



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for misoprostol

Proprietary Product Name: Misodel/Misopess

Sponsor: Ferring Pharmaceuticals Pty Ltd

April 2014

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 AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Copyright

© Commonwealth of Australia 2014

This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the *Copyright Act 1968* or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given specific written permission from the Commonwealth to do so. Requests and inquiries concerning reproduction and rights are to be sent to the TGA Copyright Officer, Therapeutic Goods Administration, PO Box 100, Woden ACT 2606 or emailed to <tga.copyright@tga.gov.au>.

Contents

Abbreviations Table	5
I. Introduction to product submission	7
Submission details	7
Product background	8
Regulatory status	9
Product Information	9
II. Quality findings	9
Drug substance (active ingredient)	9
Drug product	11
Biopharmaceutics	11
Quality summary and conclusions	13
III. Nonclinical findings	14
Introduction	14
Pharmacokinetics	14
Toxicology	15
Nonclinical summary and conclusions	16
IV. Clinical findings	16
Pharmacokinetics	17
Pharmacodynamics	18
Dosage selection for the pivotal studies	19
Efficacy	19
Safety	23
First Round Benefit-Risk Assessment	24
First Round Recommendation Regarding Authorisation	25
Clinical Questions	26
V. Pharmacovigilance findings	26
Risk management plan	26
VI. Overall conclusion and risk/benefit assessment	34
Quality	34
Nonclinical	34
Clinical	34
Efficacy	34
Safety	35
Table 7. Caesarean section rate	35
Risk management plan	37

Delegate's considerations	38
Outcome	47
Attachment 1. Product Information	48
Attachment 2. Extract from the Clinical Evaluation Report	48

Abbreviations Table

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
AE	Adverse event
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
AUC	Area under the plasma concentration time curve
AUC _{0-t}	The area under the plasma concentration time curve over a dosing interval
BHA	Butylated hydroxyanisole
C _{max}	Maximum concentration
CTG	Cardiotocograph
DVI	Dinoprostone vaginal insert
EU	European Union
FDA	Food and Drug Administration
GCP	Good clinical practice
GI	Gastrointestinal
GMP	Good manufacturing practice
GRAS	Generally recognised as safe
ICU	Intensive Care Unit
IR	Infrared
MBS	Modified Bishop Score
MRP	Modified release pessary (vaginal insert)
MTD	Maximum tolerated dose
MVI	Misoprostol vaginal insert
NICE	National Institute for Health and Care Excellence
NOEL	No observable effect level
PD	Pharmacodynamic

Abbreviation	Meaning
PI	Product Information
PK	Pharmacokinetics
PO	Oral
PSUR	Periodic safety update reports
RMP	Risk Management Plan
$t_{1/2}$	Half life
T_{max}	The time after administration of the drug when maximum plasma concentration is reached.
TTC	Threshold of toxicological concern
USA	United States of America

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Major variation (extension of indication, new dose form, new route of administration).
<i>Decision:</i>	Approved
<i>Date of decision:</i>	21 February 2014
<i>Active ingredient:</i>	Misoprostol
<i>Product name(s):</i>	Misodel, Misopess
<i>Sponsor's name and address:</i>	Ferring Pharmaceuticals Pty Ltd PO Box 135 Pymble NSW 2073
<i>Dose form:</i>	Modified release pessaries
<i>Strength:</i>	200 micrograms (mcg)
<i>Container:</i>	Aluminium desiccant foil
<i>Pack size(s):</i>	1 (one) and 5 (five).
<i>Approved therapeutic use:</i>	Indicated for the induction of labour in women with an unfavourable cervix, from 36 weeks gestation: <ul style="list-style-type: none">· in whom induction is clinically indicated· in a hospital where continuous electronic foetal monitoring is available.
<i>Route of administration:</i>	Vaginal insert.
<i>Dosage:</i>	Misodel is a controlled release vaginal insert containing 200 micrograms of misoprostol which is released at a mean rate of approximately 7 micrograms/hour over a period of 24 hours. The maximum recommended dose is one Misodel vaginal insert (200 micrograms). Remove Misodel <ul style="list-style-type: none">· at the onset of labour· if uterine contractions are prolonged or excessive· if there is evidence of foetal compromise or· if 24 hours has elapsed since insertion.

If Misodel falls out do not replace it.

In case of subsequent administration of oxytocin a waiting period of at least 30 minutes is recommended following the removal of the vaginal insert.

ARTG number (s): 205336 and 205341

Product background

This AusPAR describes the application by the sponsor to register misoprostol (Misodel, Misopress) for the following indication;

For induction of labour in women with an unfavourable cervix, from 36 weeks gestation:

- *in whom induction is clinically indicated*
- *in a hospital where continuous electronic foetal monitoring is available.*

Misoprostol is a synthetic analogue of prostaglandin E1, an oxytocic compound. Prostaglandins initiate the process of cervical ripening for delivery and sensitise the myometrium to oxytocin.

Misoprostol is registered as an oral tablet (each tablet is 200 mcg) for upper gastrointestinal ulceration (Cytotec, Pfizer) and for medical termination of pregnancy (in combination with mifepristone) before 49 days (GyMiso, Ms Health).

Misoprostol tablets are sometimes used off label for the indication that is the subject of this submission: induction of labour at term; tablets are administered orally, buccally or vaginally. The extent to which off label use occurs in Australia is unknown.

At the time of this submission misoprostol tablets are not approved for this indication (that is, induction of labour) in Australia or other similar countries.

A Cochrane review of misoprostol use for induction of labour identified 121 studies. It found that misoprostol tablets (used off label), reduce the time to delivery but increase uterine hyper stimulation and meconium stained liquor.

The disadvantages of off label use of misoprostol 200 mcg tablets for cervical ripening and induction of labour are inconsistent dose, the need for repeated vaginal examinations, and the administered dose cannot be removed if labour commences or adverse events occur.

The sponsor has applied for registration of a new form of misoprostol: a controlled release vaginal insert (MVI), containing a 200 mcg dose reservoir of misoprostol. The product can be removed if labour starts or adverse events occur (a putative advantage over off label use of the tablets). This is potentially safer and more effective than the current off label use of misoprostol oral tablets for vaginal administration for the induction of labour

The product (MVI) is to be marketed in individual sealed aluminium/polyethylene laminate sachets each containing 1 pessary (vaginal insert), in packs of 1 and 5. It is only intended for use in hospitals.

The MVI contains 200 mcg of misoprostol as the active ingredient and BHA as an antioxidant but is otherwise identical to the 10 mg dinoprostone vaginal insert (DVI), which is also manufactured by Ferring Controlled Therapeutics Ltd, and is marketed in Australia.

A hydrogel polymer was selected as the drug delivery system for MVI because it gives controllable swelling kinetics, which has a direct impact on the drug release

characteristics of the polymer, enabling accurate dose delivery gradually over a 24 hour period.

About 1 in 5 pregnant women, whose pregnancies reach 36 weeks, require medical intervention to induce labour. Common reasons for induction include post term pregnancy, hypertension, diabetes, and intra uterine growth restriction

Many methods to induce labour are used, including mechanical (for example, membrane stripping or sweeping, Foley catheter insertion, amniotomy) and pharmacologic agents (for example, oxytocins, and prostaglandins). Prostaglandin E2, (dinoprostone) is the only prostaglandin registered in Australia for cervical ripening in pregnant women at or near term with a medical or obstetric need for induction of labour. There are two forms, Prostin E2, (dinoprostone 2 mg vaginal gel) and Cervidil/Propess (dinoprostone 10 mg vaginal insert).

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 21 February 2014.

At the time the TGA considered this application, similar applications had been submitted in the United States (US), the European Union (EU), Canada and Switzerland. The indications are below:

- US: Application date 27 July 2012 for '*decreasing the time to safe vaginal delivery in women with an unfavorable cervix (modified Bishop Score (mBS)¹) less than or equal to 4) when used in a sequential regimen with oxytocin augmentation, if needed.*'
- EU: Application date 27 July 2012 for '*induction of labour in women with an unfavourable cervix at or near term from 36 weeks gestation, in whom induction is clinically indicated.*'
- Canada: Application lodged in April 2012, the indication was not provided.
- Switzerland: Application lodged on 28 September 2012 for '*induction of labour in women with an unfavourable cervix at or near term, from 36 weeks gestation, in whom induction is clinically indicated.*'

The product has been approved in Mexico as Myspess in dose reservoirs as 100 mcg and 200 mcg misoprostol in June 2010 but has not yet been launched.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared and can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

II. Quality findings

Drug substance (active ingredient)

Misoprostol is a synthetic analogue of Prostaglandin E1 (PGE1), a naturally occurring oxytocic compound. Prostaglandins of the F and E series have been shown to increase

¹ Bishop score, also known as Bishop's score and as cervix score, is a pre-labour scoring system to assist in predicting whether induction of labour will be required.

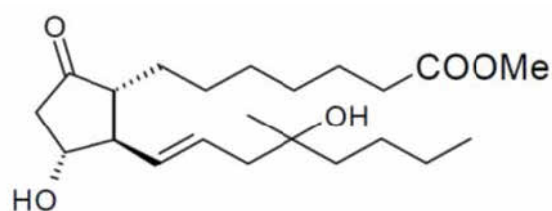
collagenase activity in rabbit uterine cervix fibroblasts in vitro and to cause cervical ripening and uterine contraction in vivo. These pharmacodynamic effects are considered to be the mechanism of action relevant for the clinical effect of the proposed product. PGE analogues also have a number of other effects, for example, relaxation of bronchial and tracheal muscles, increase of mucus secretion and decrease of acid and pepsin secretion in the stomach, increase of renal blood flow, increase of circulating concentrations of adrenocorticotrophic hormone and prolactin. These pharmacodynamic effects are considered to be of no clinical importance with the short treatment.

In non pregnant women, the proposed vaginal insert has a controlled mean in vivo release rate of approximately 7 mcg/hour over a period of 24 hours.

The maximum oral dose of Misoprostol is 1200 mcg per day when used for prevention of stress induced mucosal bleeding and lesions in post-surgical intensive care unit (ICU) patients (Cytotec PI). For the proposed product, indication and route of administration, the maximum exposure is 200 mcg in a single dose, releasing approximately 168 mcg in a 24 hour period, based on the release rate of 7 mcg per hour.

Misoprostol has the chemical structure, nomenclature and basic physical properties shown below:

Figure 1. misoprostol



Chemical-name/s [□]	(±)-(11a,13E)-11,16-dihydroxy-16-methyl-9-oxo-prost-13-en-1-oic-acid-methyl-ester [¶] OR [¶] Prost-13-en-1-oic-acid, 11,16-dihydroxy-16-methyl-9-oxo-, methyl-ester, -(1R*,2R*,3R*,E)- [¶] OR [¶] (±)-Methyl{1R,2R,3R}-3-hydroxy-2-[(E)-(4R5)-4-hydroxy-4-methyl-1-octenyl]-5-oxocyclopentaneheptanoate [¶] OR [¶] Mixture of Methyl-7-[(1R5,2R5,3R5)-3-hydroxy-2-[(1E,4R5)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl]heptanoate and Methyl-7-[(1R5,2R5,3R5)-3-hydroxy-2-[(1E,4SR)-4-hydroxy-4-methyloct-1-enyl]-5-oxo-cyclopentyl]heptanoate [¶]
Australian-Approved-Names: (AAN) [□]	Misoprostol (BAN) [□]
Synonyms [□]	Misoprostol-anhydrous [□]
CAS-Number [□]	59122-46-2 [□]
Molecular-Formula [□]	C ₂₂ H ₃₈ O ₅ [□]
Molecular-Weight [□]	382.53 g/mol [□]
Appearance [□]	Clear, colourless or light yellow viscous liquid. [□]
Solubility [□]	Soluble in ethanol (96%), ethyl acetate, acetone, toluene and tetrahydrofuran. Practically insoluble in water and hexane and sparingly soluble in acetonitrile. [□]
Hygroscopicity [□]	Hygroscopic. [□]

Drug product

Quality control of the drug substance applied by finished product manufacturer

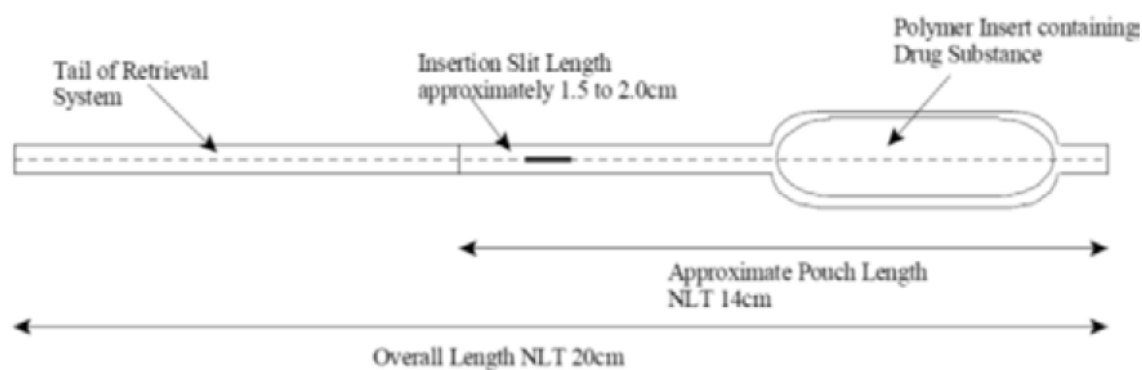
It is recommended that the sponsor be requested to provide to the TGA a copy of the formal Good Manufacturing Practice (GMP) drug substance specification that is signed and dated and includes a unique document number and expiry/revision date.

