Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for MS-2 Step Composite Pack

Active ingredients: mifepristone, misoprostol

Sponsor: MS Health Pty Ltd

October 2026

OFFICIAL

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List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ACOG	American College of Gynaecologists
AEs	Adverse event(s)
ARTG	Australian Register of Therapeutic Goods
AUC	Area under the concentration-time curve
CI	Confidence interval(s)
CMI	Consumer Medicines Information
NICE	National Institute for Health and Care (UK)
PI	Product Information
RANZCOG	Royal Australian and New Zealand College of Obstetricians and Gynaecologists
RCTs	Randomised controlled trials
RMP	Risk management plan
RR	Relative risk
SAEs	Serious adverse event(s)
TGA	Therapeutic Goods Administration

Product submission

Submission details

Type of submission:	Extension of indication
Product name:	MS-2 Step Composite Pack
Active ingredients:	Mifepristone Linepharma (mifepristone) and GyMiso (misoprostol)
Decision:	Approved
Approved therapeutic use for the current submission:	MS-2 Step is indicated in females of childbearing age for: • the medical termination of an intrauterine pregnancy, up to 70 days of gestation. • the medical management of missed miscarriage up to 70 days of gestation. For the medical termination of an intrauterine pregnancy, it is recommended that the duration of pregnancy (i.e. up to 70 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. Missed Miscarriage: the embryo or foetus has died, but the pregnancy tissue has not passed and is still in the uterus. Women who have had a missed miscarriage may be asymptomatic or have a small amount of vaginal bleeding or pain. For the medical management of missed miscarriage, it is recommended that the duration of pregnancy (i.e., up to 70 days gestation) and diagnosis of miscarriage be confirmed by ultrasound rather than last menstrual period. Repeat assessments with ultrasound may be needed to confirm the diagnosis. The safety and efficacy of MS-2 Step in other types of miscarriage, such as incomplete miscarriage has not been established. MS-2 Step is not indicated for threatened miscarriage.
Date of decision:	13 October 2026
Date of entry onto ARTG:	20 October 2026
ARTG numbers:	210574, 462239
▼*Black Triangle Scheme*	No
Sponsor's name and address:	MS Health Pty Ltd, Ground Floor East, 678 Victoria Street, Richmond, VIC, Australia, 3121
Dose form:	Tablet (mifepristone and misoprostol)
Strength:	Mifepristone Linepharma: each tablet contains 200 milligrams of mifepristone.

	GyMiso Each tablet contains 200 micrograms of misoprostol
Container:	Each MS-2 Step composite pack consists of: • One green carton containing Mifepristone Linepharma 200 mg tablet packaged in a PVC/PVDC/Aluminium blister. Pack size of 1 tablet. • One purple carton containing GyMiso® misoprostol 200 microgram tablet packaged in a dual-faced Aluminium strip or blister. Pack size of 4 tablets (2 tablets per blister).
Route of administration:	Oral (mifepristone); Buccal (misoprostol)
Dosage:	Mifepristone: 200 mg of mifepristone (1 tablet containing 200 mg) orally, followed 36 to 48 hours later by the administration of GyMiso®. GyMiso®: 800 micrograms of misoprostol (4 tablets, each tablet containing 200 micrograms) in a single dose buccally, i.e. kept between the cheek and the gum for 30 minutes before any fragments being swallowed with water. For further information regarding dosage, refer to the Product Information.

Product background

This AusPAR describes the submission by MS Health Pty Ltd (the Sponsor) to register (mifepristone, misoprostol) for the following proposed extension of indications:[1]

MS-2 Step is indicated in females of childbearing age for:

- *the medical termination of an intrauterine pregnancy, up to 70 days of gestation.**
- *the medical management of miscarriage up to 70 days of gestation, determined by ultrasound equivalence rather than last menstrual period.*

**It is recommended that the duration of pregnancy (i.e., up to 70 days of 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.

The submission by the Sponsor was literature-based, relying solely on published literature to support safety and efficacy claims.

The current indication for MS-2 step Composite Pack is:

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

[1] This is the original indication proposed by the Sponsor when the TGA commenced the evaluation of this submission.

Medical termination of pregnancy up to 70 days of gestation

Abortion or termination of pregnancy is defined as the ending of a pregnancy due to intervention. Medical termination of pregnancy is the use of medications to end the pregnancy and remove the pregnancy tissue. Current Australian legislation permits abortions to be performed in all states and territories beyond the first trimester when certain conditions are met. The first trimester is generally considered to consist of the first 12 weeks of pregnancy (84 days).[2]

Abortion rates in Australia are difficult to ascertain but have been estimated at 88,287 (17.3 abortions per 1000 women aged 15-44 years) during 2017-2018.[3] Of note, rates of surgical abortion have declined since the Pharmaceutical Benefits Scheme (PBS) listing of combination mifepristone/misoprostol in 2015. The number of PBS prescriptions for combination mifepristone/misoprostol for medical abortion was 51,261 in the 2024-2025 financial year.[4]

It is widely accepted that early medical abortion using mifepristone followed by misoprostol to end an early pregnancy is significantly more accessible, less invasive and less costly than surgical termination of pregnancy and can be provided to patients in a large range of settings. In addition, rates of unintended pregnancy are disproportionately higher among women who are socio-demographically disadvantaged and those living in rural areas, which also supports the rationale for increasing the gestational age for safe and effective medical terminations of pregnancy.[5]

Medical management of miscarriage up to 70 days gestation

Miscarriage is the involuntary, spontaneous loss of a pregnancy up to 20 weeks. In Australia, after 20 weeks gestation, the loss is classified as a stillbirth. Early pregnancy loss is a miscarriage which occurs in the first trimester. Early pregnancy loss can also include threatened miscarriage, recurrent miscarriage and losses from extra-uterine pregnancies. Miscarriage may be associated with unprovoked vaginal bleeding, with or without pain. Miscarriage is common but no specific data about miscarriages exist for Australia as no national register currently exists. Miscarriage rates after 14 weeks drop to 1-2% of pregnancies. The lifetime risk of miscarriage is nearly 25% with the risk increasing with age.[6]

For the purposes of this application, it is important to note that there are different types of miscarriage, as listed by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG):[6]

- **Incomplete miscarriage**: the partial loss of pregnancy tissue within the first 20 weeks' gestation. Incomplete miscarriage presents with moderate to severe vaginal bleeding, sometimes with the noticeable passage of tissue, that is typically associated with lower abdominal and pelvic pain.
- **Complete miscarriage**: refers to a miscarriage in which all the pregnancy tissue is expelled from the uterus. A complete miscarriage is characterized by vaginal bleeding, pelvic pain,

[2] WHO Abortion Care Guideline 2022 – Accessed 17 June 2026

[3] Keogh, LA, Gurrin, LC and Moore, P. Estimating the abortion rate in Australia from National Hospital Morbidity and Pharmaceutical Benefits Scheme data. Research Letters MJA, May 2021.– Accessed on 17 June 2026

[4] Services Australia. Pharmaceutical Benefits Schedule Item Statistics: MS-2 step. Item number 10211K. PBS items processed between 1 July 2024 to 30 June 2025.

