Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for mifepristone/misoprostol

Proprietary Product Name: MS-2 Step

Sponsor: MS Health Pty Ltd

October 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.

Contents

List of the most common abbreviations used in this AusPAR

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

I. Introduction to product submission

Submission details

Type of submission:	New combination of active ingredients
Decision:	Approved
Date of decision:	28 May 2014
Active ingredients:	Mifepristone / misoprostol
Product name:	MS-2 Step
Sponsor's name and address:	MS Health Pty Ltd Suite 129, 135 Cardigan Street Carlton VIC 3053
Dose form:	Tablet blister pack
Strengths:	Mifepristone: one 200 mg tablet, in a blister and misoprostol: four 200 microgram tablets, in a blister pack
Container:	Blister
Pack sizes:	One (1) mifepristone tablet and four (4) GyMiso® tablets per MS-2 Step pack.
Approved therapeutic use:	MS-2 Step is indicated in females of childbearing age for the medical termination of a developing intrauterine pregnancy, up to 63 days of gestation. It is recommended that the duration of pregnancy (that is, up to 63 days gestation) be confirmed by ultrasound. In the event that an ultrasound is not possible, extra caution should be exercised. Ultrasound is also useful to exclude ectopic pregnancy.
Route of administration:	Oral/buccal
Dosage:	One mifepristone tablet 200 mg (orally), followed in 36 to 48 hours by 800 microgram of misoprostol (4 tablets of 200 microgram (buccally)).
ARTG number:	210574

Product background

This AusPAR describes the application by the sponsor to register MS-2 Step (mifepristone/misoprostol) for the following indication:

> *Females of childbearing age for the medical termination of a developing intrauterine pregnancy up to 63 days gestation.*

Mifepristone and misoprostol are already registered for use as two mono products. MS-2 Step represents a composite pack.

This represents an extension of the indications from 49 to 63 days.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 04 June 2014.

The original formulation of mifepristone was registered in France in 1988. Since then, mifepristone (either the originator or a generic) has been approved in over 50 countries, including United Kingdom (1991), United States (2000), and New Zealand (2001).

At the time the TGA considered this application;

- The extension of indications from 49 to 63 days for Mifepristone Linepharma would bring Australia into line with other countries; the main exception is the United States, where the indication is 49 days (in South Africa the indication is 56 days).
- Mifepristone is included on the World Health organisation's list of essential medicines for developing countries.
- GyMiso® has been approved in France since 2004 and applications have been filed in Canada and South Africa. Besides Australia, France is the only country in which both of these specific products are currently registered (as opposed to the originators or other generics).
- A composite pack is not approved in any country but an application has been filed in Canada.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared 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

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

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

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

Marie Stopes International (London), which is a registered charity in the UK and a global partner with Marie Stopes International (Australia) (MSIA).

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

The rationale for the composite pack presentation is therefore logical and according to the sponsor *'will allow a simplification in the use of the mifepristone – misoprostol method for termination of pregnancy and will ensure a better compliance (less risk that a woman omits to take the misoprostol tablets after having taken the mifepristone tablets).'*

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

Contents of the clinical dossier

The submission contained the following clinical information:

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

Paediatric data

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

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

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

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

Good clinical practice

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

Pharmacokinetics

Studies providing pharmacokinetic data

The dossier included one pharmacokinetic study which has been summarised.

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

Evaluator's conclusions on pharmacokinetics

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

Pharmacodynamics

There were no pharmacodynamic studies submitted.

Dosage selection for the pivotal studies

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

Efficacy

Studies providing efficacy data

Study 1.1.4, the Authorised prescriber program and a literature review were provided to the TGA. Discussion of this information may be found in the CER extract (Attachment 2).

Evaluator's conclusions on efficacy

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

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

Under the Authorised Prescriber Program in Australia in 2012, there were 7166 medical terminations, with 2678 for GA greater than or equal to 49, performed using mifepristone

200 mg followed by misoprostol 800 microgram buccally. The overall success rate was 96.6% and success rates for GA 49-63 (94.6% to 96.9%) were in line with gestational age < 49 (97.4%). The ongoing pregnancy rate was slightly higher 0.6%-0.9% at 49-62 days compared to 0.3% at < 49 days.

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

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

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

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

Safety

Studies providing safety data

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

Patient exposure

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

Safety issues with the potential for major regulatory impact

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

There were no deaths in the Authorised Prescriber Program.

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

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

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

- Acute necrotising pancreatitis following second trimester TOP with mifepristone 600 mg and gemeprost (reference 980, Hallberg 2004).
- Vasospastic angina pectoris with loss of consciousness, bradycardia and seizures following mifepristone 600 mg and gemeprost 1 mg (reference 981, Lindhardt 2000).
- Uterine rupture following termination of pregnancy at 12 weeks with mifepristone 200 mg and misoprostol 800 microgram vaginally and 400 microgram orally (reference 982, Willmott 2008).
- Birth of child with Mobius syndrome (facial palsy, microretrognathia, axial hypotonia) following foetal exposure to mifepristone 600 mg and misoprostol 400 microgram orally during 7th week of pregnancy (reference 983, Bos 2008).
- Congenital abnormalities (vascular abnormalities and early amniotic rupture with resultant limb deformities) were reported in two cases with exposure during pregnancy to misoprostol (reference 984, Rosa 2007 and reference 985, Genest 1999)
- A reported congenital malformation rate of 4.2% in a prospective review of 105 pregnancies exposed of mifepristone or mifepristone and misoprostol (reference 987, Bernard 2013).

Postmarketing data

The dossier included two PSURs.

