failure and need for subsequent surgical intervention.
- Ongoing pregnancy with a risk of malformations from foetal exposure.
- Severe asthma risk with prostaglandins and prostaglandin analogues.
- Limited data in women under 18 years of age.
- Lack of follow up of patients post treatment.

8.1.3. First round assessment of benefit-risk balance

The current application had two purposes: to register a combination pack of mifepristone and misoprostol and to extend the indication for medical abortion to pregnancies of gestational age up to 63 days (from 49 days). For this extended gestational age group of 50-63 days it is proposed that the route of administration of misoprostol is buccal rather than being optional buccal or oral.

The proposal of a combination pack containing both mifepristone and misoprostol makes clinical sense in that it provides the two required products together. This may assist patients with taking the medication in the correct order and may lead to improved compliance with taking the second component of the treatment regimen. It is noted, however, that no data on lack of compliance with the misoprostol tablets were provided to demonstrate that this actually is an issue in clinical practice.

The sponsor provided three sources of data to support extending the indication out to 63 days of gestation. The submitted Phase III clinical trial was open label and non-comparative with data summarised in a clinical study report which appeared abbreviated. In addition, while efficacy was provided by gestational age, this was not the case for the safety data. The trial data were supported by the larger dataset from the Authorised Prescriber Program in Australia which did provide some safety data by gestational age. The efficacy data from the literature were also

supportive, although the evaluator found a lack of detail on the search methodology and a question on this has been raised.

When combining the three sources of data, which covered a variety of settings and populations, an efficacy rate of about 95% was reported for the extended gestational age of 50 to 63 days. There appeared to be a very small numerical decline in efficacy with increasing gestational age, the significance of which could not be confirmed due a lack of statistical testing. Nonetheless, the evaluator believes the efficacy rates at this later gestation are sufficiently similar to that seen at <49 days and are clinically acceptable.

Safety for the extended gestation was primarily assessed from the Authorised Prescriber Program dataset which was moderate in size (approximately 2600 in the 49-63 GA group). In general, the safety risks were similar across the gestational age groups apart from a small increasing risk of haemorrhage, although the numbers on which this was based were limited. Sepsis is the other major risk and one death was reported from post-marketing surveillance. There was no indication that this risk was increased in the 50-63 gestational age group. These risks will need ongoing monitoring as the dataset is too small to detect differences in such rare events.

It is noted that the sponsor does not propose to extend the gestational age for the respective monotherapies. If medical termination was required at 50 to 63 GA, the treatment would be with the two agents and so the composite pack would have to be prescribed rather than the two monotherapies. However, should a second dose of misoprostol be required, this would be prescribed as a monotherapy and the prescriber would be forced to use it off label as its current indication is to “up to 49 days”. This conflict needs to be addressed by the sponsor. The sponsor has also been requested to justify why there is no intention to change in the mifepristone indication.

In terms of the route of administration of misoprostol at 50 to 63 gestational age, there was evidence for improved efficacy with buccal compared to oral misoprostol in a randomised controlled trial in the literature, particularly for GA 57 to 63 days. These data were supported by non-comparative data from the clinical trial and the Authorised Prescriber Program. The safety of buccal compared to oral misoprostol was found to be similar, apart from an increased risk of fever/chills and patient acceptability, as reported in the literature, was also similar. Given these factors, the evaluator agrees with the sponsor that misoprostol must be given by the buccal route for GA 50 to 63 days. Nonetheless, the current dosage and administration instructions appear overly complicated. Given the positive data on buccal administration it would seem more sensible to offer only one route of administration across gestational ages. Therefore, the sponsor has been asked to justify the proposed dosage instructions.

Overall, the dossier provided evidence on the safety of the mifepristone/misoprostol combination from the clinical trial and the Authorised Prescriber Program which included over 3000 terminations at 49 to 63 days. No new safety signals were identified apart from a single reported case in the literature of acute necrotising pancreatitis. This has been included in the product information. The major safety risks with the combination are rare, the reported risk of haemorrhage requiring transfusion was ≤0.15% at 49 to 63 GA, and, as mentioned above, the overall haemorrhage risk appeared to increase with gestational age. Given these factors, the evaluator believes it is necessary to formally continue to assess risks in the older gestational age group. It is noted that there is a phase IV study proposed to assess adverse event, failure and follow up rates in the ≤49 GA group. This study could be extended to include the 50 to 63 GA group with appropriate adjustment of the sample size so that comparisons by gestational age may be undertaken.