[5] Rowe H, Holton S, Kirkman M, Bayly C, Jordan L, McNamee K, McBain J, Sinnott V, Fisher J. Prevalence and distribution of unintended pregnancy: the Understanding Fertility Management in Australia National Survey. Aust N Z J Public Health. 2016 Apr;40(2):104-9

[6] Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG). Miscarriage. Version 2, 2025

and the passage of pregnancy tissue. With a complete miscarriage, the bleeding pain should subside quickly.

- **Missed miscarriage**: the embryo or foetus has died, but the pregnancy tissue has not passed and is still in the uterus. Women who have a missed miscarriage may be asymptomatic or have small amounts of vaginal bleeding or pain. A missed miscarriage diagnosis may be made during a routine antenatal visit.
- **Threatened miscarriage**: refers to vaginal bleeding and uterine cramping in an otherwise viable pregnancy before 20 week's gestation, though more commonly occurring in the first trimester. Threatened miscarriage is strictly speaking not an early pregnancy loss and management of this condition is considerably different to other types of miscarriage.
- **Recurrent miscarriage**: two or more miscarriages in pregnancies up to 20 weeks' gestation (whether or not a gestational sac is present and whether or not the miscarriages are consecutive). Recurrent miscarriage also differs to other types of miscarriage in terms of management.

Current treatment options

Medical termination of pregnancy up to 70 days gestation

MS-2 Step is currently approved by the TGA for medical termination of an intrauterine pregnancy up to 63 days of gestation (9 weeks), subject to certain conditions. The RANZCOG Clinical Guideline for Abortion Care recommends a regimen comprising 200 mg of mifepristone delivered orally followed 24-48 hours later by 800 µg misoprostol delivered via the buccal, sublingual or vaginal route for early medical abortion up to 10 weeks of pregnancy (70 days).[7] Importantly, for the termination of pregnancies exceeding 63 days of gestation, no approved medicines are available in Australia and a surgical option for termination is the only alternative currently available for these patients without off-label use.

Medical management of miscarriage up to 70 days gestation

In general, patients experiencing early pregnancy loss are assessed for any conditions which require urgent management followed by treatment options which include expectant management, medication and/or a surgical suction aspiration (or manual aspiration). Patient preference, availability of treatment options and the benefit-risk balance of each method are considered when choosing treatment options. Expectant management refers to the process of waiting for products of conception to pass naturally without the use of medication or surgery. In the first trimester, efficacy rates of 70 – 80% have been reported for this approach. Medical management for early pregnancy loss can be considered in women without infection, haemorrhage, severe anaemia, or bleeding disorders who want to shorten the time to complete expulsion but prefer to avoid surgical evacuation.[8]

The RANZCOG Clinical Guideline for Miscarriage, Recurrent Miscarriage and Ectopic Pregnancy recommends use of 200 mg oral mifepristone followed by 800 µg (vaginal, buccal or sublingual) misoprostol 24 – 48 hours later for women choosing medical management of a missed miscarriage. For women choosing medical management of an incomplete miscarriage, the recommended regimen differs and includes only misoprostol 600 µg (sublingual or buccal) or

[7] Clinical Guideline for Abortion Care: An evidence-based guideline on abortion care in Australia and Aotearoa New Zealand (version 1.4) (2026). RANZCOG, Melbourne, Australia – Accessed 17 June 2026

[8] Neilson JP , Hickey M, Vazquez JC . Medical treatment for early fetal death (less than 24 weeks) . Cochrane Database of Systematic Reviews 2006, Issue 3.

800 µg (vaginal, buccal or sublingual). If bleeding has not commenced 24 – 48 hours after the first dose of misoprostol, then repeated doses of misoprostol 400 µg may be administered. Of note, mifepristone is not recommended in this guideline for medical management of an incomplete miscarriage.[9]

Misoprostol is currently approved by the TGA for induction of labour. The current TGA-approved indication for mifepristone is 'in females of childbearing age for: Preparation for the action of registered prostaglandin analogues that are indicated for the termination of pregnancy for medical reasons beyond the first trimester'.[10,11] Neither misoprostol or mifepristone have a specific miscarriage indication. Therefore, there are no approved medicines with an indication specifically for the medical management of miscarriage in Australia.

Regulatory status

Australian regulatory status

The component products of MS-2 Step, mifepristone and misoprostol, were first registered on the Australian Register of Therapeutic Goods (ARTG) with indications for pregnancy termination up to 49 days' gestation on 29 August 2012.[12,13]

The MS-2 Step composite pack was first registered on the ARTG on 4 June 2014, and the indication was extended to pregnancies up to 63 days' gestation in the same application.[14]

Further changes were made to the boxed warning to amend 'medical practitioner' to 'healthcare practitioner' and to amend Section 4.2 of the Product Information document from 'doctors with the appropriate qualifications and certified training' to 'healthcare practitioners with the appropriate qualifications and training' (in accordance with individual state and territory requirements), following approval on 28 June 2023, with registration on the ARTG on 10 July 2023.

A generic product, Arzestra (mifepristone, 200 mg tablet, and misoprostol, 200 µg tablet, blister pack, composite pack), was registered in February 2026.[15]

International regulatory status

In 2016, the United States Food and Drug Administration (FDA) approved mifepristone, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation.

The Sponsor has stated that a similar application (proposed for the medical management of first trimester miscarriage) is currently under review in the European Union under the decentralised procedure (a regulatory pathway allowing simultaneous marketing authorisations for a medicinal product in multiple European Union member states). An earlier EU decentralised procedure application for medical management of first-trimester miscarriage (submitted 28

[9] Miscarriage, Recurrent Miscarriage and Ectopic Pregnancy (C-Gyn 38) (version 1) (March 2025). RANZCOG, Melbourne, Australia

[10] TGA approved PI for ANGUSTA misoprostol – Accessed 17 June 2026

[11] TGA approved PI for Linepharma mifepristome. Accessed 17 June 2026

[12] ARTG Entry: MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet blister pack (175671)

[13] ARTG Entry: GyMiso misoprostol 200 microgram oral tablet blister pack (188015)

[14] ARTG Entry: MS-2 Step composite pack [MIFEPRISTONE LINEPHARMA 200 MG TABLET mifepristone 200 mg tablet blister; GyMiso misoprostol 200 microgram tablet strip] (210574)

[15] ARTG Entry: ARZESTRA mifepristone 200 mg tablet and misoprostol 200 microgram tablet blister pack composite pack (476885)

March 2025) was withdrawn by the marketing authorisation holder for non-safety reasons, as the reference member state did not accept the composite pack presentation. It was resubmitted on 31 March 2026 and is under evaluation.

MS Health confirmed that this application had not been refused market approval or withdrawn in any region or country.