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

The GyMiso® (misoprostol) 200 microgram tablet PSUR covered the period from 29 October 2012 to 28 April 2013. This was the first Australian PSUR for GyMiso® following approval on 29 August 2012. During the period a total of 13138 packs (containing 2 x 200 microgram tablets) were distributed in France. There was no distribution in Australia. (It is noted that the pack size in Australia is 4 x 200 microgram). A further 1960 packs were distributed for Gynuity Health Projects leading to a total patient exposure of 15,098 women.

Details of adverse events reported are discussed in the Delegate's Overview below (pages 30-32 of this AusPAR).

One death was reported in Australia in May 2013; the patient took mifepristone Linepharma 200 mg followed by misoprostol 800 microgram (different brand to the current application) a day later at 47 days of gestation. The patient developed sepsis with acute renal failure and died 12 days after taking the medication. [1,2]

[1] Sponsor comment: "The cause of death is awaiting a coroner's final determination" .

[2] See also *Delegate's Overview Overall conclusion and risk/benefit assessment, General comments on safety and Infection* below (page 31 of this AusPAR).

Evaluator's conclusions on safety

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

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

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

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

There were no deaths reported in the clinical trials or in the Authorised Prescriber Program data analysed. There was one death from sepsis 12 days post treatment reported in post-marketing surveillance.[1,2]The subject had received mifepristone and a different brand of misoprostol at 47 days of gestation.

Serious adverse events occurred in 1.1% of the study 1.1.4 population. All were related to hospitalisation for D&C to manage bleeding. There was one reported case requiring transfusion and one IV antibiotics (0.1% each). In the Authorised Prescriber Program the rate of rate of incomplete abortion requiring surgical aspiration was 3.0%, haemorrhage requiring transfusion 0.07%, haemorrhage not requiring transfusion 0.25% and infection (known or suspected) 0.54%.

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

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

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

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

First round benefit-risk assessment

First round assessment of benefits

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

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

First round assessment of risks

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

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

First round assessment of benefit-risk balance

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

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

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

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

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

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

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

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

Other risk management processes must continue such as appropriate training of medical practitioners, limiting the access and distribution of the medicines to appropriate practitioners and mandatory follow up of patients. In addition, there should be ongoing monitoring of off label use beyond 63 days as well as in women aged <18 years in whom safety data are lacking.

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

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

First round recommendation regarding authorisation

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

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

Any possible future authorisation would need to be subject to:

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

Clinical questions

Efficacy and safety

There were two key questions for this application:

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

The dosing instructions need to be clarified:

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

Other questions relating to the evidence base:

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

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan dated 31 May 2013 which was reviewed by the TGA.

Contents of the submission

With the current application, the sponsor has provided a RMP dated 31 May 2013, although no version number is provided. The sponsor has not included a summary of the changes from previous RMP versions which has complicated the evaluation process.

The sponsor states that only routine pharmacovigilance activities are require for MS-2 Step. However, a post-marketing study is proposed. This is considered additional pharmacovigilance.

Summary of ongoing safety concerns

Table 1. Summary of ongoing safety concerns as specified by the sponsor

Identified risk:	Bleeding Infection, toxic shock syndrome Method failure Uterine contractions / cramping Uterine infection (endometritis, pelvic inflammatory disease) Nausea, vomiting Diarrhoea Hypotension Skin rashes, urticaria
Potential risk:	Inadvertent pregnancy exposure and risk of incomplete abortion with severe bleeding Inadvertent pregnancy exposure (risk of malformations) Potential interaction with CYP3A4 inhibitors or inducers Potential interaction with products interacting with the glucocorticoid receptor Severe asthma uncontrolled by treatment Effects in lactating women
Missing information:	Inherited porphyria Theoretical interaction with NSAIDs Potential interaction with products interacting with the progesterone receptor Use in adolescents
Pharmacological class effect	Risks related to the use of prostaglandin

It was recommended the following be added to the list of ongoing safety concerns:

- Potential for missed ectopic pregnancy:
  - For terminations from 50-63 days gestation, the potential for missed ectopic pregnancy is an important consideration compared to terminations <49days.
  - In previous evaluations for both Mifepristone Linepharma and GyMiso®, the potential for delayed diagnosis of an ectopic pregnancy has been raised. The evaluator does not contend that mifepristone or misoprostol cause ectopic pregnancy. However, given the difficulty of diagnosing some ectopic pregnancies and the catastrophic consequences of missed or late diagnosis including death, it is reasonable to include this as an important potential risk.
  - Since 2002, the WHO Global Database of individual Case Safety Reports (ICSRs) lists a total of 65 ectopic pregnancies/ruptured ectopic pregnancies in women treated with mifepristone and misoprostol.
  - This is an important potential risk that should be reported on within PSURs.
- Potential for postnatal developmental delay:

- In the evaluation process for Mifepristone Linepharma, the non-clinical evaluator raised the potential concern for postnatal development delay if a pregnancy is continued after exposure to mifepristone.
- In the current RMP under evaluation, the sponsor makes the following statement, under the nonclinical safety specification: *"These results indicate that in case a woman carries her pregnancy to term despite exposure to mifepristone during pregnancy, there is some potential for postnatal development to be delayed."*
- The potential for postnatal development delay is a crucial piece of information that will assist physicians to counsel women for whom there has been method failure when considering their options for further management (for example continue with the pregnancy or proceed to surgical termination). This should also be included in the Australian PI and physician educational materials.
- Since 2003, the WHO Global Database of individual Case Safety Reports (ICSRs) lists a total of 9 adverse events of developmental delay (and related conditions) in children who experienced foetal exposure to mifepristone and misoprostol.
- This is an important potential risk that should also be reported on within the PSURs.

· Potential for off-label use, including use beyond the first trimester of pregnancy.

· Potential safety risks in vulnerable groups including rural, indigenous and non-English speaking women (with particular regard to the risks of being lost to follow-up for bleeding or infection).