The sponsor has been requested to better define the Infrared (IR) identification procedure used

Description and Composition

The misoprostol modified release pessaries are referred to as Misoprostol Vaginal Insert (MVI) throughout the dossier, this being the pharmaceutical dose form description used in the USA. The correct dose form in Australia is modified release pessary. The pessary consists of a hydrogel polymer vaginal insert containing 200 mcg misoprostol. The insert is contained within a polyester retrieval system:

Figure 2. misoprostol product



The non-biodegradable hydrogel polymer insert (cross linked polyethylene oxide/urethane polymer) measures approximately 30 mm in length, 10 mm in width and 0.8 mm in thickness. It is rectangular in shape with radiused corners, buff coloured and semitransparent. The polyester retrieval system consists of an inert woven polyester pouch and tail.

A 5% overage is used in the solution to load the polymer, which is acceptable; the overage required to achieve the desired loading of 200 mcg per insert is determined by the loading solvent used and loading conditions (duration, concentration, temperature, agitation, etcetera), and is therefore determined by the method of manufacture.

None of the excipients used in the pessary are of human or animal origin; they are all of synthetic origin.

Biopharmaceutics

No specific bioequivalence or bioavailability studies have been included in the dossier, based on the sponsor's assessment that the relevant guidelines do not specifically address the circumstances of the present application, which is for a new indication, new dose form, and a new route of administration of a well known substance.

The development of the proposed product relies on relevant clinical and nonclinical studies to demonstrate efficacy and safety of the new dosage form of a well known substance for a new indication and route of administration, and the sponsor has stated that, in this situation, bioequivalence to the "originator" product, namely Cytotec (misoprostol) tablets for gastrointestinal (GI) indications, is neither relevant nor

appropriate. Moreover, the sponsor has indicated that as misoprostol is not a new chemical entity, absolute bioavailability studies are also not necessary.

Justification of the above has been provided, specifically addressing the requirements outlined in the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) Appendix 15.² For Section 3 of the Appendix (Products for which Biopharmaceutic Studies need to be submitted), sub-sections 3.1 to 3.3 and 3.5 to 3.7 were not applicable to this application (that is, new innovator medicine containing a new chemical entity, new salt, new fixed combination product, new strength, new generic medicine, new formulation of a registered product where the change(s) may affect bioavailability). Sections 3.4 and 3.8 were considered relevant for this application; however the sponsor has argued that they cannot be applied to the proposed product.

New dose form

The biopharmaceutic data usually required for a new dose form is bioequivalence of the new dose form to the currently approved dose form(s). As there is no approved dose form for the intended indication and route of administration of misoprostol, and no accepted target pharmacokinetic parameters to reference, the sponsor argued that there is no relevant comparator for such a study, and indicated that while there is off label vaginal use of misoprostol oral tablets (Cytotec) it would not be appropriate to conduct a bioequivalence study in such circumstances.

In an effort to quantify relative blood levels and thus assure relative safety of the proposed new dose form and route of administration, an estimate of comparative bioavailability of the inserts at 100 mcg, 200 mcg and 400 mcg reservoirs versus 200 mcg oral Cytotec tablets was assessed in non-pregnant women in a pharmacokinetic (PK) Study Miso-Obs-001. The main conclusions from this study were that the area under the plasma concentration time curve over a dosing interval (AUC_{0-t}) and the maximum concentration (C_{max}) were dose proportional for the 100 mcg through to the 400 mcg inserts, that misoprostol acid was eliminated rapidly from the systemic circulation, and that total exposure to misoprostol acid from the 200 mcg insert after 24 hours in situ was approximately 2.8 fold higher than that of a single 200 mcg dose of oral Cytotec. The data also indicated that the C_{max} was 12% that of Cytotec. The sponsor indicated that this provides reassurance that the formulation will not reach the high systemic concentrations observed for Cytotec.

Use of an overseas reference product in Study Miso-Obs-001

The TGA requested that the application should justify the use of an overseas sourced referenced product (Cytotec), if applicable. The sponsor has provided a justification for not using an overseas reference product, with reference to the requirements of ARGPM Appendix 15, Section 7:

- Cytotec is a conventional immediate release oral dosage form
- Cytotec is registered in and was obtained in the UK, a country with a regulatory system comparable to Australia
- Cytotec was marketed by the innovator company, Pharmacia, in the same dosage form and strength in Australia as in the UK (Pharmacia has since been acquired by and merged into Pfizer worldwide)

² Department of Health and Ageing, Australian regulatory guidelines for prescription medicines, Appendix 15: Biopharmaceutic studies, June 2004 <<http://www.tga.gov.au/pdf/pm-argpm-ap15.pdf>>

- Product Information has been provided for the UK and Australian product. These documents show that the qualitative composition of Cytotec is identical: microcrystalline cellulose, hypromellose, sodium starch glycollate and hydrogenated castor oil.

The sponsor has stated that the quantitative composition of the excipients is not known, and no comparative analyses have been provided. Discussion of the pharmacokinetic and safety profile of misoprostol has not been included in the discussion.

While the information given for the justification does not meet the usual requirements for use of a non-Australian reference product, the pharmacokinetic parameters obtained for the Cytotec batch used in Study Miso-Obs-001 (that is, the time after administration of a drug when the maximum plasma concentration is reached (T_{max}) equals 19 minutes, half life ($t_{1/2}$) equals 37 minutes) are similar to those given for the innovator product in the Australian Cytotec PI (T_{max} approximately equal to 30 minutes, $t_{1/2}$ equals 20 to 40 minutes), and the study should be sufficient to provide an indication of the relative blood concentrations of the drug substance of the proposed product and the reference oral tablet, and therefore the relative safety of the proposed product.

New modified release formulation

The ARGPM requires in vitro and in vivo studies to establish the release and absorption characteristics of the new product, with reference to CPMP/QWP/604/96 (Note for Guidance on Quality of Modified Release Products: A: Oral Dosage Form. B: Transdermal Dosage Forms; Section 1 (Quality)). As discussed, there is no relevant comparator for a bioequivalence study and thus such a study was not considered appropriate. In addition, the proposed product is neither an oral nor a transdermal modified release dosage form, the focus of the quoted ICH guideline.

The sponsor has provided data elsewhere in the dossier showing that the product is a modified release pessary and does not dose dump. Release data from vaginal inserts collected at various time points in Miso-Obs-001, Miso-Obs-002, and Miso-Obs-003 revealed no initial peak in release and showed that misoprostol was released from the vaginal insert at a controlled and sustained rate (measured by the mean percentage dose released per hour) in non-pregnant and in nulliparous and parous pregnant women. *In vitro* dissolution studies have been conducted that demonstrate batch to batch consistency and constant performance between routine production batches and the batches used in clinical studies. Adherence to the proposed specifications should assure consistency between the results of the clinical trials and results for patients treated with future marketed batches.

Quality summary and conclusions

The justification provided for not providing bioavailability and bioequivalence studies is suitable from a quality perspective, and should be referred to the clinical evaluator for assessment from a clinical perspective.

With the exception of the questions raised, the study design, conduct, results and conclusions drawn from the study appear to be valid. The following conclusions drawn by the sponsor appear to be valid from a quality perspective:

- Misoprostol release from the vaginal delivery systems was comparable for each of the reservoir doses (100, 200 and 400 mcg); approximately [information redacted.]
- The AUC_{0-t} and C_{max} pharmacokinetic parameters are dose proportional.
- Misoprostol acid is eliminated rapidly from the systemic circulation.

- Plasma misoprostol acid levels increased gradually over approximately 8 hours and then decreased gradually over the following 16 hours. Levels were still measurable at 24 hours.
- The exposure to misoprostol acid from the 200 mcg 24 hour vaginal insert was approximately 2.6 to 2.8 fold higher than that of the oral 200 mcg Cytotec tablet.
- Across all doses, there was evidence of a correlation between vaginal pH and percentage release for 4 and 8 hours duration of treatment. After 24 hours when most of the misoprostol has been released, release weakly correlates with pH. However, overall, C_{max} (normalised) and 4 and 8 hour plasma misoprostol acid concentrations did not correlate with pH.

III. Nonclinical findings

Introduction

Misodel and Misopess contain 200 mcg misoprostol incorporated in a hydrogel polymer reservoir, which is contained in an inert woven polyester pouch with a tail to facilitate removal. The hydrogel polymer and polyester retrieval system are not novel, having been approved with use of Cervidil pessaries (containing dinoprostone as the active ingredient). The antioxidant, butylated hydroxyanisole (BHA) is added to the hydrogel polymer to improve its stability, and this compound is a novel excipient by the intravaginal route.

The nonclinical submission contained studies on the pharmacokinetics of misoprostol and local tolerance of the pessary, conducted in pregnant rats. The pivotal study was GLP compliant.

Pharmacokinetics

The plasma area under the curve (AUC) for misoprostol acid (the rapidly de-esterified, pharmacologically active metabolite of misoprostol) was shown to be higher in rats and humans with intravaginal administration of the pessary compared with oral administration of tablets at the same 200 mcg misoprostol dose which is associated with a slower rate of absorption. However, peak and overall plasma exposure to misoprostol acid with use of this product do not exceed that approved with use of existing oral misoprostol products given the much higher doses that are approved for the oral (PO) route (up to 1200 mcg/day for Cytotec) and considering the pattern of clinical use (with the pessary removed at the onset of active labour or no later than 24 hours after insertion). In addition, this product is administered as a single dose and is expected to be used once or only a few times throughout a woman's childbearing years, in contrast to the repeated daily use of oral misoprostol. The maximum potential human dose of butylated hydroxyanisole (BHA) with use of Misodel and Misopess is 193 mcg. This compound has GRAS ("Generally Recognised As Safe") status in the USA, is an approved food additive in Australia and other countries, and is present at higher doses in existing prescription medicine products administered by the oral route, from which it is readily absorbed.

The systemic safety of misoprostol and BHA is therefore considered to be adequately established from existing data and the focus of the safety assessment falls on local tolerance associated with administration by the new route.

Toxicology

Developmental toxicity and pregnancy classification

As reported in the Australian Public Assessment Report for Gymiso, a no observable effect level (NOEL) of 1 mg/kg/day was established for misoprostol in a pre/postnatal development study in rats, involving oral dosing from late gestation through to weaning; postnatal body weight gain was reduced in pups with maternal dosing at 10 mg/kg/day PO. Relative exposure at the NOEL in rats is estimated to be 23 (based on animal to human plasma AUC for misoprostol acid, with reference to a clinical AUC of 326 pg.h/mL, obtained in at term subjects in Study Miso-Obs-205). In the sponsor's studies, no adverse effects on litter viability were observed with intravaginal administration of misoprostol at up to 82 mcg/kg in late gestation, yielding 29 times the clinical AUC. These exposure ratios should be interpreted with caution however, as the affinity of misoprostol acid for rat prostaglandin E2 prostanoid receptors is very much lower than for the human isoforms (approximately 140 fold lower affinity for the rat compared with human EP3 receptor, the preferred subtype).³

Misodel/Misopress is to be contraindicated for use before week 36 of gestation, and the sponsor has proposed assignment to Pregnancy Category C.⁴ Placement in this category is considered inappropriate. Under the Australian classification scheme, Category C is for *'drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations'* yet the use of misoprostol during gestation has been associated with birth defects — as reported in the approved Product Information documents for Cytotec, Arthrotec 50 and Gymiso, as well as posing a risk of abortion, premature birth and fetal death. The classification needs to consider use in pregnancy more broadly than for the specific indication. All existing misoprostol containing products are either placed in Category X⁵ (Cytotec; Arthrotec 50) or have no category due to their indication (Gymiso). Given that the product is to be specifically indicated for use in pregnancy, albeit at term, as opposed to use during earlier stages (organogenesis) where the major hazard exists, Category X is also considered inappropriate. Instead, the product should be exempted from pregnancy categorisation.