Registration timeline

Table 1 captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 1. Registration timeline for MS-2 Step (mifepristone, misoprostol), submission PM-2025-03355-1-2

Description	Date
Submission dossier accepted evaluation commenced	30 September 2025
Evaluation completed	23 June 2026
Advisory Committee Meeting	6 August 2026
Registration decision (Outcome)	13 October 2026
Registration in the ARTG completed	20 October 2026
Number of working days from submission dossier acceptance to registration decision*	264 days

*Statutory timeframe for standard submissions is 255 working days.

Assessment overview

A summary of the TGA's assessment for this submission is provided below.

Quality evaluation summary

Quality evaluation is not required for this submission as there are no proposed changes to the quality of the currently approved product in Australia. The quality of the currently approved product is suitable for the proposed changes in this submission. A full quality evaluation was conducted at the time this product received initial registration.[16,17]

Nonclinical evaluation summary

No new nonclinical data or further nonclinical evaluation were required for this submission. The TGA considers that previously submitted and evaluated data satisfactorily address nonclinical aspects of safety/efficacy relating to this submission.[16,17]

[16] Therapeutic Goods Administration. 2012. Australian Public Assessment Report for Misoprostol

[17] Therapeutic Goods Administration. 2012. Australian Public Assessment Report for Mifepristone

Clinical evaluation summary

Clinical guidelines

Medical termination of pregnancy up to 70 days gestation

The National Institute for Health and Care (NICE) guideline for Abortion Care (NG140 2019 updated in May 2025) recommends offering interval treatment (usually 24 to 48 hours) with mifepristone and misoprostol to women who are having a medical abortion up to and including 10+0 weeks' gestation.[18]

The World Health Organization's 2022 Abortion Care Guideline recommends the use of mifepristone followed by misoprostol for medical management of abortion up to 12 weeks.[19]

Medical management of miscarriage up to 70 days gestation

National Institute for Health and Care (UK) guidelines

The NICE guideline for Ectopic Pregnancy and Miscarriage: Diagnosis and Initial Management (NG126 2019, updated June 2026) classifies early pregnancy as up to 13 completed weeks of pregnancy.[20] The guideline recommends expectant management for 7-14 days as first-line management of confirmed miscarriage followed by a pregnancy test to confirm the miscarriage has completed. Medical management can be considered if there is a higher risk of bleeding or adverse effects from bleeding, evidence of infection or previous adverse/traumatic experience associated with pregnancy. Medical management is also discussed if the process of miscarriage has not started or is persisting/increasing after expectant management as is surgical management.

Of note, the recommended medical management of miscarriage differs depending on whether it is missed or incomplete:

- For the medical management of missed miscarriage, the recommendation is for:
  - 200 mg oral mifepristone and
  - 48 hours later, 800 µg misoprostol (vaginal, oral or sublingual) unless the gestational sac has already been passed.

For the medical management of incomplete miscarriage, the guideline specifies a single dose of 600 µg of misoprostol (vaginal, oral or sublingual). Misoprostol (800 µg) can be used as an alternative to allow alignment of treatment protocols for both missed and incomplete miscarriage. The guideline specifies mifepristone not to be used as a treatment for incomplete miscarriage. Importantly, management of threatened miscarriage (patient with a confirmed intrauterine pregnancy with a foetal heartbeat and vaginal bleeding) differs considerably.

American College of Gynaecologists Practice Bulletin Number 200

The American College of Gynaecologists' (ACOG) clinical practice guidelines recommend mifepristone and misoprostol in the protocol for the medical management of early pregnancy loss with no miscarriage subtype specified.[21]

[18] NICE NG140. 27 May 2025. Abortion care - Accessed 17 June 2026

[19] Abortion care guideline. Geneva: World Health Organization; 2022. Accessed 17 June 2026

[20] NICE NG126. 17 June 2026. Ectopic pregnancy and miscarriage: diagnosis and initial management - Accessed 18 June 2026

[21] American College of Gynaecologists. Early Pregnancy Loss Practice Bulletin, Number 200, November 2018. – Accessed 29 June 2026.

Medical termination of pregnancy up to 70 days gestation

A total of 36 publications were submitted by the Sponsor in this application to support the extension of indication of medical termination of an intrauterine pregnancy from up to 63 days to up to 70 days of gestation. However, only 8 of these studies were considered to be directly relevant to the proposed extension of indication, with 6 studies including women with pregnancies up to 70 days' gestation and 2 studies including women with pregnancies of gestation exceeding 70 days. The remaining 28 studies included women with pregnancies up to 63 days' gestation and as such were of limited applicability to the extension of indication being sought. Seven of the 8 studies examined the efficacy of mifepristone and misoprostol using the same dose and route of administration as MS-2 Step (i.e. mifepristone 200 mg orally followed by misoprostol 800 µg buccally). The eighth study investigated oral mifepristone in combination with misoprostol administered vaginally.

Complete abortion without the need for surgical intervention was generally the primary outcome across the studies. No single study was considered pivotal and instead evaluation of efficacy of this indication has been based on the collective evidence provided by the 8 studies.

Conclusions on clinical efficacy

It was concluded that the Sponsor's submitted body of literature which reported on the of effectiveness of combination mifepristone and misoprostol for the medical termination of pregnancies up to 70 days' gestation was relatively small in comparison to the literature for pregnancies up to 63 days' gestation. Nevertheless, the collective evidence provided in this application overall was considered to demonstrate high clinical efficacy of mifepristone and misoprostol in achieving complete abortion rates in pregnancies between 64-70 days.

There were high complete abortion rates ranging from 91.2% to 100% in women with pregnancies of gestation 64-70 days. However, the proportion of women in the 64-70 days' gestation category were relatively small in some studies which limit the robustness of these findings.[22,23,24] Additionally, in Olavarrieta et al. (2015)[25], the distribution of women with pregnancies of gestation between 64-70 days was not specified and as such no firm conclusions could be drawn regarding the clinical effectiveness of mifepristone and misoprostol.[25] In comparison, overall complete abortion rates with the same treatment regimen in women with pregnancies up to 63 days' gestation ranged from 92.9% to 97.8%.

Results from several studies suggested a general trend towards decreased efficacy of mifepristone and misoprostol with increasing gestational age. However, clinical efficacy in pregnancies up to 70 days' gestation remained high (>90%), despite being generally lower than that observed in pregnancies below 63 days' gestation. Young et al. (2022) observed complete abortion rates of 98.0% in pregnancies ≤63 days' gestation compared to 93.2% in pregnancies 64-70 days' gestation.[26] However, this study was not designed for this comparison, and the clinical significance of this difference is unclear. In Sanhueza Smith et al. (2015), complete

[22] *Sanhueza Smith P, Peña M, Dzuba IG, et al. Safety, efficacy and acceptability of outpatient mifepristone-misoprostol medical abortion through 70 days since last menstrual period in public sector facilities in Mexico City. Reprod Health Matters. 2015;22(44 Suppl 1):75-82.*

[23] *Tan YL, Singh K, Tan KH, et al. Acceptability and feasibility of outpatient medical abortion with mifepristone and misoprostol up to 70 days gestation in Singapore. Eur J Obstet Gynecol Reprod Biol. 2018;229:144-147.*