Other risk management processes must continue such as appropriate training of medical practitioners, limiting the access and distribution of the medicines to appropriate practitioners

and mandatory follow up of patients. In addition, there should be ongoing monitoring of off label use beyond 63 days as well as in women aged <18 years in whom safety data are lacking.

There are several changes that need to be made to the product information. In particular, the Clinical Trial section needs rewording to adequately describe the sources of efficacy and safety data and the Precautions section need to be made clearer.

In summary, the evaluator finds that the possible small increase in risk of haemorrhage does not outweigh the similar efficacy and tolerability seen with the combination for the older gestation group of 50 to 63 days. At this gestation, the buccal route of administration is found to be necessary to maintain efficacy. There is also a clinical place for an option of medical rather than surgical termination at this gestation. Nonetheless, the safety risks warrant further elucidation and the evaluator recommends post-marketing surveillance in the extended gestational age group and continuation of the active risk management program which includes mandatory patient follow up. There are also a number issues which need to be addressed prior to any recommendation being made on approval. In particular, the sponsor needs to address the discordance of the indication between the composite pack and the monotherapies and look at simplification of dosage and administration instructions.

9. First round recommendation regarding authorisation

Responses to the evaluator's questions are required prior to the evaluator being able to make a recommendation on the authorisation of MS-2 Step, a combination pack of mifepristone and misoprostol with the following indication:

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

Any possible future authorisation would need to be subject to:

Conduct of post-marketing surveillance, such as via a Phase IV study, to further detail rare safety risks in the gestational age group of 50-63 days. This study could be incorporated in the proposed HREC2012001 study with appropriate amendments and sample size adjustment. Risks will need to be regularly monitored in the gestational age groups during the conduct of the study to ensure continued positive benefit-risk balance. Monitoring should be conducted by an independent safety monitoring committee.

Maintenance of an active risk management program which includes physician training, controlled medication access and distribution, and mandatory patient follow up.

10. Clinical questions

10.1. Pharmacokinetics

Not applicable.

10.2. Pharmacodynamics

Not applicable.

10.3. Efficacy and safety

There are two key questions for this application:

1. It is noted that there is no proposal to extend the gestational age for the respective monotherapies. If medical termination was required at 50-63 GA, the treatment would be with the two agents and so the composite pack would have to be prescribed rather than the two monotherapies. However, should a second dose of misoprostol be required in this scenario, this would be prescribed as a monotherapy and the prescriber would be forced to use it off label as its current indication is to "up to 49 days". Could the sponsor explain the rationale for not proposing a concordant change in the indication for GyMiso?
2. Could the sponsor also discuss why there is no intention to apply for an altered indication for mifepristone in relation to gestational age of 50 to 63 days?

The dosing instructions need to be clarified:

3. Given the efficacy with buccal administration of misoprostol across the proposed gestational ages, it is not clear why the buccal route is not proposed for all women. The sponsor should outline the rationale for the dosage and administration instructions and discuss options for making these simpler.

Other questions relating to the evidence base:

4. In light of the data from study 1.14 being pivotal in supporting an extension of gestational age to 63 days, it is important to determine the accuracy of the GA variable. From the study report it was not clear if women had an ultrasound to confirm gestational age or if this was solely determined by the date of the last menstrual period. What were the methods used for determining gestation and what was the frequency of use of these methods in the Mexican study? Similarly, how was gestation determined in the Authorised Prescriber Program? Discuss if potential inaccuracies in GA determination could have influenced results.
5. Could the sponsor confirm if all women in the Authorised Prescriber Program took the misoprostol 800 microgram via the buccal route? If not, provide frequency of use for the different routes of administration. Are there any data on acceptability of this route of administration?
6. In Module 2, a literature search method has been outlined and then 23 articles have been tabulated. It is stated that 17 of these articles were rejected, 2 were kept for safety analysis and 4 kept for efficacy analysis. These 4 articles included 2 of the 6 discussed for efficacy. Given the difference in this reported literature search output and the literature actually analysed, it is not clear how the process has been conducted. This needs clarification. Include the actual results of the literature search and describe which articles have been included or excluded for the relevant efficacy and safety issues discussed in the dossier.

11. Second round evaluation of clinical data submitted in response to questions

No formal second round evaluation was conducted for this submission. The sponsor's responses were noted and considered by the Delegate prior to the Delegate's Overview.

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