Reconciliation of issues outlined in the RMP report

Table 2 summarises the TGA's first round evaluation of the RMP, the sponsor's responses to issues raised and the TGA's evaluation of the sponsor's responses.

Table 2. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
An application was made to the United States (US) in November 2009 which is also still pending. It is recommended that the sponsor clarify the reason for the delay in this application process in the US.	Linepharma's application in the US (for an Abbreviated New Drug application, ANDA) is currently on hold until Linepharma provides the results of a bioequivalence (BE) study after subjects have taken a meal: indeed a new regulation for ANDAs requires that BE studies are performed in the fasting state and after a calibrated meal. Linepharma is currently exploring the optimal conditions for such a study.	This was acceptable.
It is noted that the following important potential risks have been removed from the list of ongoing safety concerns compared to the previously evaluated RMP	The sponsor confirms that these ongoing safety concerns are included	This was acceptable.

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
dated 27th March 2012. It is recommended that these be added to the list of important potential risks, unless the sponsor can provide compelling justification for their exclusion: Effects in women with impaired liver function Effects in women with impaired renal function Effects in women with malnutrition		
The following should also be added to the list of ongoing safety concerns (see RMP evaluation Round 1 Report for further details): Potential for missed ectopic pregnancy: Potential for postnatal developmental delay: Potential for off-label use, including use beyond the first trimester of pregnancy (see Section 9.2). Potential safety risks in vulnerable groups including rural, Indigenous and non-English speaking women (with particular regard to the risks of being lost to follow-up for bleeding, infection etc).	The sponsor confirms that these potential risks have been added to the ongoing safety concerns in the RMP. The potential risk of postnatal development delay has also been included in the PI.	This was partially acceptable. There was no reference to vulnerable groups including women living in rural areas, Aboriginal and Torres Strait Islander or non-English speaking women.
Routine risk minimisation activities are insufficient to appropriately mitigate all the specified ongoing safety concerns, and this should be reflected in the proposed use of additional risk minimisation activities	The sponsor confirms that these changes have been made in the RMP.	This was acceptable.
The sponsor has not given sufficient consideration in the RMP or educational materials to the potential risk of medication error as a result of variations in approved indications. It is recommended that the sponsor update the relevant sections of the RMP to include consideration of this risk. Furthermore, the RMP should include post-marketing data regarding rates of medication error of the component products.	After consideration of the situation for the single pack products the sponsor now proposes the following: Steps will be taken that will prevent variations in indication occurring for the marketed products used in the indication of medical termination of first trimester pregnancy. Response relating to the RMP question 5. In view of the	This is partially acceptable One RMP section still contains statements that require updating.

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
	steps being taken with regard to resolving any difference in product indications, the sponsor proposes that there is no special need to implement other steps with regard to the potential for medication errors, beyond those described in the RMP Potential for medication errors.	
It is also noted in the CMI instruction insert that the Mifepristone Linepharma tablet is inscribed with the initials "MF", and the GyMiso® tablet is inscribed with the initials "ML" This may confuse consumers and lead to medication error as "ML" may be interpreted as the initials for "Mifepristone Linepharma".	The CMI Instruction Insert has been changed so that the tablets depicted do not show any inscription of letters.	This was acceptable.
The potential for off-label adult use of MS-2 Step is not adequately addressed in the RMP. The statements made regarding mifepristone are misleading as they appear to refer to other brands and doses of mifepristone. This section should specifically refer to mifepristone linepharma and MS-2 Step. Where reference is made to products other than Mifepristone Linepharma, this should be clearly stated. Furthermore, the potential for off-label use of MS-2 Step should be specifically addressed in this section. It is recommended that the sponsor update this section with postmarketing data regarding off-label use of Mifepristone Linepharma and GyMiso.	The sponsor confirms that this section of the RMP has been revised accordingly.	This was only partially acceptable. While some improvements have been made to this section of the RMP, the sponsor has not stated the number of reported cases of off-label use of Mifepristone Linepharma or GyMiso®. The sponsor should amend this section with the next update of the RMP to provide adequate data on off-label use.
A number of issues regarding the risk management plan for MS-2 Step require clarification: There is no mention of the medical education programme in this section. The sponsor should include an overview of the	The sponsor has made revisions to the RMP that specifically address the points, including an update on the number of risk minimisation tools and an overview of the Medical	This was acceptable.

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
aims of this programme with a list of published versions and changes/updates to the programme. One section states that there are three specific risk minimisation tools, which contradicts the activities presented in another section. In Appendix 5 MS Health Proposed Australian Education programme, 24-hour after care and follow-up text messaging is listed as part of the risk management plan. The RMP does not mention this activity and should be updated accordingly. The sponsor states in the RMP the following as part of the risk management plan "The set of recommendations implemented in the MS-2 Step Product Information and/or Consumer Medicine Information for Mifepristone and GyMiso®." It is recommended that the sponsor clarify this statement and define to which recommendations they are referring.	Education programme. The RMP and the Appendix 5 have been made consistent with regard to mention of the after-care and follow-up text services provided.	
Medical Education Programme: There is internal inconsistency throughout the training manual when referring to MS-2 Step, mifepristone and misorpostol, mifepristone linepharma and GyMiso. In some cases, reference to MS-2 Step (shown in red text with strikethrough) has been removed completely for no apparent reason. It is recommended that the sponsor review this document and improve the consistency of referring to each product. It is recommended that the education programme should emphasise that the proposed indication of MS-2Step (that is, up to 63 days gestation), is different from that of it's component products (that is, up to 49 days gestation). This will reduce the likelihood of inadvertent off-label use of the component products. Regarding termination of pregnancy after the first trimester: The sponsor Clarifies that GyMiso is not approved for this indication, however there is no mention of	The sponsor confirms that the points have been taken into account in the revised Medical Education Programme. The Medical Education Programme has been reviewed and updated to remove inconsistencies when referring to MS-2 Step. The difference in the indication for MS-2 Step and the mifepristone monoproduct has been clearly articulated within the amended Medical Education Programme. A Statement confirming that MS-2 Step is not indicated for medical termination of pregnancy beyond 63 days of gestation has been added to the Medical Education Programme. The method of assessment is	This was only partially acceptable. The Medical Education Programme still contains internal inconsistency.