[24] *Boersma AA, Meyboom-de Jong B, Kleiverda G. Mifepristone followed by home administration of buccal misoprostol for medical abortion up to 70 days of amenorrhoea in a general practice in Curaçao. Eur J Contracept Reprod Health Care. 2011;16(2):61-66.*

[25] *Olavarrieta CD, Ganatra B, Sorhaindo A, et al. Nurse versus physician-provision of early medical abortion in Mexico: a randomized controlled non-inferiority trial. Bull World Health Organ. 2015;93(4):249-258.*

[26] *Young D, Fitzgerald K, Laursen L, Whitaker AK. Comparison of vaginal and buccal misoprostol after mifepristone for medication abortion through 70 days of gestation: A retrospective chart review. Contraception. 2022;115:62-66.*

abortion rates in pregnancies of 8, 9 and 10 weeks' gestation were 94.9%, 90.0% and 91.2%, respectively[22]. Differences in the complete abortion rates between the 8th and 10th weeks' gestation and 9th and 10th weeks' gestation were not considered to be statistically significant. Likewise, in Winikoff et al. (2012), although complete abortion rates were higher for pregnancies in the 57-63 days' gestation group compared to the 64-70 days' gestation group, such differences were not considered statistically significant (93.5% vs 92.8%, p=0.41).[27]

Patient acceptability was generally considered to be high with mifepristone and buccal misoprostol in studies which reported on this outcome. It is appreciated though that acceptability of the method for termination of pregnancy is likely to have been significantly influenced by a combination of factors including patient preference and the success of the method itself.

It was concluded that in studies where comparative data was available between the 2 gestation groups (≤63 days' gestation vs 64-70 days' gestation), no significant difference in complete abortion rates was observed.

Conclusions on clinical safety

Data on clinical safety outcomes in women with pregnancies of gestation between 64-70 days who received oral mifepristone 200 mg and buccal misoprostol 800 µg was generally limited in the literature publications submitted in this application. Relevant safety data in this patient group was retrieved from 7 studies and additional supportive safety data were submitted by the Sponsor.

Nausea, vomiting, diarrhoea, fever, chills and bleeding were the most commonly reported adverse events (AEs) in this patient population across different studies. Data which compared the incidence of AEs between women with pregnancies of 64-70 days' gestation and 57-63 days' gestation was available from Winikoff et al. (2012)[27] and Sanhueza Smith et al. (2015).[22]

Winikoff et al. (2012)[27] observed that AEs of nausea, diarrhoea, heavy bleeding, fever and chills were all similar between the 64-70 days' gestation group and the 57-63 days' gestation group. Only vomiting occurred at a higher incidence in the 64-70 days' gestation group compared to the 57-63 days' gestation group (45.7% vs 35.8%, p<0.008). Incidence of severe vomiting however, was similar between both groups (12.0% vs 10.7%, p=0.35). Sanhueza Smith et al. (2015) observed a higher incidence of fever/chills (54.7% vs 47.9%), diarrhoea (52.7% vs 38.4%) and weakness (20.9% vs 13.2%) in the 64-70 days' gestation group compared to the 57-63 days' gestation group.[22] The overall clinical significance of these differences was unclear. Other AEs were generally comparable between the 2 groups.

No specific serious adverse events (SAEs) or deaths were reported in the 64-70 days' gestation group. Winikoff et al. (2012)[27] showed that there was no significant difference in the incidence of emergency department attendance, requirement for blood transfusion, and admission to hospital between women with pregnancies of 64-70 days' gestation and 57-63 days' gestation.

It was concluded that the safety data supporting this extension of indication, especially pertaining to women with pregnancies between 64-70 days' gestation, was limited and generally poorly reported upon. Nevertheless, the available data did not suggest any new safety concerns for this patient population and incidence of adverse events was generally consistent with those of women with pregnancies of gestation up to 63 days for which safety has been previously well established.

[27] *Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. Obstet Gynecol. 2012;120(5):1070-1076.*

Medical management of miscarriage up to 70 days gestation

A total of 36 literature publications were identified from the Sponsor's literature search which supported the efficacy of the combined treatment regimen of mifepristone and misoprostol for the medical management of miscarriage up to 70 days of gestation as determined by ultrasound evidence. This consisted of 19 studies which investigated the efficacy of mifepristone and misoprostol using the same dose as MS-2 Step (i.e. mifepristone 200 mg and misoprostol 800 µg). These were further grouped into 9 randomised controlled trials (RCTs) and 10 observational studies where the dosage of mifepristone (200 mg) and misoprostol (800 µg) was aligned with that sought in this application. Another 9 studies were identified which reported on the use of mifepristone and misoprostol at doses other than that being sought in this application.

A further 4 meta-analyses and 4 literature reviews examined the use of mifepristone with misoprostol for managing first trimester miscarriage, either independently or in comparison with surgical methods, expectant management, or misoprostol-only regimens.

Evaluation and conclusions on clinical efficacy

Key publications

Chu et al. (2020)[28] and Schreiber et al. (2018)[29] were considered to be the key studies which provided comparative data pertaining to the efficacy of combination mifepristone and misoprostol for medical management of first trimester miscarriage. Both of these were well designed, large, multicentre RCTs which compared combination treatment of mifepristone and misoprostol with misoprostol alone for the medical management of first trimester miscarriage.

Chu et al. (2020)[28] included women in both treatment arms who received misoprostol via vaginal, oral and sublingual routes of administration. However, despite this, approximately 90% of subjects in each treatment group ultimately received misoprostol vaginally. The study found that treatment with mifepristone and misoprostol in women with missed miscarriage up to 14 weeks' gestation resulted in a lower failure rate for passing the gestational sac within 7 days (17% vs 24%, relative risk [RR] 0.73, 95 CI: 0.54, 0.99; p=0.043). Likewise, women who received mifepristone and misoprostol were less likely to require surgical intervention to complete miscarriage up to discharge (17% vs 25%, RR 0.71, 95 CI: 0.53, 0.95; p=0.021) (Table 3). Gestational age was not observed to have a subgroup effect on treatment success, with women with missed miscarriage of gestation <70 days and ≥70 days having comparable success rates (p=0.97).