Local tolerance

Histopathological examination of the vagina and cervix revealed no significant local irritation associated with intravaginal administration of the hydrogel pessary in pregnant rats. The pessaries tested in the animals were comprised of the same hydrogel polymer as used in Misodel and Misopress and contained doses of misoprostol and BHA up to 20.5 and 8.6 times higher than the maximum clinical dose of the respective compounds (based on body weight and assuming 50 kg human body weight). Published studies using higher strengths of BHA than in Misodel and Misopress found minimal to mild ocular irritation in

³ Boie Y., Stocco R., Sawyer N., Slipetz D.M., Ungrin M.D., Neuschäfer-Rube F., Püschel G.P., Metters K.M. and Abramovitz M. (1997) Molecular cloning and characterization of the four rat prostaglandin E2 prostanoid receptor subtypes. *Eur. J. Pharmacol.* 340: 227–241; Abramovitz M., Adam M., Boie Y., Carrière M., Denis D., Godbout C., Lamontagne S., Rochette C., Sawyer N., Tremblay N.M., Belley M., Gallant M., Dufresne C., Gareau Y., Ruel R., Juteau H., Labelle M., Ouimet N., Metters K.M. (2000) The utilization of recombinant prostanoid receptors to determine the affinities and selectivities of prostaglandins and related analogs. *Biochim. Biophys. Acta.* 1483: 285–293.

⁴ Pregnancy Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Specialised texts should be consulted for further details.

⁵ Pregnancy Category X: Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

rabbits, and that dermal application in humans was generally non sensitising and only minimally or mildly irritating, although some cases of contact dermatitis were noted.⁶

Impurities

One impurity required toxicological qualification and was found to be acceptable based on application of the staged threshold of toxicological concern (TTC) concept.

Nonclinical summary and conclusions

With regard to potential systemic toxicity, exposure to misoprostol acid (the rapidly formed active metabolite) in patients with the proposed product does not exceed that approved for existing oral misoprostol products. As well, this product is administered as a single dose and is expected to be used once or only a few times throughout a woman's childbearing years, in contrast to the repeated daily use of oral misoprostol.

Systemic exposure to BHA with use of Misodel/Misopess does not exceed existing acceptable levels associated with oral intake.

Pessaries with the same hydrogel polymer composition as used in Misodel/Misopess and containing doses of misoprostol and BHA that are significant multiples of the maximum human dose (20.5 and 8.6 times for the respective compounds, based on body weight) were shown to be well tolerated locally following intravaginal administration to pregnant rats in late gestation and to not adversely affect litter viability.

There are no nonclinical objections to the registration of Misodel/Misopess for the proposed indication.

Amendments to the draft PI were recommended by the nonclinical evaluator but these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Clinical rationale

This is implied by the following extract from the sponsor's Clinical Overview:

'There is therefore an unmet medical need for a product that combines the dose administration attributes of Cervidil/Propess, such as consistent dose reservoir, single vaginal administration, controlled release at a known rate, removal once exogenous drug is no longer required, and sustained release for up to 24 hours for those women who need that duration of exposure, with the enhanced uterine contractility effects of misoprostol and potential for shorter times to delivery.'

Contents of the clinical dossier

The submission contained the following clinical information:

- 2 clinical pharmacology studies, including 2 that provided pharmacokinetic data and none that provided pharmacodynamic data.
- 0 population pharmacokinetic analyses.

⁶ Final Report on the Safety Assessment of Butylated Hydroxyanisole. J. Am. Coll. Toxicol. 3: 83-146.

- 1 pivotal efficacy/safety studies.
- 3 dose finding studies.
- 1 other efficacy/safety study.
- Literature references.

Paediatric data

The submission included paediatric safety data relating to neonates born to mothers treated with the drugs studied.

Good clinical practice (GCP)

GCP compliance was asserted for all 7 studies for which detailed reports were included in the dossier.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic (PK) topic.

Table 1. Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK - Single dose	MISO-OBS-001	*
	- Multi-dose	None	
	Bioequivalence† - Single dose	None	
	- Multi-dose	None	
	Food effect	None	
PK in special populations	Target population § - Single dose	MISO-OBS-205	*
	- Multi-dose	None	
	Hepatic impairment	None	
	Renal impairment	None	
Genetic/gender-related PK		None	
PK interactions		None	
Population PK analyses		None	

* Indicates the primary aim of the study.

† Bioequivalence of different formulations.

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

Study Miso-Obs-001 obtained some PK data relating to use of MVI 200 in non-pregnant women, but kinetics may well be significantly different in advanced pregnancy. Study Miso-Obs-205 studied MVI 200 at pregnancy term, but the results are difficult to interpret

because duration of insertion of the product was variable and generally short, and actual amount of drug released while product was in situ was not measured.

Pharmacodynamics

Studies providing pharmacodynamic data

None submitted.

Evaluator's conclusions on pharmacodynamics

The proposed usage is unsupported by pharmacodynamic data.

The sponsor's Pharmacology Written Summary states: '*No nonclinical studies relating to the intended primary pharmacological action of the misoprostol vaginal insert have been conducted in vitro or in animals.*'

The sponsor's Clinical Overview states '*In the MVI clinical programme, the pharmacodynamic response was assessed through clinical endpoints. Due to logistical issues and the attempt to disturb the woman's labour course as little as possible, plasma samples obtained for PK analysis were obtained at scheduled time points during Miso-Obs-205 rather than at milestone time points such as onset of labour or the time at which an adverse event occurred; therefore the relationship between misoprostol acid plasma concentrations and pharmacological activity of MVI 200 is not known.*'

In the evaluators opinion this is a deficiency in the program. The rationale for vaginal application is vague. Whether there is a significant local effect on the cervix or uterus is not known with certainty. A few literature references were provided but no integrated discussion of these was included.

The literature reports studies of both oral and vaginal misoprostol in connection with induction of labour.⁷ However, it is not clear whether local effects within the pelvis, or differences in rate or extent of absorption following the different routes of administration, were responsible for differences in outcomes. Reports of some in vitro studies of interest were included in the list of Literature references submitted:

The effects of PGE₂ on needle biopsy specimens of pregnant human cervix have been studied and reported to be:

*'Spontaneous phasic activity appeared in 58% of the specimens studied, with a mean frequency of 3.0 contractions/min. The addition of PGE₂ at concentrations of 0.1 pg/ml to 1.0 ng/ml strikingly inhibited contractile activity in all specimens. In most cases total inhibition occurred at 100 pg/ml and above but in strips from a few patients peak inhibition was encountered at 1.0 pg/ml. PGF₂α at similar concentrations had no effect on contractile activity. 6-keto-PGF₁α, the stable metabolite of PGI₂, abolished the contractions at 10 to 100 ng/ml but had no significant effect at lower concentrations.'*⁸

The effects of various prostaglandins on myometrial biopsy specimens from women undergoing caesarean section to be:

⁷ Alfrevic Z and Weeks A. Oral misoprostol for induction of labour (Review). 2010. Cochrane Database of Systematic Reviews, Issue 1. (First published as Art. No.: CD001338. DOI:

10.1002/14651858.CD001338.pub2.); Hofmeyr GJ et al. 2010. Vaginal misoprostol for cervical ripening and induction of labour. Cochrane Database of Systematic Reviews, Issue 10. Art. No.: CD000941. DOI: 10.1002/14651858.CD000941.pub2.

⁸ Bryman I et al. 1982. Extreme sensitivity of cervical musculature to prostaglandin E₂ in early pregnancy. Lancet 2:1471.

*'Prostaglandin E2 (PGE2) produced a biphasic effect consisting of an initial excitation followed by a dose related inhibition. The EP2/EP3 receptor agonists, rioprostil and misoprostol, produced similar effects to PGE2, however, the excitatory event of the misoprostol response was related to dose.'*⁹

The effects of PGE1, PGE2 and oxytocin on myometrial biopsy specimens from women undergoing caesarean section to be:

*'Oxytocin and prostaglandins have different effects on myometrial contractility accounting for different mechanisms of action and side effects. The increased uterine contractility observed with PGE1 as compared with PGE2 can contribute to explain the higher success of vaginal delivery.'*¹⁰

Dosage selection for the pivotal studies

The sponsor explains that based on the Phase II studies, the decision was taken to compare MVI 100 and DVI in a Phase III Study (Miso-Obs-004), which was designed to demonstrate superiority of MVI 100 over DVI in the time to vaginal delivery and non inferiority in the rate of caesarean delivery. As the first objective was not achieved, and given 'the unmet medical need to reduce the time to vaginal delivery compared to alternate methods of labour induction, further investigation of higher dose reservoirs was necessary. Therefore, a comparison of MVI 100 to MVI 150 and MVI 200 was conducted in Miso-Obs-204. Based on the results of this study, MVI 200 was chosen as the dose reservoir for the Phase III Study Miso-Obs-303.

Studies Miso-Obs-003, Miso-Obs-002, Miso-Obs-204 and Miso-Obs-004 each provide some information on the efficacy and safety at various doses.

In the evaluators' opinion, the basis for choosing the 200 mcg dose reservoir is inadequate. However, the evaluator believes it is not possible to separate this aspect from the question of overall justification for the vaginal route of administration.

Efficacy

Studies providing efficacy data

Pivotal efficacy study

Study Miso-Obs-303

This was a Phase III, double blind, randomised, multicentre study of subjects at or near term requiring cervical ripening and induction of labour.

Other efficacy studies

Study Miso-Obs-002

This was a Phase II, multi centre, randomised, parallel group, double blind study in parous women at term (37 to 42 weeks gestation) for whom labour induction was indicated. The primary objective was to assess the efficacy of four dose reservoirs (25 mcg, 50 mcg, 100 mcg, 200 mcg) of intravaginal controlled release misoprostol administered for up to

⁹ Senior J et al. 1999. In vitro characterization of prostanoid receptors on human myometrium at term pregnancy. Br J Pharmacol 108: 501-506.

¹⁰ Chioffi G et al. 2012. In vitro myometrial contractility profiles of different pharmacological agents used for induction of labor. Am J Perinatol. 1 February. Note: Whether this document has ever been published is not clear.

24 hours. Efficacy was measured in terms of time from insert placement to vaginal delivery.

Following insertion, the delivery system was to remain in situ for up to 24 hours except in any of the following circumstances, when it was to be removed immediately:

- The onset of active labour.
- Evidence of maternal complications.
- Evidence of foetal distress.
- Oxytocin planned in the following 30 minutes.
- The woman was to undergo caesarean section.

At the end of the dosing period the delivery system was removed. If it fell out of the vagina spontaneously before the end of the dosing period or was removed for any reason, it was not replaced.

Some 124 women were randomised; all completed. Mean exposure was 14.2, 12.4, 10.5 and 8.8 hours, for the 25, 50, 100 and 200 mcg MVIs, respectively (excluding 4 patients in whom the time of removal of the MVI was not recorded).

Study Miso-Obs-204

This was a Phase II, randomised, double blind, dose ranging study to assess the efficacy and safety of up to 24 hours treatment with the MVI 100, MVI 150 or MVI 200. The primary objective was to compare the efficacy of MVI 100 and MVI 200 based on the proportion of vaginal deliveries within 24 hours in women requiring cervical ripening and induction of labour.

Subjects were stratified by parity and centre. During and following treatment, subjects were assessed for delivery mode, time to delivery and safety. Modified Bishop Score (MBS)¹¹ was assessed at 6, 12, 18 and 24 hours after study drug insertion. The insert was removed before 24 hours when any of the following events occurred:

- Onset of active labour.
- Uterine hypertonus.
- Uterine tachysystole.
- Need for tocolysis.
- Evidence of foetal compromise.
- Uterine hyper stimulation syndrome.
- Maternal or foetal AEs necessitating discontinuation of dosing.

Some 374 subjects were randomised, of whom 373 completed, 1 being lost to follow up within 24 hours of drug treatment.

Study Miso-Obs-003

This was a Phase II, multi-centre study conducted in two parts; Part A and Part B. Part A was an open label dose escalation study in which cohorts of subjects were treated with ascending reservoir doses of the MVI from 25 to 300 mcg, or until the maximum tolerated dose (MTD) had been reached. Subjects were to be entered in cohorts of up to six. Entry into a cohort was to be stopped and no further dose escalation undertaken when two subjects in that cohort experienced hyper stimulation syndrome. Part B was a randomised,

¹¹ Bishop score, also Bishop's score, also known as cervix score is a pre-labour scoring system to assist in predicting whether induction of labour will be required.

controlled, double blind study of the efficacy and safety of three dose reservoirs of the MVI. Based on the preliminary efficacy and safety profiles seen in Part A, the dose reservoirs used in Part B were 25, 100 and 200 mcg. The overall primary objective of Parts A and B combined was assessment of the relative efficacy of varying drug reservoir doses of the MVI measured by the time from start of treatment (insertion of the MVI) to vaginal delivery of the baby.