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
MS-2 Step in this section. It is recommended that a statement to the effect of "MS 2-step is not approved in Australia for termination of pregnancy for gestations beyond 63 days" be added to this section. The sponsor does not clarify the method of assessment of practitioners completing the training programme. It is recommended that the sponsor clarify how Australian prescribers who participate in the education programme will be assessed. In light of the difference in proposed indication for MS-2 Step compared to its component products, the effectiveness of the updated MS-2 Step educational materials should be evaluated. The sponsor is requested to clarify the methods that will be used to achieve this and the expected timelines/milestones for this process. Healthcare professionals are directed to the MS Health Website for the healthcare practitioner training <www.mshealth.com.au>. However, the sponsor has not provided the TGA with access to the online training, or provided screenshots of this training programme within the RMP. It is recommended that the sponsor clarify that the content of the online training is exactly the same as that provided in the training manual. Ideally, the RMP should contain screenshots of the proposed online training to ensure consistency with future evaluations and updates.	clearly defined within the training programme (refer to the copy of the training information provided in Appendix 5 to the revised RMP). The content of the online Medical Education Programme is derived from the Medical Education Training Manual. The updated Medical Education Training Programme and Manual are provided as Appendix 5 of the revised RMP.	
Patient Information Sheet and Consent Form: Section three: How to take the medicines contained within MS-2 Step: This section may be confusing to consumers regarding the important difference in the misoprostol administration method for terminations after 50 days gestation. It is recommended that this section be restructured to improve clarity. For example the two methods of administration should be listed as	The sponsor confirms that the above points have been taken into account in the revised Patient Information Sheet and Consent Form.	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
alternatives, with an option for the prescribing doctor to circle/tick box the correct method for the individual patient. In light of patients performing these steps days after receiving medical instructions from their doctor and without medical supervision, it is important that patients have a clear memory aid regarding their prescribed administration method. See table footnote* below. The patient information sheet does not direct patients to their local emergency department for emergency care. A statement to this effect is recommended (please note, this was also raised in earlier evaluations but remains unchanged). The consent form shown in Section 7 does not address minor's and "mature minor's". It is recommended that the Patient Information Sheet and Consent Form contain a space for physicians to record the follow up appointment time/date under Section Six titled "Follow up". In light of the new combination pack and differences in administration methods for MS -2 Step depending on gestational age, the effectiveness of this updated form should be evaluated. It is recommended that the sponsor provide details of how this will be achieved.		
MS-2 Step CMI Instruction Insert The MS-2 Step CMI instruction insert does not mention the importance of medical follow up after completion of treatment, regardless of the presence of adverse events. The statement placed on the instruction insert states "If you have any questions please contact your doctor, or the MS-2 Step 24-hour Nurse Aftercare Telephone Service...". Although the prescribing doctor is likely to discuss follow-up and make the appropriate appointments for the patient, this statement at the end of treatment may imply that medical follow is only required if they have questions. It is recommended that a statement be added after the purple "Step 2" section regarding the importance	The sponsor confirms these changes have been made to the CMI Instruction Insert.	This was acceptable.

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
of seeing a doctor after taking MS-2 Step to ensure that the therapy has been effective.		
In regard to the proposed routine risk minimisation activities, the Delegate may wish to revise the draft product information document as follows: Under "Use in pregnancy", the wording should be strengthened regarding the importance of counselling women on the risk of postnatal developmental delay, should the patient wish to continue with her pregnancy after exposure to MS-2 Step. Under "Dosage and Administration" a statement should be added to the effect of "doses higher than 200mg should not be given". Under "Dosage and administration", an additional section should be added to the effect of "before prescribing MS-2Step". This section should list the important preparation steps of identifying gestational age, rhesus status, STI screening, prophylactic antibiotics, pain management, completing the informed consent process, advising on the importance of follow up and ensuring that the patient has received the Patient Information Sheet. Under "Precautions" a statement should be added to the effect of "uterine hyperstimulation and rupture have been reported with the use of misoprostol beyond the first trimester when a much lower dosage of misoprosotol may be required to induce abortion". This is important to clarify in light of the conflicting approved indications of the component products of MS-2 Step. Under "Adverse Effects" the Delegate may wish to consider if this section should be re-structured.	The sponsor confirms that the points in the first 4 bullets shown above can be included in the respective revised CMIs, pending the decision of the Delegate in the Delegate's Overview (refer to instructions in the RMP Report, Section 11, page 29). As per discussion with TGA at the 26 November 2013 meeting, the option in bullet 5 to change the format of the tabulation of the Adverse Effects has been agreed, and is already included in the revised PI.	This was acceptable.
In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicine information document be revised as follows: The section "How to take misoprostol"	The sponsor confirms that the revisions can be included in the respective revised CMIs, pending the decision of the Delegate in the Delegate's Overview).	This was acceptable.

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
should be re-structured. See table footnote* below. The CMI for both Mifepristone Linepharma and GyMiso® should have a statement added to the Section titled "After being given the mifepristone tablet/misoprostol" regarding the important of medical follow-up after taking mifepristone/misoprostol regardless of adverse events. If the Delegate wishes to make any changes to the product information, the CMI should be updated accordingly.		