Table 3. Chu et al. (2020)[28] – Primary and secondary outcomes

	Mifepristone plus misoprostol (n=357)	Placebo plus misoprostol (n=354)	RR estimate* (95% CI)	p value
Primary outcome				

[28] Chu JJ, Devall AJ, Beeson LE, et al. Mifepristone and misoprostol versus misoprostol alone for the management of missed miscarriage (MifeMiso): a randomised, double-blind, placebo-controlled trial. Lancet. 2020;396(10253):770-778. doi:10.1016/S0140-6736(20)31788-8

[29] Schreiber CA, Creinin MD, Atrio J, Sonalkar S, Ratcliffe SJ, Barnhart KT. Mifepristone Pretreatment for the Medical Management of Early Pregnancy Loss. N Engl J Med. 2018;378(23):2161-2170. doi:10.1056/NEJMoa1715726

	Mifepristone plus misoprostol (n=357)	Placebo plus misoprostol (n=354)	RR estimate* (95% CI)	p value
Failure to pass the gestational sac spontaneously within 7 days after random assignment	59/348 (17%)	82/348 (24%)	0.73 (0.54 to 0.99)	0.043
Key secondary outcome				
Surgical intervention to complete the miscarriage up to discharge	62/355 (17%)	87/353 (25%)	0.71 (0.53 to 0.95)	0.021
Other secondary outcomes				
Surgical intervention to complete the miscarriage up to and including day 7 after random assignment	23/355 (6%)	19/353 (5%)	1.23 (0.68 to 2.21)†	-
Surgical intervention to complete the miscarriage from after day 7 and up to discharge	39/355 (11%)	68/353 (19%)	0.56 (0.39 to 0.81)	-
Need for further doses of misoprostol within 7 days after random assignment	34/356 (10%)	48/354 (14%)	0.71 (0.47 to 1.08)	-
Need for further doses of misoprostol up to discharge	50/357 (14%)	65/354 (18%)	0.77 (0.55 to 1.09)	-
Infection requiring outpatient antibiotic treatment	8/351 (2%)	11/351 (3%)	0.73 (0.29 to 1.82)‡	-
Infection requiring inpatient antibiotic treatment	5/351 (1%)	4/351 (1%)	1.25 (0.33 to 4.74)‡	-
Negative pregnancy test result 21 days (±2 days) after random assignment	237/308 (77%)	230/302 (76%)	1.03 (0.94 to 1.14)§	-
Pregnancy test not provided	33	28	-	-
Missing	16	24	-	-
Duration of bleeding reported by woman, days	16.0 (12.6; 32.6)	16.3 (15.2; 33.0)	−0.3 (−2.5 to 1.8)	-

	Mifepristone plus misoprostol (n=357)	Placebo plus misoprostol (n=354)	RR estimate* (95% CI)	p value
Time from random assignment to discharge, days	27.0 (14.2; 34.0)	27.3 (14.4; 33.7)	-	-

Data are n (%), n, or mean (SD; N), unless otherwise indicated. Missing data are <3% unless otherwise presented. RR=risk ratio. *Value <1 favours mifepristone plus misoprostol combination group; the RR was adjusted for the following minimisation variables: maternal age, body-mass index, previous parity, gestational age, and amount of bleeding; the clustering effect of randomising centres was accounted for by using robust standard errors at the centre level. †Centre removed from the model because of non-convergence. ‡Unadjusted model used because of non-convergence. §Poisson model used because of non-convergence.

In Schreiber et al. (2018)[29], treatment success defined as gestational sac expulsion by the first follow-up visit was higher in women with miscarriages between 5-12 weeks' gestation who received mifepristone and vaginal misoprostol compared to vaginal misoprostol alone (83.8% vs 67.1%, RR 1.25, 95% CI: 1.09, 1.43). As the median time to follow-up was 2.0 days (0.5 – 5.5) in the mifepristone and misoprostol group, this suggests relatively rapid resolution of missed miscarriage using this treatment regimen. However, subgroup analysis of the primary outcome by gestational age did show a lower treatment success rate for the mifepristone and misoprostol group compared to the misoprostol alone group (70.0% vs 75.0%). These findings should be considered with caution though, given the small sample size in this subgroup (n=18) and the wide 95% CIs spanning 0 for the relative risk estimate.

The systematic review and network meta-analysis by Ghosh et al. (2021) published on the Cochrane database was a key publication for the proposed miscarriage indication.[30] This systematic review and network meta-analysis of 59 trials (12,591 women) suggested that surgical methods were ranked higher than medical methods, including mifepristone and misoprostol, in achieving the primary outcome of complete miscarriage. Mifepristone and misoprostol were also found to be superior to expectant management in achieving complete miscarriage for women with miscarriages up to 14 weeks' gestation.

Subgroup analysis however, found mifepristone and misoprostol was only more effective than expectant management in the missed miscarriage subgroup and not the incomplete miscarriage subgroup. The authors postulated that this is likely attributed to expectant management being a more effective management options once the miscarriage process has commenced. Relative effects from the network meta-analysis suggested that mifepristone and misoprostol also had comparable efficacy to misoprostol alone, dilation and curettage, and suction aspiration for achieving complete miscarriage. In terms of ranking by Surface Under the Cumulative Ranking (SUCRA), mifepristone + misoprostol was ranked lower than the surgical methods, but above mifepristone alone and expectant management for achieving complete miscarriage. Key limiting factors in the evidence provided included the network inconsistency and marked heterogeneity across studies included in the meta-analysis in terms of dosage regimens, intervals between mifepristone and misoprostol, routes of administration for misoprostol and outcome measures. These factors somewhat limit the direct applicability of findings from this meta-analysis to the proposed extension of indication in this application.

The uncertainty of the conclusions from the submitted studies overall, as well as their applicability to the proposed medical management of the miscarriage indication, were noted. Importantly, individual studies varied in terms of inclusion criteria (i.e. missed vs incomplete

[30] Ghosh J, Papadopoulou A, Devall AJ, et al. Methods for managing miscarriage: a network meta-analysis. Cochrane Database Syst Rev. 2021;6(6):CD012602.

miscarriage and gestational age of pregnancy), dosage regimens (i.e. some studies allowed for additional misoprostol doses and/or repeat medical treatment) and primary outcome definitions (i.e. based on clinical findings vs ultrasonographic criteria to confirm complete miscarriage as well as differences in timepoints for measuring outcomes). The significant heterogeneity across studies was also noted in the key network meta-analysis submitted.

Type of miscarriage

There was high heterogeneity across individual studies in terms of inclusion criteria for classification of women with first trimester miscarriage. Some studies included women with all forms up miscarriage, whilst others were limited to only missed miscarriage. Gestational age also ranged from 5 to 14 weeks across individual studies and there was limited subgroup analysis of outcomes in miscarriages up to 70 days' (10 weeks) gestation. Marked heterogeneity was also noted with regards to primary outcome definitions and timing of outcome measurement between studies. Overall, across the 19 studies which examined the efficacy of mifepristone 200 mg and misoprostol 800 µg, treatment success rates ranged from 66.8% to 93.3%.

Given the findings from mifepristone and misoprostol in the key RCT and network meta-analysis studies identified in women with missed first trimester miscarriages, limiting the proposed indication was posed as a clinical question to the Sponsor for consideration. The Sponsor's response regarding limiting the proposed miscarriage indication of MS-2 Step to missed miscarriage only is summarised as follows:

- Missed miscarriage represents a physiologically more resistant condition than incomplete miscarriage. Therefore, it is inferred that if efficacy can be demonstrated in a more challenging condition (missed miscarriage), similar or potentially greater efficacy would be expected for incomplete miscarriage, where the underlying physiological processes have already begun and likelihood of spontaneous resolution greater.
- The pharmacological actions of mifepristone are applicable to both missed and incomplete miscarriage. There is also substantial clinical evidence supporting use of misoprostol in the management of incomplete miscarriage. It is therefore biologically reasonable to assume that addition of mifepristone to misoprostol would not necessarily diminish efficacy in incomplete miscarriage.
- A unified miscarriage indication is more applicable in real-world clinical settings where the differentiation between missed and incomplete miscarriage may not be clear. Having separate miscarriage indications based on diagnostic categories may create potential barriers and thresholds to access to care.