Main inclusion criteria: Pregnant women at term (37 to 42 weeks gestation); aged greater than or equal to 18 years; singleton pregnancy; cephalic presentation (normal lie); MBS less than or equal to 6; no prior deliveries; not in labour.

Following insertion, the vaginal insert was to remain in situ for up to 24 hours except in any of the following circumstances, when it was to be removed immediately:

- Onset of active labour.
- Uterine hyper stimulation syndrome.
- Non reassuring foetal heart rate pattern.
- Other maternal or foetal adverse events which, in the opinion of the investigator necessitated discontinuation of dosing.
- Oxytocin to be administered within 30 minutes.
- Caesarean section to be performed.

Part A: Subjects were entered into the 5 dose reservoir groups as follows: 25 mcg (6 subjects), 50 mcg (6 subjects), 100 mcg (6 subjects), 200 mcg (7 subjects), and 300 mcg (6 subjects).

Part B: It had been planned to enrol 150 subjects, but the study was stopped before completion as it was believed that the preliminary results of Part A together with a similar study in parous women (Miso-Obs-002) had adequately elucidated the safety and efficacy profiles of the controlled release system, and enabled the appropriate dose to be selected for subsequent Phase III studies. 13 women were entered into Part B and 12 completed the study (one was lost to follow up).

In view of the small number enrolled in Part B, data from the two parts of the study are consolidated in the evaluation report.

Study Miso-Obs-004

This was a Phase III randomised, double blind, multi-centre study whose primary efficacy objective was to demonstrate that the time to vaginal delivery in subjects treated with MVI 100 was significantly shorter than the time to vaginal delivery in subjects given Cervidil 10 mg. Nulliparous and parous women at or near term requiring induction of labour and cervical ripening were randomised to receive either MVI 50 or MVI 100 or Cervidil 10 mg, followed by oxytocin, if needed. The co-primary safety objective of the study was to demonstrate that the rate of caesarean section deliveries in subjects randomised to receive MVI 100 is non-inferior to the rate for subjects randomised to receive Cervidil.

Main inclusion criteria: Pregnant women at term (greater than or equal to 36 weeks gestation); aged greater than or equal to 18 years; singleton pregnancy; vertex presentation; MBS less than or equal to 4; parity less than or equal to 3; not in labour.

Following insertion, the vaginal insert was to remain in situ for 24 hours except in any of the following circumstances, when it was to be removed:

- Onset of active labour.
- Uterine hypertonus or tachysystole or hyper stimulation syndrome.

- Need for tocolytic drug identified.
- Evidence of foetal compromise.
- Other maternal or foetal adverse events which, in the opinion of the investigator necessitated discontinuation of dosing.

The Intent-to-Treat (ITT) population comprised 428 randomised to MVI 100, 443 to MVI 50, and 436 to Cervidil 10 mg

Evaluator's conclusions on efficacy

In terms of the chosen primary efficacy endpoint in the one pivotal study, efficacy of MVI 200 was superior to that of the comparator DVI. However, in the opinion of the evaluator:

- the route of administration has not been justified by an adequate program of PK and Pharmacodynamic (PD) studies, and in any case appears to be unreliable, judging from the frequency with which the product falls out; and
- The optimum dosage has not been established.

Compliance with "One pivotal study" criteria

This is an application where the evidence of efficacy of the proposed treatment relies upon a single study (Miso-Obs-303). The relevant guideline (EMA 2001)¹² stipulates:

'In cases where the confirmatory evidence is provided by one pivotal study only, this study will have to be exceptionally compelling, and at the regulatory evaluation special attention will be paid to:

- *The internal validity. There should be no indications of a potential bias.*
- *The external validity. The study population should be suitable for extrapolation to the population to be treated.*
- *Clinical relevance. The estimated size of treatment benefit must be large enough to be clinically valuable.*
- *The degree of statistical significance.*
- *Data quality.*
- *Internal consistency. Similar effects demonstrated in different pre specified sub populations. All important endpoints showing similar findings.*
- *Centre effects. None of the study centres should dominate the overall result, neither in terms of number of subjects nor in terms of magnitude of effect.*
- *The plausibility of the hypothesis tested.'*

Most of these conditions appear to be met, but the evaluator believes the following are not met:

- 'this study will have to be exceptionally compelling'; and
- 'All important endpoints showing similar findings'.

Reasons:

- The evaluator has reservations about route of administration and dosage; and
- One of the co-primary objectives (which is closely related to efficacy) was not met.

¹²CPMP/EWP/2330/99 Points to consider on application with 1. Metaanalysis; 2. One pivotal study.
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003657.pdf

Safety

Studies providing evaluable safety data

The following studies provided evaluable safety data:

Pivotal efficacy study

In the pivotal efficacy study, the following safety data were collected:

- General adverse events (AEs) were assessed from insertion of study drug through to hospital discharge. Neonates were followed for AEs and concomitant medications from birth to hospital discharge and for hospital readmissions and visits to the emergency room for an additional 30 days.
- Routine Cardiotocograph (CTG) data were collected.

Pivotal studies that assessed safety as a primary outcome

Study Miso-Obs-303 (see section next above) was a pivotal study that assessed safety as a primary outcome. The study had as co primary safety objective: to demonstrate that the rate of caesarean section deliveries in subjects randomised to receive MVI 200 is non-inferior to the rate for subjects randomised to receive Cervidil.

Dose response and non-pivotal efficacy studies

The dose response and non-pivotal efficacy studies provided safety data, as follows:

- Studies Miso-Obs-002, Miso-Obs-003 and Miso-Obs-204 provided data on AEs, including those ascertained by CTG monitoring.
- Study Miso-Obs-004 had as co-primary safety objective: to demonstrate that the rate of caesarean section deliveries in subjects randomised to receive MVI 100 is non-inferior to the rate for subjects randomised to receive Cervidil. The study also provided data on AEs, including those ascertained by CTG monitoring.

Evaluator's conclusions on safety

The main studies useful for assessment of safety were

- Miso-Obs-204 (comparing MVI 100, 150, 200);
- Miso-Obs-004 (comparing MVI 50, 100 with DVI); and
- Miso-Obs-303 (comparing MVI 200 with DVI).

Some relevant findings of these studies are tabulated below.

Table 2. Selected safety findings in the submitted studies

Category of observation	Study	Selected findings
AEs	MISO-OBS-204	Maternal/foetal effects: ↑ with MVI strength: <i>Abnormal labour affecting foetus, Uterine contractions abnormal.</i> Neonatal effects: ↑ with MVI strength: number of reports.
	MISO-OBS-004	No obvious differences between treatments.
	MISO-OBS-303	Maternal/foetal effects: ↑ MVI 200 <i>cf</i> DVI: <i>Abnormal labour affecting foetus.</i>
AEs classified as treatment-related	MISO-OBS-204	Maternal/foetal effects: ↑ with MVI strength: number of reports.
	MISO-OBS-004	MVI 100 approximately comparable to DVI. Number of reports fewer with MVI 50.
	MISO-OBS-303	Maternal/foetal effects: ↑ MVI 200 <i>cf</i> DVI: number of reports.
SAEs	MISO-OBS-204	No obvious relationship to strength
	MISO-OBS-004	No obvious differences between treatments.
	MISO-OBS-303	Maternal/foetal effects: ↑ MVI 200 <i>cf</i> DVI: number of reports.
Rate of C-section	MISO-OBS-204	No obvious relationship to strength
	MISO-OBS-004	MVI 100 failed to show non-inferiority to DVI
	MISO-OBS-303	MVI 200 failed to show non-inferiority to DVI

First Round Benefit-Risk Assessment

First round assessment of benefits

A question which must be considered is whether vaginal misoprostol has any advantage over the oral route. This was explicitly considered in one article:

‘The large variety of doses of both oral and vaginal misoprostol used in the direct comparisons make it very difficult to interpret these data. The only consistent finding is a reduction in low Apgar score at five minutes in those given oral misoprostol, but there is no corresponding reduction in special baby care unit admission. The cause of this improved outcome in those given oral misoprostol is not clear, but it may relate to the hyper stimulation rates which were generally lower in those given low dose oral misoprostol. The relative acceptability of the oral and vaginal routes also need to be considered alongside this clinical data. Satisfaction was only considered in one study of 200 women, and in this study only two women (one in each group) expressed dissatisfaction. However, other clinical studies comparing oral and vaginal misoprostol have found increased satisfaction with the oral route.

In summary, there is some evidence that the oral route may result in improved clinical outcomes over the vaginal route. Given the likely greater acceptability for women using an oral route, it is the authors’ opinion that the oral route should be preferred over the vaginal route.’¹³

It seems this question has not been resolved by clinical studies of efficacy and safety. Nor is definitive relevant information available from PK or PD studies, which could help to resolve the question of whether the outcomes resulting from different dosages and routes

¹³ Alfirevic Z and Weeks A. Oral misoprostol for induction of labour (Review). 2010. Cochrane Database of Systematic Reviews, Issue 1. (First published as Art. No.: CD001338. DOI: 10.1002/14651858.CD001338.pub2.)

of administration depend only on the shape and magnitude of the plasma concentration versus time curve for misoprostol acid which is achieved by the regimen.

Thus, benefits can only be assessed in comparison to other products intended for vaginal administration. In the one pivotal study, efficacy of MVI 200 was superior to that of the comparator DVI. However, as already discussed this evaluator has reservations.

First round assessment of risks

As with the benefits, from the data submitted, risks can only be assessed in comparison to other products intended for vaginal administration. As pointed out, on the basis of the criterion rate of caesarean section, Studies Miso-Obs-004 and Miso-Obs-303 failed to demonstrate that MVI 100 and MVI 200, respectively, were non inferior to DVI. In addition to this, several categories of adverse effects were observed in the main clinical studies to occur more frequently with MVI 200 than with comparators.

Overall, the evaluator thinks there are grounds for concern that the clinical safety of MVI 200 may be inferior to that of DVI.

First round assessment of benefit-risk balance

The benefit-risk balance of MVI 200, given the proposed usage, is unfavourable.

First round recommendation regarding authorisation

This evaluator recommends that registration should be refused.

The trials submitted were in the evaluators' opinion insufficient in overall number of patients studied, too narrowly focused on a specific route of administration, and insufficiently supported by PK and PD data, to justify approval of the application. For a broader perspective on this area of therapeutics, the evaluator recommended 2 reports of the Cochrane Collaboration, from which extracts are copied below. The most recent of these¹⁴ was included in the present dossier, in the list of literature references.

Alfirevic and Weeks expressed the opinion:

*'[Oral misoprostol] as an induction agent is effective at achieving vaginal delivery. It is more effective than placebo, as effective as vaginal misoprostol and results in fewer caesarean sections than vaginal dinoprostone.... If using [oral misoprostol], clinicians should use a dose of 20 to 25 mcg in solution. Given that safety is the primary concern, the oral regimens are recommended over vaginal regimens. This is especially important in situations where the risk of ascending infection is high and the lack of staff means that women cannot be intensely monitored.'*¹⁵

The summary of a subsequent Cochrane review¹³ stated:

'Misoprostol is a hormone given by insertion through the vagina or rectum, or by mouth to ripen the cervix and bring on labour. The review of 121 trials found that larger doses of misoprostol are more effective than prostaglandin and that oxytocin is used in addition less often. However, misoprostol also increases hyper stimulation of the uterus. With smaller doses, the results are similar to other methods. The trials reviewed are too small to determine whether the risk of rupture of the uterus is

¹⁴ Hofmeyr GJ et al. 2010. Vaginal misoprostol for cervical ripening and induction of labour. Cochrane Database of Systematic Reviews, Issue 10. Art. No.: CD000941. DOI: 10.1002/14651858.CD000941.pub2.

¹⁵ Alfirevic Z and Weeks A. Oral misoprostol for induction of labour (Review). 2010. Cochrane Database of Systematic Reviews, Issue 1. (First published as Art. No.: CD001338. DOI: 10.1002/14651858.CD001338.pub2.)

increased. More research is needed into the safety and best dosages of misoprostol. Another Cochrane review has shown that the oral route of administration is preferable to the vaginal route.'

Clinical questions

None.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP version 2.0, dated 26 September 2012) which was reviewed by the TGA.

Safety specification

Subject to the evaluation of the nonclinical aspects of the Safety Specification (SS) by the and the clinical aspects of the SS by the TGA, the summary of the Ongoing Safety Concerns as specified by the sponsor is summarised in the Table below.