* The route of administration for GyMiso® 800 micrograms of misoprostol (4 tablets, each tablet containing 200 micrograms) was altered to be buccally (that is, kept between the cheek and the gum for 30 minutes before any fragments being swallowed with water) for medical termination of developing intra-uterine pregnancy up to 63 days of gestation (that is, not different for intra-uterine pregnancies up to 49 days and 50-69 days).

VI. Overall conclusion and risk/benefit assessment

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

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

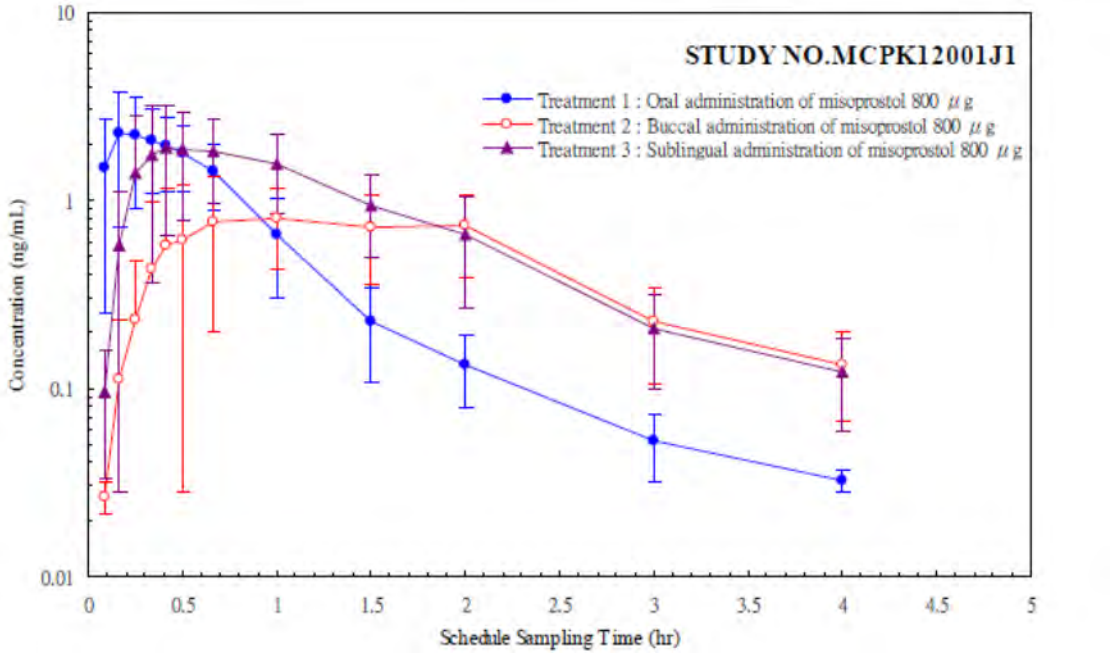
There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Pharmacokinetic study

Study MCPK12001J1 was a 3-way (oral versus sublingual versus buccal) cross-over study conducted in 10 healthy women.

Table 3. Concentration-time profile



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

The higher bioavailability by sublingual route of administration may be explained by the absence of a first-pass effect by the liver. For buccal administration, some portions of the dose may be swallowed and metabolised by the liver before reaching the systemic circulation and so result in a lower exposure than the sublingual route.

Efficacy

Four main sources of data on efficacy (for the extension from 49 days to 63 days) were provided:

- Phase III study conducted in Mexico (Study 1.1.4).
- Literature review.
- A summary of authorised prescriber experience at MSIA clinics in 2012.
- Interim results for the post-registration study (4 months: March 2013 to June 2013; 1957 women).

Phase III study conducted in Mexico (Study 1.1.4)

Table 4. Study 1.1.4, 2010-2011, 3 sites in Mexico

Patients	Women requesting termination of pregnancy at < 63 days. Gestational age was confirmed by US for all women enrolled. Exclusions: IUD users, suspected ectopic pregnancy Mean age: 24 years, mean gravidity: 2.3, previous abortion: 9.6%, previous medical abortion: 7.4%, < = 49days: 57%, 50-63 days: 43%
Intervention	Women were given mifepristone (200mg) (Mifepristone Linepharma 200 mg), and then self-administered misoprostol (800microgram) (Cytotec Pfizer USA) buccally at home, 1-2 days later. The instructions were to hold the tablets in the cheek pouch for 30 minutes and then swallow remnants. If termination was incomplete at day-8, a second dose of misoprostol (800microgram) was given (25 women),
Comparator	Nil, single arm study
Endpoint	The primary endpoint was abortion status. The outcome of complete abortion was defined as uterine evacuation with study drugs alone without recourse to surgical uterine evacuation for any reason. This was determined by history, clinical/pelvic examination and ultrasound one week post medication.
Follow-up	Follow-up at day-8 assessed termination status. Women with complete termination finished the study. Those with an incomplete termination had a second dose of 800microgram misprostol and were followed-up sometime between days 15-36. Those with an incomplete termination had surgery.
Sample size	A sample of 500 participants was estimated to be sufficient to demonstrate 95% efficacy with a 95% confidence interval of ± 2%. A sample of 1000 was chosen to allow for subject variability. 29 women did not return for their follow-up visit and are excluded from the analysis.