Although there was a lack of confirmatory clinical evidence demonstrating efficacy using the combination regimen for incomplete miscarriage, it was acknowledged that the absence of data in the literature does not necessarily suggest there is an absence of efficacy in this patient population. The data from studies by Chu et al. (2020)[28] and Schreiber et al. (2018)[29] was re-reviewed and it was acknowledged that the data from these studies do not necessarily suggest that the combined regimen of mifepristone + misoprostol was not efficacious in the context of incomplete miscarriage. Rather, no conclusions on efficacy in this population could be drawn from these studies as patients with incomplete miscarriage were specifically excluded.

Likewise, it was acknowledged that the data from the Ghosh et al. (2021)[30] review do not necessarily diminish the efficacy of mifepristone and misoprostol for management of incomplete miscarriage. Whilst the analysis suggested that combined mifepristone + misoprostol regimen was not significantly more effective than expectant management in achieving complete miscarriage, other treatment modalities (including both surgical management and misoprostol-only) were also noted to have comparable effectiveness to combined mifepristone + misoprostol.

The TGA concluded that a unified indication would take into consideration the realities of everyday clinical practice. Issues presented regarding diagnostic ambiguity and overlap between miscarriage subtypes are clinically valid and it was acknowledged that in these settings, a broader miscarriage indication may minimise potential barriers to care.

Buccal route of administration

The buccal route of administration for misoprostol was only used in one study, Baker et al. (2023)[31], for initial treatment and limited to 4 women; with no efficacy or specific safety outcomes in this subgroup described. Evidence from the literature supporting oral and sublingual routes of administration for misoprostol when used in combination with mifepristone were also substantially limited.

It was noted that only the buccal route of administration for misoprostol is being sought for this extension of indication and therefore the relative lack of data in the provided literature pertaining to the efficacy of mifepristone in combination with buccal misoprostol is considered a significant limitation of this application. Further supporting evidence for the buccal route of administration of misoprostol was requested from the Sponsor.

In their response, the Sponsor provided detailed justification for extrapolating findings from the extensive miscarriage evidence base generated with vaginal misoprostol, together with extensive data on combination regimens using buccal misoprostol in medical abortion to support the use of the MS-2 Step product with buccal misoprostol for the medical management of miscarriage. The following are the key points from the Sponsor's response:

- The pharmacokinetic properties of misoprostol administered vaginally are stated to closely resemble that of misoprostol administered buccally. Specifically, although buccal misoprostol has reduced bioavailability compared to vaginal misoprostol, uterine contractility patterns and uterine tone between the 2 routes of administration are similar.
- Clinical studies and systematic reviews of first-trimester medical abortion demonstrate buccal misoprostol to have high efficacy (complete abortion rates) that was comparable to vaginal misoprostol, when both were used in combination regimens with mifepristone. Likewise, data from systematic reviews as well as international and Australian specific datasets of early medical abortion consistently demonstrate high complete abortion rates when the identical mifepristone 200 mg + buccal misoprostol 800 µg regimen as the MS-2 Step product is used.
- Per local and international guidelines for the medical management of miscarriage, buccal misoprostol is seen as clinically interchangeable with other routes of administration for misoprostol when used in combination regimens for the management of both abortion and miscarriage, with route selection guided by practical considerations, patient preference and service context.
- Interim findings from the Sponsor's Miscarriage Practice Survey demonstrate that medical management using the combined regimen of mifepristone 200 mg + misoprostol 800 µg is already a well-established modality for management of miscarriage used in clinical practice in Australia. Buccal administration of misoprostol forms the predominant route (51.7%).
- In the miscarriage-specific clinical trials which used combination of mifepristone and misoprostol, mifepristone pretreatment was considered the primary driver of improved outcomes, rather than the precise route of administration for misoprostol.

[31] Baker CC, Wu BT, Han G, Flynn AN, Creinin MD. Early pregnancy loss medical management in clinical practice. Contraception. 2023;126:110134. doi:10.1016/j.contraception.2023.110134

Considerable differences in the pharmacokinetic profile of misoprostol when given via different routes of administration were noted. In a study performed by Meckstroth et al. (2006),[32] women with first trimester pregnancies who received 400 µg of misoprostol via vaginal-dry and vaginal-moistened routes had higher peak serum levels compared to buccal routes (445.9 and 427.1 compared with 264.8 pg/mL) and higher serum concentration AUC_{0-5h} (1025.0 and 1279.4 compared with 519.6 pg-hr/mL). Uterine tone and activity, however, were observed to be similar for buccal and the 2 vaginal routes.

A more recent study by Vorontsova et al. (2022)[33], which compared the pharmacokinetics of buccal vs vaginal routes of misoprostol in women at labour induction, found the bioavailability of vaginal administration was 2.4 times higher than that of buccal administration. Consistent with the differences in bioavailability, the median AUC_{0-4h} following a 25 µg dose of misoprostol was 16.5 pg-hr/mL for buccal and 34.3 pg-hr/mL for vaginal administration. The rate of absorption, however, was 2 times faster with buccal route than the vaginal route. Given the significant differences in pharmacokinetics between these two routes, the extrapolation of findings from clinical studies which have primarily used vaginal misoprostol was not considered to be acceptable for supporting the use of the buccal misoprostol for the proposed miscarriage indication.

Whilst biologically justifiable, abortion outcomes are not entirely interchangeable with miscarriage outcomes. Uncertainty therefore remains regarding the translation of abortion-related data to miscarriage efficacy and safety claims. In addition, it was highlighted that clinical guidelines are considered supportive but regulatory decisions should be made on the basis of high-quality clinical data that are directly relevant to the proposed indication, dose and routes of administration. It was concluded that substantial uncertainty continues to remain regarding the proven efficacy and safety of buccal misoprostol administration when used in conjunction with mifepristone for medical management of miscarriage, and this remains a crucial evidentiary gap in this submission preventing recommendation of approval for the Sponsor's proposed miscarriage indication.

Dosage regimen

The dosage regimen differed across the 19 RCTs and observational studies and was generally not consistent with that proposed in this application. Several studies included treatment regimens which allowed for additional doses of misoprostol and/or repeat medical treatment in instances where treatment success had not been achieved by a certain timepoint. Time intervals between mifepristone and misoprostol were also not consistent between studies. The optimal time interval between mifepristone pretreatment and misoprostol administration is therefore yet to be determined. Flynn et al. (2021) observed that treatment success rates were highest when misoprostol was administered 7-20 hours after mifepristone (96.6%), followed by 21-48 hour (87.5%) and 0-6 hours (49.6%).[34] Contrary to this, Schreiber et al. (2021) observed that the rate of treatment success was lower in women who were administered misoprostol <24 hours following mifepristone compared to >24 hours after mifepristone (79.7% vs 86.9%).[35] The study by Sinha et al. (2018) additionally demonstrated treatment success of 86.7% in

[32] Meckstroth KR, Whitaker AK, Bertisch S, Goldberg AB, Darney PD. Misoprostol administered by epithelial routes: Drug absorption and uterine response. Obstet Gynecol. 2006;108(3 Pt 1):582-590.