Table 3. Ongoing safety concerns

Important identified risks	Uterine contractions abnormal Abnormal labour affecting foetus (Foetal heart rate disorder; Foetal acidosis; Meconium in amniotic fluid; Apgar score low; Neonatal respiratory distress syndrome) Postpartum haemorrhage Premature separation of the placenta Uterine rupture Hypoxic ischaemic encephalopathy
Important potential risks	Disseminated intravascular coagulation
Important missing information	None

Notwithstanding the evaluation of the nonclinical and clinical aspects of the SS, it is noted that patients aged less than 18 years were not included in the clinical development program and therefore, no information is available about the use of this product in the adolescent patient population. The European Medicines Agency has agreed to a paediatric waiver to the obligation to submit results of clinical studies with Misodel in all subsets of the paediatric population in the granted indication. This waiver is based on review of a literature study provided by the sponsor containing analysis of "in house data" and published data referring to the use of misoprostol for labour induction and medical abortion in paediatrics/adolescent females. It is noted that:

- Only part of the data in this literature study refers to the use of misoprostol for labour induction, and
- No data is presented referring to the use of the slow release formulation (evaluated in this application) in subjects aged less than 18 years.

Therefore, it is recommended that the sponsor adds the use of the product in adolescent females as important missing information in the table of ongoing safety concerns. Risk

minimisation activities and pharmacovigilance activities should be assigned as appropriate.

Pharmacovigilance plan

As there was no Australian Specific Annex (ASA) provided, no statement about the sponsor's pharmacovigilance system in Australia can be made.

Enhanced pharmacovigilance activities are proposed to monitor all identified and potential risks. Enhanced pharmacovigilance is defined by the sponsor as follows:

'Safety surveillance of any studies as well as post-marketing adverse event reporting of AEs (identified and potential risks) will be performed. Results from these safety analyses will be included in all PSURs for a period of at least 5 years after marketing authorisation has been obtained. No studies are planned.'

Please note, the pharmacovigilance activities described by the sponsor as enhanced routine pharmacovigilance are considered routine pharmacovigilance activities by the RMP evaluator.

The proposed activities are generally acceptable. The RMP evaluator considers the use of this particular dosage form, for the proposed indication, for use in female adolescents as important missing information. Therefore, it is recommended that the sponsor implements additional activities to accurately capture information about the use of the product in adolescent females, and associated side effects experienced by the mother and their offspring, in daily clinical practice in Australia. Reporting of the captured data should occur in every PSUR. This could include, but is not limited to, an Australian or a global patient registry for patients below the age of 18 years. Reporting of the captured data should occur in every PSUR.

Risk minimisation activities

The sponsor proposes to address all identified and potential risks by routine risk minimisation activities.

At this time routine risk minimisation activities are considered acceptable.

In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicine information is acceptable. Revisions to the draft product information document were recommended to the Delegate (details of these revisions are beyond the scope of this AusPAR).

Table 4. Summary of the EU risk management plan

All figures and tables in this section that have been copied from the original dossier are considered by the evaluator to be an accurate representation of the reviewed data, unless qualified as such in the commentary of the report.

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Uterine contractions abnormal	Enhanced Pharmacovigilance	<p>SmPC sections:</p> <p>4.2 Posology and method of administration: Remove MISODEL –at the onset of labour – if uterine contractions are prolonged or excessive</p> <p>4.4 Special warning and precautions for use: MISODEL can cause excessive uterine stimulation if left in place after onset of active labour. If uterine contractions are prolonged or excessive, or there is a clinical concern for the mother or baby, remove the vaginal delivery system. If excessive uterine contractions continue after drug removal, tocolytic treatments should be considered.</p> <p>4.8 Undesirable effects: Common: Uterine contractions abnormal</p> <p>4.9 Overdose: Leaving MISODEL in place after onset of active labour may lead to symptoms of prostaglandin overdose. If this occurs, remove MISODEL and manage in accordance with local protocol.</p> <p>Enhanced Pharmacovigilance: Safety surveillance of any studies as well as post-marketing adverse event reporting of AEs of abnormal uterine contractions or uterine hypertonus will be performed. Results from these safety analyses will be included in all PSURs for a period of at least 5 years after marketing authorisation has been obtained.</p> <p>No studies are planned.</p>

<p>Abnormal labour affecting foetus (Foetal heart rate disorder; Foetal acidosis; Meconium in amniotic fluid; Apgar score low; Neonatal respiratory distress syndrome)</p>	<p>Enhanced Pharmacovigilance</p>	<p>SmPC sections: 4.2 Posology and method of administration: Remove MISODEL – if there is evidence of fetal compromise 4.3 Contraindications: When there is suspicion or evidence of fetal compromise prior to induction (e.g., failed non-stress test, meconium staining or diagnosis or history of non-reassuring fetal status) 4.4 Special warning and precautions for use: MISODEL should only be administered by trained obstetric personnel in a hospital setting where continuous fetal and uterine monitoring is available. The condition of the cervix should be assessed carefully before MISODEL is used. After insertion, uterine activity and fetal condition must be carefully monitored. If uterine contractions are prolonged or excessive, or there is a clinical concern for the mother or baby, remove the vaginal delivery system. If excessive uterine contractions continue after drug removal, tocolytic treatments should be considered. 4.8 Undesirable effects: Common: Abnormal labour affecting foetus, Foetal heart rate disorder, Meconium in amniotic fluid; Uncommon: Foetal acidosis, Apgar score low, Neonatal respiratory distress syndrome No studies are planned.</p>
<p>Postpartum haemorrhage</p>	<p>Enhanced Pharmacovigilance</p>	<p>SmPC sections: 4.8 Undesirable effects: Uncommon: Postpartum haemorrhage No studies are planned.</p>
<p>Premature separation of the placenta</p>	<p>Enhanced Pharmacovigilance</p>	<p>SmPC sections: 4.3 Contraindications: When there is placenta praevia or unexplained vaginal bleeding after 24 weeks gestation with this pregnancy 4.8 Undesirable effects: Uncommon: Premature separation of placenta, Antepartum haemorrhage No studies are planned.</p>

Uterine rupture	Enhanced Pharmacovigilance	<p>SmPC sections:</p> <p>4.3 Contraindications: When there is suspicion or evidence of uterine scar resulting from previous uterine or cervical surgery, e.g. caesarean delivery; and In women who have had more than 3 previous vaginal deliveries after 24 weeks gestation.</p> <p>4.4 Special warning and precautions for use: MISODEL should only be administered by trained obstetric personnel in a hospital setting where continuous fetal and uterine monitoring is available. The condition of the cervix should be assessed carefully before MISODEL is used. After insertion, uterine activity and fetal condition must be carefully monitored. If uterine contractions are prolonged or excessive, or there is a clinical concern for the mother or baby, remove the vaginal delivery system. If excessive uterine contractions continue after drug removal, tocolytic treatments should be considered.</p> <p>4.8 Undesirable effects: Uncommon: Uterine rupture No studies are planned.</p>
Hypoxic ischaemic encephalopathy	Enhanced Pharmacovigilance	<p>SmPC sections:</p> <p>4.3 Contraindications: When there is suspicion or evidence of fetal compromise prior to induction (e.g., failed non-stress test, meconium staining or diagnosis or history of non-reassuring fetal status)</p> <p>4.4 Special warning and precautions for use: MISODEL should only be administered by trained obstetric personnel in a hospital setting where continuous fetal and uterine monitoring is available. The condition of the cervix should be assessed carefully before MISODEL is used. After insertion, uterine activity and fetal condition must be carefully monitored. If uterine contractions are prolonged or excessive, or there is a clinical concern for the mother or baby, remove the vaginal delivery system. If excessive uterine contractions continue after drug removal, tocolytic treatments should be considered.</p> <p>4.8 Undesirable effects: Uncommon: Hypoxic ischaemic encephalopathy No studies are planned.</p>
Disseminated intravascular coagulation	Enhanced Pharmacovigilance	<p>SmPC sections:</p> <p>4.4 Special warning and precautions for use: an increased risk of post-partum disseminated intravascular coagulation has been described in patients whose labour has been induced by any physiological or pharmacological method. No studies are planned.</p>

Reconciliation of issues outlined in the RMP report

The table below summarises the TGA's first round evaluation of the RMP, the sponsor's responses to issues raised and the evaluation of the sponsor's responses.

Table 5. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
It is recommended that EU-RMP version 2.0, dated 26 September 2012, and any future updates are implemented as a condition of registration.		This is considered acceptable
	<p>Ferring has no objection to this recommendation. Please note that the EU-RMP has been updated. A new document, version 5.0, dated 3 May 2013 is provided. Please also note that the associated document, Summary of Pharmacovigilance System Master File, was also updated in May 2013 to reflect a change in the name of the EU QPPV and this updated document is also supplied.</p> <p>Compared to the initially submitted version of the EU-RMP dated September 2012, the following is a summary of major changes in the updated EU-RMP dated May 2013:</p> <p>Important identified risks: no changes</p> <p>Important potential risks: 2 additions:</p> <p>Labour induction for non-clinical reasons</p> <p>Cardiovascular and cerebrovascular events</p> <p>Important missing information: 2 additions:</p> <p>Use in women with more than three vaginal deliveries</p> <p>Use in women aged less than 18 years</p>	This is considered acceptable
It is recommended that the sponsor provides an ASA containing information relevant to the Australian context of the submission as specified in the TGA RMP guideline document.	Ferring is pleased to supply the requested ASA. The document is supplied as an appendix to the updated EU-RMP, version 5.0 dated May 2013.	This is considered acceptable

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
<p>It is recommended that the sponsor adds the use of the product in adolescent females as important missing information in the table of ongoing safety concerns. Risk minimisation activities and Pharmacovigilance activities should be assigned as appropriate.</p>	<p>The EU-RMP has been updated to include the use in women under 18 years (as well as use in women with more than three vaginal deliveries) as important missing information in Table 20: Ongoing Safety Concerns. Routine Pharmacovigilance activities are proposed and further discussed in the updated EU-RMP and in the ASA.</p>	<p>This is considered acceptable</p>
<p>It is recommended that the sponsor implements additional activities, to accurately capture information about the use of the product in adolescents, and associated side effects experienced by the mother and their offspring in daily clinical practice in Australia. Reporting of these captures data should occur in every PSUR</p>	<p>As mentioned above and presented in the ASA, use in women aged less than 18 years has been added to the updated version of the RMP, as young women aged 18 years (that is, teenagers) and above were included in the Misodel development programme. All safety information captured both in Australia and abroad in women aged less than 18 years will be included in every PSUR.</p>	<p>Health aspects of newborns of adolescent mothers should be collected in the patient registry and reported to the TGA as recommended in section 1.</p>
<p>It is recommended that the delegate draw the attention of the clinical/non-clinical evaluators to assess the validity of the statements made by the sponsor in terms of the possibility of using the product to induce abortion.</p>	<p>n/a (this recommendation is not directed to Ferring).</p>	<p>It is recommended that the delegate draw the attention of the clinical/non-clinical evaluators to assess this point.</p>
<p>It is recommended that the graphic which shows how to administer and remove the product which is included in the European SmPC will be included in the Australian PI.</p>	<p>The graphic mentioned by the evaluator is included in the proposed package insert. Nevertheless, Ferring has no objections to these suggested changes to the PI and will include the graphic within the body of the PI as well.</p>	<p>This is considered acceptable.</p>

Summary of recommendations

Issues in relation to the RMP

- It is recommended that the Delegate draw the attention of the clinical and nonclinical evaluators to assess the validity of the statements made by the sponsor within the RMP in terms of the possibility of using the product to induce abortion.
- Amendments to the RMP as recommended by the nonclinical evaluator.
- The following recommendation is made as a consequence of concerns specified by the clinical evaluator. This point has not been raised with the sponsor in the first round RMP report and therefore, the sponsor was not able to address this recommendation previously.
 - It is recommended that the sponsor implements a patient registry, collecting data about aspects related to the health of newborns, following labour induction with Misodel. This registry should also include data regarding aspects of the health of newborns from adolescent mothers.
 - Once supply of the product has commenced in Australia, this data should be submitted to the TGA on a three monthly basis for review, until the TGA is satisfied that there is no existing safety concern for newborns associated with use of the product. Submission of data, which allows a meaningful comparison about the health of newborns, following labour induction with products currently registered in Australia, should also be submitted.
 - It is recommended that the sponsor comments on the design of the registry, the data to be collected to address the relevant safety concerns mentioned by the clinical evaluator, the time frame for the implementation of the registry and any other points relevant for the implementation for a registry.

Suggested wording for conditions of registration

- RMP

Implement EU-RMP (version 5.0, dated 3 May 2013) with Australian Specific Annex (version 1.0, dated 22 July 2013) and any future updates as a condition of registration.

- PSUR

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 annually until the period covered by such reports is not less than three years from the date of this approval letter. No fewer than three annual reports are required. The reports are to at least meet the requirements for Periodic Safety Update Reports (PSURs) as described in the European Medicines Agency Guideline on Good Pharmacovigilance Practices (GVP) Module in I-Periodic Safety Update Report. 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 datalock point for that report.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The evaluator had no objections to registration. There are no material quality issues. Should the product be approved for registration, the name of the dosage form should be included in the PI title (Modified Release Pessary (MRP) (vaginal insert)).

Nonclinical

There were no non clinical objections to the registration. The evaluator required some changes to the PI.