Table 5. Outcome by gestational age (n = 971)

	< = 49days	50-56 days	57-63 days	64+ days	Total
Complete medical termination, n (%)	540 (98.0)	239 (96.8)	164 (95.9)	2 (100.0)	945 (97.3)
Surgical evacuation, n (%)	11 (2.0)	8 (3.2)	7 (4.1)	0 (0.0)	26 (2.7)

Table 6. Outcome by gravidity (n=971)

	primip	multip	Total
Complete medical termination, n (%)	342 (97.2)	603 (97.4)	945 (97.3)

	primip	multip	Total
Surgical evacuation, n (%)	10 (2.8)	16 (2.6)	26 (2.7)

Table 7. Reasons for surgical evacuation

Reason	N
Bleeding problem	16
On-going pregnancy	6
Persistent sac	2
Other	2
Total	26

Literature review

The sponsor identified 6 studies, where the method was mifepristone (orally) followed by misoprostol (800 microgram buccally); and where method failure was stratified by gestational age. The sample size for 50 + days stratum ranged from ~ 40 to ~ 400 women. The method failure rates were: 50-56 days: 2% to 14%; 57-63 days: 0% to 7%. Heterogeneity in study design and study quality; and concerns about the applicability of data from middle and low income countries to a high income country like Australia, make this literature review difficult to interpret. Further, the review only includes those studies that happened to provide data stratified by gestational age. These might be an unrepresentative sample of all studies.

A systematic review (Raymond 2012) assessing first trimester medical abortion with mifepristone 200 mg and misoprostol identified 87 trials with 47,283 treated women, with pregnancies of up to 63 days. There was no breakdown by gestational age.

The method failure rate in the subgroup who received mifepristone with misoprostol ≥ 800 microgram for the various routes of administration of misoprostol was 3.2% (71/2205) for buccal, 6.5% (158/2449) for oral, 5.2% (52/1003) for sublingual and 3.4% (653/19210) for vaginal.

Data from the Australian Authorised Prescriber Program, 2012

The sponsor collected efficacy and safety data during the Authorised Prescriber Program in 2012.

Table 8. Authorised Prescriber data

Patients	Women attending prescribers who were part of the Marie Stopes International Australia Authorised Prescriber Program 4488/7166 (63%) had pregnancies <49 days gestation. 2678/7166 (37%) had pregnancies 49-63 days gestation

Intervention	Medical terminations were performed using mifepristone 200 mg followed by misoprostol 800 microgram bucally. If no bleeding occurred within 24 hours of the misoprostol dose a second 800 microgram dose was given.
Comparator	nil
Endpoint	Method failure
Follow up	Patients were followed up at 14-21 days post mifepristone dose. (79% returned for follow-up)

Table 9. Outcome by gestational age, Authorised Prescriber Program (n=7166)

	< 49 days	49-55 days	56-63 days	Total
Complete medical termination, n (%)	4370 (97.4)	1846 (94.6)	704 (96.8)	6920 (96.6)
Surgical evacuation, n (%)	103 (2.3)	94 (4.8)	17 (2.3)	214 (3.0)
Continuing pregnancy	15 (0.3)	11 (0.6)	6 (0.8)	32 (0.4)

The categories are slightly different from Mexican study (only by one day; < 49 rather than < = 49)
For 49-63 days: 128 / (2550 + 128) x 100% = 4.8%

Interim data from the post-registration study (Mar 2013-Dec 2013)

Four months of data from MSIA clinics (Melbourne, Sydney, Brisbane, Canberra, Perth, Newcastle, Gold Coast, Rockhampton, Townsville). Women are either self-referred or referred by their GP. (In Western Australia, all women must be referred by a doctor, by law.) All women had ultrasound dating. All women who returned to the clinic for follow-up had a repeat ultrasound.

Table 10. Data from Marie Stopes International Australia clinics

Patients	Women attending Marie Stopes International Australia clinics. Average age: 29 years.
Intervention	All had mifepristone 200mg, followed by misoprostol 800 microgram, buccally
Comparator	Nil
Endpoint	Method failure
Follow-up	3561 (79%) returned to the clinic. 355 (8%) had telephone follow-up 574 (17%) were lost to follow-up; these women did not respond to repeated phone calls and a registered letter.

Table 11. Outcome by gestational age, Post-registration study (n=4490), March 2013-December 2013

	<=49 days (on label)	50-63 days (off label)
Method-failure	126/3641 (3.5%)	53/849 (6.2%)

Safety

Safety for the extension of indication from 49 days to 63 days

Safety data from the Phase III Mexican study and from the literature review were not stratified by gestational age; and consequently are of limited use for this submission to extend the indication from 49 to 63 days.

Data from the Australian Authorised Prescriber Program, 2012

Haemorrhage requiring transfusion occurred in 5/7166 (0.07%); <49 days: 1/4488 (0.02%); 49-63 days: 4/2688 (0.1%). Any haemorrhage occurred in 16/7166 (0.2%); <49 days: 3/4488 (0.07%); 49-63 days: 13/2688 (0.5%). This was substantially lower than in the post-registration study, but the definitions may have differed (the sponsor will be asked if the definitions differed; see questions below).

Suspected infection occurred in 7 (0.4%) women with < 49-day pregnancies and 1 woman at 49-63 days. Known infection occurred in 2 women with < 49-day pregnancies (none: 50 + days). The category "sepsis" was not reported.

There were no cases of uterine rupture or death.

Table 12. Interim data from the post-registration study (Mar 2013-Sep 2013) (data provided for Oct-Dec 2013 were similar)

	< = 49 days (on label)	50-63 days (off label)	Total
Bleeding with clots	75(3)	32 (6)	107 (3)
Blood transfusion	6 (0.2)	1 (0.2)	7 (0.2)
Uterine rupture/hysterectomy	0	1	1
Reproductive tract infections	3	0	3
Death (due to sepsis)	1	0	1

There was one death due to sepsis (awaiting coroner's case) and two other cases of infections.

General comments on safety

Termination by any method carries risks and complications; as does pregnancy and childbirth.