[33] Vorontsova Y, Haas DM, Flannery K, et al. Pharmacokinetics of vaginal versus buccal misoprostol for labor induction at term. Clin Transl Sci. 2022;15(8):1937-1945.

[34] Flynn AN, Roe AH, Koelper N, McAllister A, Sammel MD, Schreiber CA. Timing and efficacy of mifepristone pretreatment for medical management of early pregnancy loss. Contraception. 2021;103(6):404-407.

[35] Schreiber CA, Flynn AN, Roe AH, Koelper N, McAllister A, Sammel MD, Schreiber CA. Timing and efficacy of mifepristone pretreatment for medical management of early pregnancy loss. Contraception. 2021;103(6):404-407.

women who received misoprostol 48 hours after mifepristone.[36] It was concluded that, in general, the evidence appears to suggest that intervals anywhere between 7-48 hours allow for high rates of treatment success exceeding 80% and that this aligns with the existing dosage regimen for MS-2 Step.

Off-label use of MS-2 Step

The Sponsor provided an interim analysis of the Miscarriage Practice Survey commissioned by the Sponsor to demonstrate real-world evidence of off-label prescribing of combination mifepristone and misoprostol for miscarriage management. This survey captured real-world data from 60 Australian healthcare professionals (75 % Obstetrician-Gynaecologists) alongside 593 European counterparts to evaluate clinical behaviours in the absence of a dedicated approved product. Pertinent findings from the survey are as follows:

- Medical treatment accounted for 33% of miscarriage management in Australia and 53% of miscarriage management in Europe.
- Respondents in both regions have converged on the 200 mg mifepristone plus 800 µg misoprostol combination as the most commonly used regimen (55.0% of Australian prescribers and 46.7% of European prescribers).
- In Australia, buccal administration of misoprostol is the most frequently used route (51.7%), followed by oral and vaginal (38.3% each) and sublingual (31.7%).
- For Australian respondents, the off-label status remains a practical barrier, influencing prescribing decisions for 37% of prescribers, and acting as a barrier to offering medical management in 20% of prescribers.

The majority of respondents (73.3% of Australian respondents and 71.3% of European respondents) consider that an approved combination product would support broader, more consistent use of medical management for miscarriage.

Conclusions on clinical safety

The data on clinical safety outcomes in women who received mifepristone 200 mg and misoprostol 800 µg for the medical management of early miscarriage were generally sparsely provided in the individual literature publications submitted in this application. Studies also did not generally attribute causality to adverse events and hence it was not possible to evaluate incidence of treatment related adverse events.

Common adverse events reported were gastrointestinal (nausea, vomiting, diarrhea, upset stomach, and loose stools), neurological (headache and dizziness), fever, chills, pain, fatigue, cramping, shivering, uncomplicated infection, and bleeding. Data from individual studies which compared the incidence of adverse events between the combined regimen of mifepristone and misoprostol vs misoprostol alone did not generally identify significant differences in incidence

[36] Sinha P, Suneja A, Guleria K, Aggarwal R, Vaid NB. Comparison of Mifepristone Followed by Misoprostol with Misoprostol Alone for Treatment of Early Pregnancy Failure: A Randomized Double-Blind Placebo-Controlled Trial. J Obstet Gynaecol India. 2018;68(1):39-44.

of adverse events between the 2 treatment arms.[37,38,39,40] Amongst women who received mifepristone and misoprostol, SAEs were reported in 5/357 (1.4%) women in the Chu et al. 2020) study[28] (no further information on this was provided) and 5/149 (3.3%) women in the Schreiber et al. (2021)[35] study (2 women with pelvic infection and 3 women with bleeding resulting in blood transfusion). In both studies, no significant difference in incidence of SAEs was identified between women who received the combined regimen of mifepristone and misoprostol vs misoprostol alone. No deaths were reported in any of the included studies.

In the network meta-analysis review by Ghosh et al. (2021)[30], the combined regimen of mifepristone and misoprostol was found to have a comparable effect on the composite outcome of death and serious complications when compared with expectant management or placebo for managing miscarriage. The exception to this was for the outcome of pelvic inflammatory disease, sepsis or endometritis, for which mifepristone and misoprostol was ranked highest i.e. it was the method least likely to lead to the development of pelvic inflammatory disease, sepsis or endometritis.

Overall, it was concluded that the safety data supporting this extension of indication did not suggest any significant safety concerns with the use of combined mifepristone and misoprostol in this patient population. Incidence of serious complications were rare and had a similar risk profile to other methods for managing miscarriage. However, the significant heterogeneity between individual studies as well as the overall lack of studies which evaluated safety of buccal misoprostol when given sequentially after mifepristone limit these overall safety conclusions.

Risk management plan

- Medical termination of pregnancy –EU-RMP version 0.2; date 23 January 2026; DLP 19 January 2026
- Miscarriage – EU-RMP version 1.0; date 25 March 2026; DLP 31 January 2026
- Australia-specific annex version 1.1; date 17 April 2026

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 4.

Table 4. Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Congenital anomaly	✓	–	✓‡	✓§
	Cardiovascular disorder	✓	–	✓	–

[37] Bettencourt-Silva B, Rego MT, Miranda C, et al. The role of mifepristone on first trimester miscarriage treatment - A double-blind randomized controlled trial - MiFirsT. Eur J Obstet Gynecol Reprod Biol. 2023;289:145-151.
[38] Dalmia K, Jaiswal P, Nair M. Comparison of mifepristone followed by misoprostol with misoprostol alone for management of early pregnancy failure: a randomized controlled study. Int J Life Sci Biotechnol Pharma Res. 2023;12(4): 995-1001.
[39] Chu JJ, Devall AJ, Beeson LE, et al. Mifepristone and misoprostol versus misoprostol alone for the management of missed miscarriage (MifeMiso): a randomised, double-blind, placebo-controlled trial. Lancet. 2020;396(10253):770-778.
[40] Sinha P, Suneja A, Guleria K, Aggarwal R, Vaid NB. Comparison of Mifepristone Followed by Misoprostol with Misoprostol Alone for Treatment of Early Pregnancy Failure: A Randomized Double-Blind Placebo-Controlled Trial. J Obstet Gynaecol India. 2018;68(1):39-44.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	Misuse	✓	–	✓‡	✓§
	Uterine haemorrhage	✓	–	✓‡	✓§
Important potential risks	Interaction with CYP3A4 inhibitors or inducers	✓	–	✓	–
	Infection and toxic shock syndrome due to inappropriate route of administration	✓	–	✓‡	✓§
Missing information	Hepatic impairment	✓	–	✓	–
	Renal impairment	✓	–	✓	–

‡ Boxed warning
§ Patient Information Booklet

The TGA may request an updated RMP at any stage of a product's life-cycle, during both the pre-approval and post-approval phases. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach. Information on the Australia-specific annex (ASA) can be found on the TGA website.