Clinical

The clinical evaluator recommended that the product not be approved. Three of the clinical evaluator's concerns (inadequate justification for the vaginal route of administration, concern about the release rate, and dose selection) were resolved during the evaluation process. The residual concern is around the trade-off between benefit (shorter time to delivery and reduction of protracted labour) and risk (tachysystole and associated foetal harm) as observed in the pivotal Phase III trial (Miso-Obs-303).

Clinical data/evidence comprised:

- 2 Pharmacokinetic (PK) studies
- 3 dose finding studies
- 1 pivotal efficacy/safety study (Miso-Obs-303)
- 1 supportive efficacy/safety study

Clinical pharmacology

Study Miso-Obs-001 was in healthy non pregnant women.

Study Miso-Obs-001 showed a linear relationship between mass of drug in reservoir and absorption parameters, in the range of 100 to 400 mcg.

No Pharmacodynamic (PD) studies were submitted.

Dose selection

Miso-Obs-004 compared MVI 100 to DVI on time to vaginal delivery and caesarean section. Miso-Obs-204 compared MVI 100, MVI 150, and MVI 200.

There are no material residual issues around dose selection.

Efficacy

Miso-Obs-303 was the pivotal Phase III study; conducted in 35 sites across the US, 2010 to 2012. The key issues for this submission are around the balance of benefits to harms, as observed in this pivotal trial.

Table 6. Characteristics of Miso-Obs-303

Participants	1358 (MVI:678; DVI:680) mothers, 18+ years, who were candidates for pharmacological induction of labour. Mean age: ~26 years in both groups Nulliparous: ~66% Gestational age: mean: 39.5 weeks (all women were >36 weeks) Reason for induction: similar across the two groups: post-term, elective, hypertension, pre-eclampsia, oligohydramnios, diabetes, IUGR, PRoM (see CER, p19). All women had an unfavourable cervix (modified Bishop score of 4 or less; mean=2.4)
Exclusions	Uterine or cervical scarring Foetal malpresentation or congenital anomaly Any condition requiring urgent delivery Any evidence of fetal compromise (category II or III fetal heart rate pattern or meconium staining) Bleeding after 24 weeks Fever RoM >48 hours
Intervention	MVI 200, controlled release vaginal insert. The insert was kept in place for 24 hours unless there was onset of active labour (3+ contractions (45s or longer) in 10mins or 4cm cervical dilatation) or an AE (category III FHR pattern, thick or fresh meconium, scalp Ph<7.2, uterine tachysystole, foetal distress requiring CS, tocolytic therapy). IV oxytocin was permitted 30mins after removal of the insert if the patient was not in active labour and had reassuring fetal status. Mechanical cx ripening methods (intracervical Foley bulb use) were permitted
Comparator	DVI (CERVIDIL) 10mg vaginal insert. This appears to have been left in place for 24 hours before oxytocin was considered, whereas the PI advises only 12 hours. This could have delayed the initiation of oxytocins, which could affect the primary and secondary endpoints. Also, some Australian hospitals allow a second pessary to be inserted after 12 hours if labour has not commenced.
Primary endpoints	As agreed to with the FDA, there were 2 co-primary endpoints: Efficacy: time of study drug administration to vaginal delivery Safety: rate of CS
Secondary endpoints	Time to any delivery (vaginal or CS) Time to active labour Use of pre-delivery oxytocins Vaginal delivery within 24 hours Any delivery within 24 hours Vaginal delivery within 12 hours Any delivery within 12 hours Cx ripening at 12 hours
Minimal clinically important difference, Non-inferiority margin	Difference in time to vaginal delivery: 320 minutes (5 hours, 20 minutes) CS Non-inferiority margin: 10% of the DVI CS rate

Results

Co-primary endpoints

Time to vaginal delivery (patients who had a Caesarean section were censored at the time of Caesarean section).

Misoprostol vaginal insert (the subject of this submission) (MVI): 21.5 hours.

Dinoprostone vaginal insert (Cervidil) (DVI): 32.8 hours.

Difference: 11.3 hours.

$P < 0.001$

Safety

Table 7. Caesarean section rate

	MVI	DVI	Treatment difference (95% CI)
All parity	176/678 (26.0%)	184/680 (27.1%)	-1.10 (-5.79, 3.59)
Nulliparous	152/441 (34.5%)	168/451 (37.3%)	-2.78 (-9.08, 3.51)
Parous	24/237 (10.1%)	16/229 (7.0%)	3.14 (-1.93, 8.20)

Non inferiority margin was pre specified as 10% of the DVI Caesarean section rate (27.1%) or 2.71%. For the all parity group (ITT population), the upper limit of the 95% CI was 3.6% (greater than 2.71%), therefore non inferiority was not met. It was met for the nulliparous group, but not the parous group. At this point time and pending Advisory

Committee on Prescription Medicines (ACPM) advice, the Delegates preliminary view is that these statistical aspects of non-inferiority are not important in this particular instance. However, they should be reported in the PI because they were pre specified endpoints, non-inferiority margins and analyses. The Delegate believes it is reasonable to say that the overall Caesarean section rate is similar for MVI and DVI. The key issue for Caesarean section is whether the reasons for Caesarean section vary across the two groups (see secondary endpoints below)

Secondary endpoints

Efficacy

A higher percentage of mothers achieved cervical ripening in the MVI versus the DVI group 81.3% versus 66.0%. A lower percentage of mothers required predelivery oxytocin in the MVI versus the DVI group: 48.1% versus 74.1%.

It was expected that the shorter time to delivery should lead to lower rates of infection.

Table 8.

	MVI n=678	DVI n=680
Chorioamnionitis	38 (5.6)	59 (8.7)
Intrapartum IV or IM Ab use	38 (5.6)	59 (8.7)
Postpartum IV or IM AB use	31 (4.6)	57 (8.4)

However, these data are not straight forward to interpret. Chorioamnionitis includes both clinically diagnosed cases and histologically diagnosed cases. It would be more useful to report these results stratified by whether they were histologically diagnosed or not. Also, some hospitals routinely give mothers antibiotics if they have rupture of membranes greater than 24 hours. That is, less intrapartum or postpartum antibiotic use might not necessarily reflect lower rates of infection; but reflect adherence to guidelines about routine use of antibiotics following prolonged rupture of membranes.

Safety

The misoprostol vaginal insert shortened the time to delivery, but at the price of increasing uterine tachysystole and associated abnormal fetal heart rate tracings.

Table 9. Fetal effects of misoprostol vaginal insert

	MVI 200mcg (n=678) No (%)	DVI 10 mg (n=680) No (%)	RR (95% CI)
Uterine tachysystole (AE)	90 (13.3%)	27 (4.0%)	3.34 (2.20, 5.07)
With foetal heart rate involvement (late decelerations, prolonged decelerations, bradycardia)	70 (10.3%)	18 (2.6%)	3.90 (2.35, 6.48)
Tocolysis use	83 (12.2%)	28 (4.1%)	2.97 (1.96, 4.50)
Meconium in amniotic fluid	120 (17.7%)	92 (13.5%)	1.31 (1.02, 1.68)
5 min Apgar <7	14 (2.1%)	7 (1.0%)	2.01 (0.81, 4.94)
Foetal acidosis	8 (1.2%)	4 (0.6%)	2.01 (0.61, 6.63)
Neonatal encephalopathy	4 (0.6%)	1 (0.1%)	4.01 (0.45, 35.80)

There were no stillbirths or neonatal deaths, but this was expected given the sample size and the entry criteria for the study.

The number of babies with neonatal encephalopathy was small (4 versus 1). It would be useful to know how many of these had stage 3 encephalopathy.

Neonatal ICU admissions were, MVI: 61 (9.0%) versus DVI: 71 (10.4%). These percentages seem high and could include babies admitted for hypo glycaemia or other less serious problems. Some stratification of ICU admission by severity (for example, length of stay (LoS) greater than 3 days) would be helpful.

The number of caesarean sections undertaken for adverse events was similar across the two groups, but the reasons were different.

Table 10. Caesarean section (CS) for Adverse Events and reasons for CS

	MVI 200mcg (n=678) No (%)	DVI 10 mg (n=680) No (%)
CS for adverse event	170 (25.1%)	168 (24.7%)
Selected reasons for CS		
Category II fetal heart rate pattern	62 (9.1%)	42 (6.2%)
Uterine tachysystole with concerning fetal heart rate pattern	13 (1.9%)	0 (0.0%)
Uterine rupture	1 (0.1%)	0 (0.0%)

Instrumental deliveries were slightly higher in the MVI group versus the DVI.

Risk management plan

The EU RMP (version 6.0) was approved in the EU with only routine risk minimisation activities. In essence these are

- providing information in the PI (SmPC) about the risk of uterine tachysystole and associated abnormal foetal heart rate patterns;
- Stating in the PI that MVI should only be used by trained obstetric personnel in a hospital setting.

The sponsor has stated that an Australian register to monitor safety is not feasible or useful and (at this point in time, pending ACPM advice). At this point in time and pending ACPM advice, the Delegates preliminary assessment is that this is acceptable.

In their response of 28 October 2013, the sponsor has proposed post marketing surveillance through data collected by the National Perinatal Statistics Unit. This might be more feasible and useful than a standalone registry. However, the Delegates preliminary view (at this point in time and pending ACPM advice) is that we have good randomised data on safety from the pivotal Phase III Study Miso-Obs-303. This shows that MVI increases the risk of uterine tachysystole and associated abnormal foetal heart rate patterns. All observational post marketing study would be potentially confounded by differences across groups in baseline risk factors (mothers receiving MVI would presumably be compared to mothers receiving DVI and other methods of induction). The relevance of such data to the Australian setting would be greater than that the Miso-Obs-303, but its internal validity might be questionable (confounding).

Should MVI be approved for registration, the Delegates preliminary view (at this point in time and pending ACPM advice) is that 6 monthly periodic safety update reports (PSURs) along with implementation of the EU RMP (version 6.0) and the Australian specific annex is acceptable. Additional risk minimisation could be implemented via the PI.

Delegate's considerations

Risk benefit analysis

The key issue for this submission is whether the benefits of reduced time to delivery and reduction of protracted labour outweigh the risk of increased uterine tachysystole and the morbidity this might cause for the mother and her baby.

The pivotal Phase III trial (Miso-Obs-303) appears to have been competently conducted. One caveat is that the protocol specified that DVI (the comparator) was to be left in place for 24 hours (unless labour started or there was an adverse event), rather than the 12 hours recommended in the Product Information. This could delay the use of oxytocin (compared to what would happen in clinical practice in Australia) and could potentially bias the time to delivery in favour of MVI.

Nevertheless, pending ACPM advice, the Delegate thinks it is reasonable to accept that MVI reduces the time to delivery; although, for the reason given in the immediately preceding paragraph, the reduction in the real world of everyday clinical practice in Australia might not be as large as that reported in Miso-Obs-303.

Misoprostol tablets are used off label for induction of labour, particularly overseas. A Cochrane review of such off label use included 121 studies. It found that Misoprostol tablets (used off label), reduce the time to delivery, but increase uterine hyper stimulation and meconium stained liquor. Hence, the results of Study Miso-Obs-303 are as expected. For example in Miso-Obs-303, 13.3% of women in the MVI arm had uterine tachysystole reported as an adverse event versus 4.0% in the DVI arm. Uterine tachysystole does not necessarily cause morbidity; however, 10.3% of women in the MVI arm versus 2.6% of women in the DVI arm had tachysystole associated with late fetal heart decelerations, prolonged decelerations or bradycardia; and 9.1% of women in the MVI arm had a Caesarean section because of category II fetal heart rate pattern compared to 6.2% in the DVI arm.

The inclusion and exclusion criteria for Miso-Obs-303 meant that only women at low risk of placental insufficiency were enrolled. Therefore, the study was not designed and could not be expected to show a difference for severe adverse neonatal outcomes, which (as expected) were rare and did not differ in a statistically significant way across the two groups. However, there were four cases of neonatal encephalopathy in the MVI arm versus one in the DVI arm.

The results of Study Miso-Obs-303 indicate that the MVI requires careful monitoring with timely recognition of uterine tachysystole and abnormal foetal heart rate and implementation of appropriate intervention, which may range from removal of the vaginal insert, to initiation of tocolytic treatment, or to undertaking a Caesarean section.

MVI was submitted for marketing approval in the US at about the same time as in Australia and the EU. The Food and Drug Administration (FDA) has not yet made any public announcement about a decision on the US submission.

Proposed action

Taking into account the sponsor's dossier and their responses to the evaluation documents (including the EU Final Assessment Report), at this point in time (and pending ACPM advice), the Delegate is not in a position to say that the application for MVI should be approved for registration.