Many millions of women have been treated with mifepristone in single doses of 200 to 600 mg with prostaglandin for termination of pregnancy, since 1988 when mifepristone was

first registered in France. Serious adverse reactions are rare and are to infection, bleeding, undiagnosed ectopic pregnancy, and uterine rupture.

Infection

According to several reviews in large treatment populations, the infection rate is < 1%.

Fatal sepsis is rare (< 1 in 100,000).

The FDA published a Postmarketing Adverse Events Summary in 2011, after an estimated 1.5 million medical abortions with mifepristone in the United States. The Summary discusses 14 deaths associated with mifepristone of which 8 were from sepsis (Of the remainder, 2 were from ectopic pregnancy; and the other 4 were incidental [for example, drug overdose, homicide]). Of the 8 due to sepsis, 7 were positive for *Clostridium sordellii* and 1 for *Clostridium perfringens* (7 of the women used vaginal misoprostol; 1 used buccal misoprostol). Although some experts have hypothesised a link with vaginal administration of misoprostol, this hypothesis has not been formally tested.

Fatal toxic shock syndrome associated with *Clostridium sordellii* also occurs in association with childbirth and spontaneous termination.

The symptoms of *Clostridium sordellii* infection are sometimes not the usual symptoms of sepsis. Therefore, the possibility of sepsis should be considered in all women who are undergoing medical termination and who present with nausea, vomiting, or diarrhoea and weakness with or without abdominal pain. These symptoms, even without a fever, may indicate *Clostridium sordellii* infection. Strong consideration should be given to obtaining a complete blood count in these patients. Significant leukocytosis with a marked left shift and haemo-concentration may be indicative of sepsis. Doctors should consider immediately initiating treatment with antibiotics that includes coverage of anaerobic bacteria such as *Clostridium sordellii*.

Prophylactic antibiotics

This was considered at the August 2012 ACPM. Prophylactic antibiotics were not recommended in line with overseas regulatory agencies. The reasons given by the FDA for not recommending prophylactic antibiotics are:

- fatal sepsis in women undergoing medical abortion is rare.
- prophylactic antibiotic use carries its own risk of serious adverse events such as severe or fatal allergic reactions.
- prophylactic antibiotics use can stimulate the growth of antibiotic-resistant bacteria
- there is a lack of evidence as to which antibiotic and regimen (what dose and for how long) would be effective.

Severe bleeding

Vaginal bleeding (and some degree of abdominal/pelvic/uterine pain) is intrinsic to the process of medical termination. Blood transfusion is sometimes used as an indicator of severe bleeding. Most studies report low rates of blood transfusion (<0.1%). The risk of severe bleeding is higher in the first trimester than the second (0.1% versus 0.4%). Whether there are material differences in the risk of severe bleeding for 49 days versus 63 days is an open question. Missed ectopic pregnancy is rare, but can cause severe bleeding and death.

ACSOM advice

ACSOM noted that there was a stigma associated with termination of pregnancy, and patients may be unwilling to seek follow-up. This means that the PI, CMI and education program require further editing to provide patients with a clear and concise source of information, under the assumption that women might not seek follow-up.

ACSOM advised that the PI for MS-2 Step should only contain information about that product. ACSOM further advised that references to repeat doses of misoprostol (in the event of method failure) should be removed from the PI and a statement added that patients should seek medical follow-up in the event of method failure.

ACSOM noted that the indication (before 49/63 days) referred to the time of starting the procedure; the end of the procedure may extend beyond that time.

ACSOM noted that, in early pregnancy, US dating was accurate to within 3 days. *'As the failure rate increases with increased gestation, the use of ultrasound to accurately date pregnancy is important.'*

Women might expect heavy bleeding. ASCOM was concerned that without medical follow-up haemorrhaging due to ectopic pregnancy could be missed.

Clinical evaluator's recommendation

There is no reason to say, at this time, that MS-2 step should not be approved.

Risk management plan

There are no outstanding RMP issues. The sponsor and the TGA are in communication about the educational materials.

Risk-benefit analysis

Delegate's considerations

The applicability/relevance of a Phase III study conducted in Mexico to the specific circumstances of MS-2 Step use in Australia is questionable. Similarly the applicability and representativeness of the studies identified in the literature review is questionable. Also, their quality is variable.

Consequently, the best data we have to compare method failure for 49 days versus 63 days is from the Australian Authorised Prescriber Program (2012) and the Australian Post-Registration Phase IV study (Mar-Dec 2013).

For the Australian Authorised Prescriber Program (2012), the failure rate was: < = 49 days: 118/4488 (2.6%) versus 50-63 days: 128 / (2550 + 128) x 100% = 4.8%.

For Australian Post-Registration Phase IV study (Mar 2013-Dec 2013), the failure rate was: < = 49 days: 126/3641 (3.5%) versus 50-63 days: 53/849 (6.2%).

The Delegate's preliminary view, at this point-in-time, and pending ACPM advice is that failure rates of 5-6% at 50-63 days are acceptable and that the extension of indications could be allowed; which would bring the indication in Australia into line with nearly all other countries (with the notable exception of the United States, where the indication is 49 days).

Safety at 50-63 days is similar to that up to 49 days. Bleeding with clots is more common, but there are no data to suggest that bleeding requiring blood transfusion is more common. Sepsis is a very rare, but serious and potentially life-threatening adverse reaction. There are no data to suggest that it is more common at 50-63 days than up to 49 days.

Proposed action

Request for ACPM advice

- Has the safety and efficacy of MS-2 step been satisfactorily established by the sponsor for women with gestations of 50-63 days?

The ACPM is asked to provide expert clinical advice on the PI. In particular:

- The information on ultrasound under indications
- Information about what to do if termination does not occur under Dosage & Administration (information about a second dose of misoprostol has been removed).

Response from sponsor

The sponsor had comments on the Request for ACPM's Advice (dated 28 February 2014) for the application to register the MS-2 Step composite pack product in Australia.

Changes to indications for the individual products

The sponsor agreed that should the composite pack product be registered, then the sponsor will remove the indication for medical termination of pregnancy from the mono product Mifepristone Linepharma, and will withdraw the mono product GyMiso® from supply to the market.

Clinical efficacy – Data from the Australian Authorised Prescriber Program

The sponsor provided a revised calculation of failure rate for terminations at 50-63 days gestation, for consideration by the ACPM. The number of women reported in the 2012 data set with complete abortion is 2550, and the number with incomplete abortion is 128, as stated. However, the failure rate calculation therefore should be:

128 / (2550 + 128) x 100% = 4.8%

Clinical efficacy – Interim data from the post-registration study

Failure rate calculations for the period March to December were 126/3641 or 3.5% for terminations at less than or equal to 49 days gestation, and as 53/849 or 6.2% for terminations at 50-63 days gestation.

The sponsor clarified that the number used to calculate the failure rate in the less than or equal to 49 days gestation group should be 128/3641 (however, the calculated percentage remains the same at 3.5%).

Clinical safety - Data from the Australian Authorised Prescriber Program

The sponsor confirmed that the definitions used to collect data on haemorrhage under the Authorised Prescriber Program and in the Phase IV study were not different.

Clinical safety - Interim data from the post-registration study

The sponsor confirmed that adverse effects reported during the period March to September 2013, and for October to December 2013, were similar, as shown in the updated tabulation (see below).

Table 13. Data for March to September 2013 (n = 3327)

	≤49 days (on-label) n=2809	50-63 days (off-label) n=518	Total n=3327
Bleeding with clots	75 (3%)	32 (6%)	107 (3%)
Blood transfusion	6 (0.2%)	1 (0.2%)	7 (0.2%)
Uterine rupture/ Hysterectomy	0	1	1
Reproductive tract infections	3	0	3
Death (due to sepsis)	1	0	1

Table 14. Data for March to December 2013 (n = 4490)

	≤49 days (on-label) n=3641	50-63 days (off-label) n=849	Total n=4490
Bleeding with clots	103 (3%)	45 (5%)	148 (3%)
Blood transfusion	7 (0.2%)	1 (0.1%)	8 (0.2%)
Hysterectomy*	0	1	1
Reproductive tract infections	3	0	3
Death (due to sepsis)	1	0	1

Further, the following additional points are included for clarification.

- Case listed as uterine rupture/hysterectomy*: Hysterectomy was required in one patient following perforation of the uterus that occurred during surgical intervention following a failed medical termination.
- Case of death due to sepsis: The death is awaiting a coroner's final determination but an autopsy report noted acute lobar pneumonia and lung necrosis, and stated 'the relationship of the recent pregnancy termination and her demise is uncertain and may have been coincidental.'

Clinical safety – General comments

The Delegate noted that the rate of fatal sepsis is rare (< 1 in 100,000).

The sponsor confirmed that the rate of fatal sepsis is indeed very rare, since it is much less frequent than the usual very rare category of < 1 in 10,000.

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 a new combination of active ingredients and to extend the indications.
- The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered MS-2 Step containing mifepristone, one 200 mg tablet, misoprostol, four 200 µg tablets in a tablet blister pack to have an overall positive benefit–risk profile for the indication;

  Females of childbearing age for the medical termination of a developing intrauterine pregnancy up to 63 days gestation.

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

  Ultrasound is also useful to exclude ectopic pregnancy.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

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

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

Specific advice

The ACPM advised the following in response to the specific Delegate's questions on this submission:

1. Has the safety and efficacy of MS-2 Step been satisfactorily established by the sponsor for females/women with gestations of 50-63 days

The ACPM noted that surgical termination of pregnancy carries a greater risk and the risk of death in pregnancy is greater still than the risk of termination of pregnancy either medical or surgical. The ACPM was reassured by the post marketing data from other jurisdictions. The ACPM considered that there is no significant increase in bleeding and complications when the timing termination is increased from 49 to 63 days and that the safety and efficacy had been satisfactorily established.

2. The ACPM is also asked to provide expert clinical advice on clinical aspects of the PI. In particular:

    a. The information on ultrasound under *Indications*

The ACPM was of the view that the wording proposed by the sponsor regarding the use of ultrasound to confirm the duration of pregnancy was appropriate. If ultrasound is not available, the ACPM considered that it was appropriate that examination by a doctor be undertaken. The ACPM agreed that ultrasound was also useful in excluding ectopic pregnancy.

    b. Information about what to do if termination does not occur under Dosage & Administration.

The ACPM noted that the wording about a repeat dose of misoprostol had been deleted in the draft Product Information and replaced by wording in the Dosage and Administration section, which refers patients back to their doctor if termination does not occur. The ACPM agreed that the proposed wording was appropriate. However patient followup needed to be emphasised.

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 this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of MS-2 Step composite pack (mifepristone Linepharma 200 mg tablet mifepristone 200 mg tablet blister; GyMiso® misoprostol 200 microgram tablet blister) indicated for:

> *MS-2 Step is indicated in females of childbearing age for the medical termination of a developing intrauterine pregnancy, up to 63 days of gestation.*
>
> *It is recommended that the duration of pregnancy (that is, up to 63 days gestation) be confirmed by ultrasound. In the event that an ultrasound is not possible, extra caution should be exercised.*

Ultrasound is also useful to exclude ectopic pregnancy.

Specific conditions of registration applying to these goods

The MS-2 Step Risk Management Plan (RMP) dated 7 January 2014, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The Product Information approved for main tradename 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

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