Preliminary consideration is that the benefits of faster delivery for a group of mothers who have already been identified as requiring induction are not well described. That is, the benefits of induction in reducing maternal and neonatal morbidity and mortality are clear,

but the benefits of additional speed in mothers who have been identified as requiring induction are not.

Specific questions for ACPM advice

1. What is the clinical relevance of faster time to delivery, in mothers who have already been identified as requiring induction and will be induced anyway?

The sponsor (in their 28 October 2013 response) cites the EU Final Assessment Report, and makes three points about the clinical relevance of shorter time to delivery.

- Shortening the duration of labour reduces maternal and foetal morbidity in pregnant women with different compromising conditions present prior to the induction of labour. Shorter time to delivery reduces infection.
- A 2005 Scottish study (referenced in the National Institute for Health and Care Excellence (NICE) Guidelines on Induction of Labour¹⁶), which found that *'with hindsight, 40% of women felt that speed of the induction to be the most important aspect, if they were to have induction again.'*

Pending ACPM advice, the Delegates preliminary views, at this point in time, are as follows:

- It is not clear that, once a mother agrees to be induced, going even faster with the induction is clinically beneficial.
 - IV or IM antibiotic use was a secondary outcome in Miso-Obs-303 and the results are difficult to interpret. There was less antibiotic use in the misoprostol insert group, but this could be associated with protocols around the routine use of antibiotics with prolonged (greater than 24 hour) rupture of membranes.
 - Besides speed of induction, mothers also value a healthy baby and might be willing to undergo a longer labour if the risks and benefits to their baby were explained.
2. Is the addition of information to the Dosage and Administration section of the PI sufficient to mitigate the risk of uterine tachysystole and abnormal foetal heart rate patterns?

The sponsor proposes that this risk will be mitigated by adding the following information to the start of the Dosage and Administration section of the PI:

'Misodel should only be administered by trained obstetric personnel in a hospital setting where continuous foetal and uterine monitoring is available. The condition of the cervix should be assessed carefully before Misodel is used. After insertion, uterine activity and foetal condition must be carefully monitored.'

At this point in time (and pending ACPM advice), the preliminary view is that addition of statements to the PI does not sufficiently mitigate the risk of adverse foetal outcomes. A problem unique to Australia is that 27% of expectant mothers live in areas classified as regional rural or remote. If they carry their pregnancy to term, they will probably deliver in a regional hospital, without specialist obstetric coverage. Uterine tachysystole and abnormal foetal heart rate patterns could be much more problematic in this setting.

3. Is the reduction in off label use of misoprostol tablets sufficient to warrant registration of misoprostol vaginal insert?

Misoprostol tablets are used off label for induction of labour, particularly in some overseas countries. The extent of off label use for induction of labour in Australia is unknown. Disadvantages of off label use include inconsistent and unknown dose and repeated

¹⁶ National Institute for Health and Care Excellence, Clinical Guidelines, Induction of labour (CG70), July 2008 <<http://publications.nice.org.uk/induction-of-labour-cg70>>

vaginal examinations and administrations. At this point in time, and pending ACPM advice, the preliminary view is that the need for a suitable dose and form of vaginal misoprostol (as an alternative to off label use of tablets) is not relevant to the decision about whether to approve MVI in Australia. The legislative requirement in Australia is that the sponsor must satisfactorily establish safety and efficacy of the product, which is the subject of the application.

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Additional question for sponsor to address in their pre ACPM response

4. Has the sponsor had any discussions with the FDA or feedback from the FDA about their application for marketing approval of MVI in the United States?
5. What is the current status of the application in Canada and other countries outside of EU and US?

Response from Sponsor

Benefits of faster delivery and MVI

The Delegate has acknowledged the clinical benefits of induction of birth per se in women in whom the procedure is indicated, but on the other hand, the Delegate states that the benefits of a faster time to delivery in this group remain unclear. Protracted labour is more common in induction of labour than in spontaneous labour and is associated with higher infection rates, more antibiotic and oxytocin use, and greater maternal distress and use of hospital resources. Therefore, it logically follows that reducing the incidence of protracted labour in women in whom induction is indicated could be of benefit. The pivotal MVI Phase III Study, Miso-Obs-303, not only provides compelling evidence that women induced with MVI are likely to have a shorter time to delivery than those administered DVI, but also that they are less likely to experience some of the undesirable aspects of protracted labour. This is discussed in the following sections.

Less likelihood of protracted labour with MVI

The principal evidence that prolonged labour is less likely to occur with MVI than DVI comes from the Miso-Obs-303 primary efficacy endpoint results, which showed that women in the MVI arm had a significantly shorter median time to vaginal delivery than those receiving DVI (21.5 hours versus 32.8 hours; difference 11.3 hours; $p < 0.001$). An even more striking difference in median time to delivery between MVI and DVI was observed in the nulliparous sub group, in which achieving cervical ripening is particularly challenging (29.2 hours versus 43.1 hours; difference 13.9 hours; $p < 0.001$).

Additionally, both the vaginal and overall delivery rates at the 24 hour time point indicated a reduction in the incidence of protracted labour in those receiving MVI compared with DVI (vaginal delivery rate: 54.6% versus 34.0%; overall delivery rate: 67.7% versus 40.7%; $p < 0.001$ for both). In other words, only 34% of women induced with DVI delivered vaginally within the first 24 hours of administration. Moreover, the mean duration of stay in a labour/delivery suite was much shorter for MVI subjects (24.7 hours) compared with DVI subjects (32.6 hours; $p < 0.001$).

The Delegate has accepted that, in Miso-Obs-303, MVI reduced the time to vaginal delivery compared with DVI. However, the Delegate has questioned whether the trial protocol requirement that allowed DVI, the trial comparator, to be left in place for up to 24 hours (rather than 12 hours, as recommended in Australia) could have delayed the use of oxytocin in this trial arm and therefore potentially biased the time to delivery in favour of the MVI group. Hence, the Delegate has asked whether the reduction in delivery time offered by MVI over DVI in Miso-Obs-303 would be as large in Australian clinical use.

There is sufficient dinoprostone in the DVI reservoir to allow continuous drug release for up to 24 hours, and the product is approved for up to 24 hour use in most countries worldwide on the basis that efficacy and safety has been established with 24 hour use. It is approved for only up to 12 hour use in Australia and in the USA, although there is evidence of routine 24 hour DVI use in at least one large Australian obstetric unit.¹⁷ An additional reason that DVI was administered for up to 24 hours in the trial was to maintain the double blind (MVI and DVI are visually identical). While Ferring accepts that this characteristic of the trial design might influence how the primary efficacy endpoint result relates to Australian clinical practice, Miso-Obs-303 also showed that important advantages of MVI over DVI were already apparent in the first 12 hours of their use, which is directly relevant to the Australian situation:

- Both the vaginal and overall delivery rates at 12 hours were significantly in favour of MVI (vaginal delivery rate: 19.8% versus 8.4%; overall delivery rate: 23.2% versus 9.3%; $p < 0.001$ for both analyses).
- The proportion of subjects with pre-defined cervical ripening at 12 hours was also significantly higher for MVI (81.3%) than for DVI (66.0%; $p < 0.001$).

Moreover, the median time to active labour for the MVI group occurred at 12.1 hours, compared with 18.6 hours for the DVI arm ($p < 0.001$).

Hence, Ferring maintains that Miso-Obs-303 provides compelling evidence of benefits in efficacy of MVI compared with DVI, and that this evidence would translate into tangible benefits in real world use in Australia.

Less antibiotic use and infection with MVI

The Delegate has commented on the secondary endpoint analyses of rates of infection and antibiotic use from Miso-Obs-303, and questioned whether the antibiotic use data would truly reflect differences in infection rate between the two study groups because some antibiotic use might have been for routine prophylaxis, rather than for treating a specific infection.

In Miso-Obs-303, prophylactic use of antibiotics was clearly distinguished from use for suspected or confirmed infection. If, for example, a mother had rupture of membranes greater than 24 hours and was given antibiotics, it was considered prophylaxis and captured separately as routine concomitant medication. In this case, no AE would have been registered, and this subject would not have been counted in the sub group “those treated with antibiotics due to an infection or suspected infection AE”. In other words, to be included in the “antibiotics” sub group there had to be an infection related AE, and therefore, reported antibiotic use was always for treating a specific infection rather than for routine prophylaxis.

Hence, Ferring maintains that antibiotic use data from Miso-Obs-303 provide a true reflection of infection rates during the intrapartum and postpartum periods, and that, it is the sponsor’s belief that it is reasonable to conclude from this trial that, compared with DVI, MVI was associated with significantly less antibiotic use needed to treat infection in both the intrapartum period and the postpartum period.

Reduced oxytocin use with MVI

In Miso-Obs-303, oxytocin administration for induction of labour was permitted 30 minutes after removal of a vaginal insert if the mother was not in active labour and had reassuring foetal status. A key finding of the trial is that markedly fewer subjects in the MVI arm required pre delivery oxytocin (48.1%) compared with those in the DVI arm

¹⁷ Tathem *et al.* Dinoprostone vaginal pessary for induction of labour: Safety of use for up to 24 hours. *Aust NZ J Obstet Gynaecol* 2012;52:582-587.

(74.1%; $p < 0.001$). Moreover, in women who required oxytocin, those in the MVI arm had a lower total oxytocin dose than those in the DVI arm (mean: 4.4 IU versus 7.2 IU; $p < 0.001$) and a shorter duration of oxytocin treatment (mean: 8.3 hours versus 11.0 hours; $p < 0.001$).

Like MVI, oxytocin should only be used under close medical supervision by staff trained in its use and in the management of any complication that might arise with its use. Hence, resorting to oxytocin for labour augmentation intensifies hospital resource use. Also, due to the variety of possible IV dosage regimens of oxytocin in use, the scope for administration errors with the medication are substantial. Indeed, oxytocin is included on the List of High Alert Medications by the Institute for Safe Medication Practices in the USA because the consequences of an administration error can be devastating to the patient.¹⁸ For example, rapid IV administration can result in acute haemodynamic changes that could lead to maternal myocardial ischaemia, particularly in women with pre-existing cardiovascular disease. Similarly, water intoxication associated with maternal and neonatal hyponatraemia has been reported in cases where high doses of oxytocin together with large amounts of electrolyte free fluid have been administered over a prolonged period of time.

It is noteworthy that, while Miso-Obs-303 reported more tachysystole with non-reassuring foetal heart rate patterns for MVI than for DVI, both treatment groups actually had the same overall rate of category II or III foetal heart rate patterns reported as an AE (26.0%). A possible explanation for this apparent correction in the imbalance of tachysystole related AEs may have been the higher use of oxytocin in the DVI group, given that oxytocin is also known to cause abnormal foetal heart rate patterns.

Hence, an important benefit of MVI is that its use is associated with less need for labour augmentation with oxytocin than with DVI, which in itself could lead to less oxytocin related morbidity and resource use within a unit.

Less Caesarean deliveries due to protracted labour with MVI

The Delegate has acknowledged that in Miso-Obs-303 the overall Caesarean delivery rates were similar between the treatment groups, but noted that there were more Caesarean deliveries due to tachysystole because of category II foetal heart rate pattern for the MVI group (9.1%) than the DVI group (6.2%).

On the other hand, it is also worth examining the rates of Caesarean deliveries due to protracted labour or failure of induction. In Miso-Obs-303, Caesarean deliveries due to arrest or failure of dilation were more common for DVI than for MVI (12.5% versus 8.6%), as were those due to arrest or failure of descent (4.1% versus 3.5%), and lack of treatment efficacy (1.5% versus 0.7%). These results indicate that Caesarean deliveries resulting from protracted labour or failure of induction were more common with DVI than with MVI.

Mothers preference for shorter labour during induction

As part of Ferring's response dated 28 October 2013 to a series of questions that were sent to us by the Delegate, the sponsor described a finding from a large survey conducted in Scotland of women undergoing induction of labour,¹⁹ as the sponsor felt it important to consider the views of mothers who have undergone labour induction. The current UK National Institute for Health and Clinical Excellence (NICE) guidelines on Induction of Labour (2008)²⁰ quoted the study publication: '*With hindsight, 40% of women felt that*

¹⁸<https://www.ismp.org/tools/institutionalhighAlert.asp>

¹⁹ Shetty *et al.* Women's perceptions, expectations and satisfaction with induced labour - a questionnaire-based study. *Eur J Obstet Gyn R B* 2005;123:56-61.

²⁰ National Institute for Health and Care Excellence (NICE) guideline, Induction of labour (CG70), 23 July 2008, <<http://publications.nice.org.uk/induction-of-labour-cg70>>

speed of the induction to be the most important aspect, if they were to have induction again.' The Delegate, on the other hand, has questioned whether the view of mothers would be the same if *'the risks and benefits to their baby were explained'*.

The purpose of the Scottish study was to assess, from the mothers' view point, issues and satisfaction with the induction process, using pre and post labour questionnaires. While Ferring accepts that risk to the baby is ultimately a central consideration in selecting the agent to be used for induction, this study has captured, nevertheless, an important sentiment among mothers who have just undergone induction: that *'women induced felt that their induction took longer than expected and the most important aspect they would consider changing in any subsequent induction would be an inducing agent with a quicker action.'*

Hence, the study provides evidence that mothers who have just undergone induction of labour perceive a shortened time to delivery as an important consideration.

Relative safety of MVI and risk management measures

Uterine tachysystole is an expected outcome with misoprostol, and thus with MVI use, and is associated with its superior efficacy over DVI. However, it was demonstrated in Miso-Obs-303 that side effects related to tachysystole can be managed in most cases by removing MVI using the retrieval system, a key safety feature of the product. In some cases, management required additional intervention with a tocolytic agent or Caesarean delivery. These aspects of MVI use serve to underscore the importance of careful cardiotocographic monitoring of the mother and foetus by trained obstetrics staff, and having ready access to facilities to manage possible complications that might arise.

To reinforce the appropriate use of the product by suitably trained staff and in units with appropriate obstetric cover and facilities, Ferring has proposed the following preface to the Dosage and Administration section of the Misodel Product Information (PI):

'Misodel should only be administered by trained obstetric personnel in a hospital setting where continuous foetal and uterine monitoring is available. The condition of the cervix should be assessed carefully before Misodel is used. After Misodel insertion, uterine activity and foetal condition must be carefully monitored by staff trained in cardiotocography interpretation. Misodel should only be used in hospitals where facilities for emergency Caesarean delivery are readily available.'

The first part of this statement was proposed by Ferring in our response to the TGA dated 28 October 2013, but the sponsor notes the Delegate's preliminary view that the addition of such PI statements "does not sufficiently mitigate the risk of adverse foetal outcomes." The Delegate goes on to point out that 27% of expectant women live in regional, rural and remote parts of Australia, where it is suggested that obstetric cover in hospitals might be inadequate and the management of the possible complications of induction potentially problematic. The sponsor understands that the Delegate's 27% figure is estimated from the Australian Institute of Health and Welfare's Perinatal Statistics publication Australia's Mothers and Babies 2010. This reports that a total of 29.6% of women who gave birth in Australia at the time resided in either an inner or outer regional area, or a remote or very remote area. Based on Australian Standard Geographical Classification used here, an inner regional area would for example cover the eastern seaboard of NSW a few hundred kilometres north and south of Sydney, whereas large towns like Townsville, Mildura or Dubbo form part of outer regional areas. From the 29.6% total, some 26.9% of women resided in these regional areas, leaving just under 3% of women who gave birth residing in remote and very remote Australia. Almost all hospitals in regional towns would have

good obstetric cover and access to theatres for emergency or urgent Caesarean delivery,²¹ and therefore could be expected to have the necessary expertise and facilities to use a product such as MVI. Ferring accepts that MVI should not be used when an appropriate level of obstetric cover and facilities are not readily available, and to emphasise this point, the sponsor added the additional wording to the PI statement above.

The Delegate has also recommended as part the Indication section of the Misodel PI a statement to highlight to prescribers the relative levels of risk of uterine tachysystole, tachysystole resulting in non-reassuring foetal heart rate patterns, and tocolysis use with MVI compared with DVI. Ferring agrees that this safety statement should be included in the Misodel PI. However, the sponsor considers that the inclusion of such a statement as part of the Indication is inappropriate, as it falls outside the requirements for an Indication section of an Australian PI document, as prescribed in subsection 7D(1) of TG Act. Ferring strongly believes that, as a means of emphasising to prescribers the increased safety risk with MVI over DVI, the statement would more appropriately fit at the beginning of the Precautions section followed by the related guidance statement "Preparedness for tocolytic therapy when Misodel is used is therefore recommended."

However, if the ACPM were to advise that the statement should form part of the Indication, Ferring is strongly of the view that, in this section of the PI, it should be modified to represent a risk benefit statement, by also mentioning the reduced time to vaginal delivery reported in Miso-Obs-303 for MVI. In this case, the suggested wording of the statement would be as follows:

'In a high quality randomised trial (Miso-Obs-303), MVI 200 resulted in a time to vaginal delivery that was more than 11 hours shorter than DVI (median time: 21.5 hours versus 38.5 hours). However, compared with DVI in the same trial, MVI resulted in about three times more uterine tachysystole reported as an adverse event (13.3% versus 4.0%), four times more uterine tachysystole associated with non-reassuring foetal heart rate patterns (10.3% versus 2.6%), and required three times more tocolysis use (12.2% versus 4.1%).'

Ferring would be willing to consider other practical measures aimed at ensuring correct and appropriate use of the MVI by specialist obstetricians in units with suitable and readily available facilities. (This statement was provided by the sponsor).

Off label misoprostol tablet use

The Delegate has acknowledged the disadvantages of off label use of misoprostol tablets for induction of labour, asking whether a reduction in this use that MVI might bring about is sufficient to warrant the registration of MVI. The Delegate has also stated that the extent of such use in Australia is unknown and that his question may not be relevant due to legislative requirement in Australia for a sponsor to demonstrate that the product which is the subject of an application is safe and effective in its own right.

Ferring considers that the efficacy and safety of MVI has been demonstrated in its own right. It is noteworthy, however, that the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) has a position statement titled "The use of misoprostol in obstetrics" (C-Obs 12). While acknowledging that the use of off label misoprostol in Australia is less common than overseas, it includes the passages

'There is considerable literature evaluating the use of misoprostol for cervical ripening and induction of labour. Both vaginal and oral administration of

²¹ Homer *et al.* Mapping maternity services in Australia: location, classification and services. *Aust Health Rev* 2011;35:222-229.

misoprostol are effective methods for cervical ripening and for induction labour. As with other prostaglandins, misoprostol can cause uterine hyper tonicity.

As with all new therapeutic agents, Fellows should take particular care to use misoprostol according to regimens for which evidence is available and to ensure that appropriate informed consent is obtained from women prior to its use. Where misoprostol is the most appropriate therapeutic option, it should be available for use according to established medical evidence. Particular caution is recommended with the use of misoprostol for cervical ripening and induction of labour. The potential risks and benefits in each individual case should be carefully evaluated and attention paid to the published information regarding minimization of dosage. As with all prostaglandin preparations, caution is recommended with the use of misoprostol in the presence of a uterine scar.'

This suggests that there is some level of off label misoprostol use for induction in Australia, which could be replaced by MVI, a product with a high quality evidence base and with the advantage of a retrieval system.

Additional questions on overseas regulatory status

Update on dealings with the FDA

The Delegate has requested the outcome of discussions and feedback that Ferring has received from the FDA on the US Misodel regulatory application. As mentioned in our previous response, the application in the US is still ongoing. Feedback from the FDA was provided to the TGA and this information was considered.

Regulatory update for countries outside of the EU and the USA

The Delegate has also asked for an update on the regulatory status of MVI in Canada and in major countries outside of the EU and the USA. Our principals have advised that there has been no change in the status of the MVI applications in Canada and in other countries outside of the EU and the USA. In these countries where the application has been lodged, evaluations are ongoing. To date, the only approval outside of the EU countries is in Mexico.

Sponsor's conclusion

Miso-Obs-303, a high quality randomised clinical trial, has provided compelling evidence that MVI reduces the time to vaginal delivery and the likelihood of protracted labour compared with DVI in both nulliparous and parous women undergoing induction of labour. Some of the anticipated benefits of reducing protracted labour were apparent in the trial. Compared with DVI, MVI was associated with significantly less antibiotic use given to treat intrapartum and postpartum infection, and a significantly reduced need for pre delivery oxytocin. Also, there were fewer Caesarean deliveries related to protracted or failed vaginal delivery with MVI.

Ferring acknowledges that a by-product of the faster time to vaginal delivery provided by MVI is the increased rate of uterine tachysystole in general and of tachysystole resulting in non-reassuring foetal heart rate patterns. While there is no evidence from Miso-Obs-303 that this led to neonatal harm, Ferring agrees fully that prescribers need to be well aware of MVI's safety profile before considering its use, and that use of the product should only be under careful and close supervision by suitably qualified obstetric staff. In most cases tachysystole resulting in foetal distress can be reversed by removing MVI using the retrieval system. However, there will be instances where tocolysis or urgent Caesarean delivery will additionally be required. Therefore, Ferring understands that the use of MVI should be limited to obstetrics units that have these services readily available.

Ferring wishes to re iterate its firm view that MVI represents a new therapeutic option which should be available to Australian obstetricians in institutions with appropriate facilities.

Advisory Committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register an extension of indications and major variations (new dose form and new route of administration) for a currently registered product.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Misodel modified release pessary (vaginal) containing 200 µg of misoprostol to have an overall positive benefit-risk profile for the indication;

Misodel is indicated for induction of labour, from 36 weeks gestation, in women with an unfavourable cervix in whom induction is clinically indicated

In making this recommendation the ACPM

- noted 15% of all pregnancies are induced
- noted the potentially competing demands of mother and foetus
- noted that the trial submitted demonstrated a shorter time to delivery with misoprostol 200 µg vaginal insert (MVI a synthetic analogue of Prostaglandin E1) compared to dinoprostone vaginal insert.
- Expressed some concern that
 - the route of administration was not fully justified by an adequate program of PK and PD studies
 - the route of administration appears to be unreliable, as exemplified by the frequency with which the product falls out
 - the optimum dosage has not been established

Specific advice:

The ACPM also provided the following specifically requested advice:

- What is the clinical relevance of faster time to delivery, in mothers who have already been identified as requiring induction and will be induced anyway?

The ACPM advised that misoprostol is currently commonly used, off label, as a means of induction when this procedure is indicated. The standard treatment is Cytotec, a quarter of a 200 mg immediate release oral tablet inserted vaginally. The proposed vaginal pessary provides a lower, more consistent and controlled dose of 7 mg/hour over 24 hours than the standard practice. The ACPM was of the view that oxytocin and the unpredictability of the quarter tablet misoprostol dose may represent a greater risk. If an adverse event does occur, the pessary is more easily removed to reduce the dose received by the patient.

The advantages of a speedier delivery include less exhaustion for the mother. The speed of labour when Misodel is used may be partially due to the dose level; the vaginal pessary may mitigate some of the adverse events reported in many of the trials analysed in the Cochrane Report. The ACPM was concerned that the advantages of reduced time to delivery lay predominantly with the mother rather than with the foetus.

- Is the addition of information to the Dosage and Administration section of the PI sufficient to mitigate the risk of uterine tachysystole and abnormal foetal heart rate patterns?

The results of Study Miso-Obs-303 show that there are several potential adverse events for the foetus which were not fully explored nor were long term foetal outcomes reported. MVI treatment requires careful monitoring with timely recognition of uterine tachysystole and abnormal foetal heart rate and implementation of appropriate intervention, which may range from removal of the vaginal insert, to tocolytic treatment, to Caesarean section. The ACPM advised that the PI statements should emphasise the need for continuous, rather than intermittent, monitoring of the foetus. The ACPM advised there was no clinical reason to restrict use to mothers over 18 years.

- Is reduction in off label use of misoprostol tablets sufficient to warrant registration of misoprostol vaginal insert?

The ACPM was of the view that the need for a suitable vaginal formulation of Misodel (as an alternative to off label use of oral tablets) is not relevant. The legislative requirement in Australia is that the sponsor must satisfactorily establish safety and efficacy of the product which is the subject of the submission.

Proposed conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- Subject to satisfactory implementation of the Risk Management Plan most recently negotiated by the TGA,
- Negotiation of Product Information and Consumer Medicines Information to the satisfaction of the TGA.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments:

The ACPM agreed with the Delegate on the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI), particularly in regards to the Adverse Events and Clinical Trials sections and specifically advised on the inclusion of the following:

- Robust statements in the Precautions section of the PI and relevant sections of the CMI to more accurately reflect the lack of long term data on foetal outcomes.
- A statement in the relevant sections of the PI and of the CMI to accurately reflect the general criteria for induction.
- The description in the Clinical Trials section of the PI of the trial submitted should be succinct to accurately reflect the data.
- Addition in the relevant section of the CMI of the diagram currently in the PI showing insertion of the pessary.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Misodel and Misopess (misoprostol 200 micrograms) modified release pessaries (vaginal inserts) in aluminium dessicant foil) for

The induction of labour in women with an unfavourable cervix, from 36 weeks gestation:

- In whom induction is clinically indicated
- In a hospital where continuous electronic foetal monitoring is available.

Specific conditions of registration applying to these goods

The Misodel/Misopess (misoprostol) EU Risk Management Plan (RMP), version 5.0 dated 3 May 2013 with Australian Specific Annex (version 1.0, dated 22 July 2013), and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The Product Information approved for main Misoprostol at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
<http://www.tga.gov.au>