Risk-benefit analysis

This application seeks to extend the indication for MS-2 Step composite pack (Mifepristone Linepharma 200 mg tablet mifepristone 200 mg tablet blister; GyMiso misoprostol 200 µg tablet blister) as follows:

> *MS-2 Step is indicated in females of childbearing age for:*
>
> - *-the medical termination of an intrauterine pregnancy, up to 70 days of gestation.**
> - *-the medical management of miscarriage up to 70 days of gestation, determined by ultrasound equivalence rather than last menstrual period.*
>
> **It is recommended that the duration of pregnancy (i.e., up to 70 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.*

The Sponsor's search terms and search strategy were reviewed and the search re-run by the TGA's Information Resources and Research Services team and it was concluded that the submission met the recommendations as per TGA's guidance for literature-based submissions.

Each proposed indication is discussed separately in the following section of the AusPAR.

Medical termination of pregnancy up to 70 days of gestation

MS-2 Step is currently approved in females of childbearing age for:

> *the medical termination of an intrauterine pregnancy, up to 63 days of gestation**
>
> **It is recommended that the duration of pregnancy (i.e., up to 63 days gestation) be confirmed by ultrasound. In the event that an ultrasound is not possible, extra caution should be exercised. Ultrasound is also useful to exclude ectopic pregnancy.*

To support the extension of indication related to medical termination of intrauterine pregnancy up to 70 days, the Sponsor presented a body of published evidence to support MS-2 Step used for this indication. However, the majority of the submitted literature to support this proposed indication pertained to duration of pregnancy up to 63 days gestation. There was also a clear lack of any Cochrane reviews, systematic reviews, randomised controlled trials or meta-analyses to provide robust data including comparison of the pertinent groups using the proposed dose and route of administration sought in the application. The route of administration and dosage regimen were found to be highly variable in the submitted literature papers.

Winikoff et al. (2012)[27] was an open-label, non-randomised study of 729 women conducted in 6 US outpatient abortion clinics using oral mifepristone 200 mg in the clinic followed by buccal misoprostol 800µg 24-48 hours later at home. Results showed no significant difference in successful abortion rates between the 57-63 days gestation group (93.5% (95% CI: 90.1, 95.9) compared to the 64-70 days gestation group (92.8% (95% CI: 89.1, 95.3) (p=0.41).

Young et al. (2022)[26] was a large and relatively recent retrospective cohort study of patients who presented for medical abortion in Planned Parenthood clinics in Illinois. A subgroup analysis was conducted in the 64-70 days' gestation subgroup in this study, which found complete abortion rates were 92.7% for vaginal administration of misoprostol compared to 93.2% for buccal administration of misoprostol (following 200 mg mifepristone) with no statistically significant difference found. However, amongst women who received buccal misoprostol following mifepristone, rates of complete abortion were higher in those with pregnancies ≤63 days of gestation compared to those 64-70 days of gestation (98.0% vs 93.2%) which was found to be statistically significant in the study. It can be argued that the study was not adequately designed for this comparison, and the high loss to follow-up and relatively small number of women in the 64-70 days of gestation subgroup (609 patients or 6.9%) makes this specific finding (particularly in a retrospective analysis) difficult to interpret.

Despite the lack of a pivotal study, it is important to highlight that complete abortion rates of 92.8% and 93.2% from the above studies published a decade apart and in the context of the overall data submitted, can be considered to be highly supportive of the efficacy of the proposed regimen of MS-2 Step (200 mg oral mifepristone and 800 µg buccally-administered misoprostol 24-48 hours later) for the medical termination of intrauterine pregnancies 64-70 days of gestation. In addition, the benefit over the need for less accessible, more costly and risky surgical intervention has been clearly demonstrated in the proposed patient group by the presented data.

Overall, there was considered to be a paucity of safety data related specifically to the proposed MS-2 Step regimen for the extension of indication of medical termination of pregnancy from 64 days to 70 days of gestation with poor reporting noted in the submitted studies. Nevertheless, the limited safety data support the established safety profile of MS-2 Step for this patient population with nausea, vomiting, diarrhoea, fever, chills and bleeding remaining the most commonly reported adverse events across different studies. In addition, no new safety issues were identified in women with pregnancies between 64-70 days gestation who were given mifepristone followed by misoprostol for the purposes of medical termination of pregnancy.

In summary, the totality of the evidence presented pertaining to the proposed dose and regimen of mifepristone and misoprostol used for the medical termination of pregnancy up to 70 days gestation was considered acceptable. The submitted data support the efficacy and safety of the proposed regimen of MS-2 Step for the proposed indication of medical termination of intrauterine pregnancy up to 70 days of gestation and the benefit-risk assessment for this indication is considered favourable.

Medical management of miscarriage up to 70 days gestation

MS-2 Step is not currently approved for use in miscarriage. The Sponsor has submitted a body of published data to support the efficacy and safety of the proposed regimen of mifepristone and misoprostol for the medical management of miscarriage up to 70 days of gestation. MS-2 Step is administered as oral mifepristone and buccal misoprostol as the only proposed routes of administration for the indications sought.

The dose and method of administration section of the draft Product Information for MS-2 Step contains the following information:

> *Mifepristone: 200 mg of mifepristone (1 tablet containing 200 mg) orally, followed 36 to 48 hours later by the administration of GyMiso.*
>
> *GyMiso: 800 micrograms of misoprostol (4 tablets, each tablet containing 200 micrograms) in a single dose buccally, i.e. kept between the cheek and the gum for 30 minutes before any fragments being swallowed with water.*

Despite a large volume of data submitted by the Sponsor related to the medical management of miscarriage, there are no data that directly support the proposed indication of all types of miscarriage up to 70 days gestation, nor do the data directly support the buccal route of administration for misoprostol for the proposed indication.

The submission had a relatively large volume of miscarriage data spanning well over a decade that supported the use of mifepristone followed by vaginal misoprostol for missed miscarriage in early pregnancy. However, given the heterogeneity of the submitted data in terms of patient group, gestational age, type of miscarriage, medication regimen and overall diagnosis and management plan, it is difficult to use these data to provide a robust benefit-risk assessment and a clear regulatory decision on MS-2 Step and its use in miscarriage. This is known to be an inherent challenge of literature-based submissions.

The MifeMiso RCT led by Chu et al. (2020)[28] was a large UK multicentre RCT with inclusion criteria that included women aged ≥16 years old with a diagnosis of missed miscarriage on pelvic ultrasound (as per NICE guidelines) and with gestation up to 14 weeks who chose to have medical management of miscarriage. Participants were randomised to receive a single dose of oral mifepristone 200 mg (357 women) (or placebo (354 women)), both followed by a single dose of vaginal, oral, or sublingual misoprostol 800 µg administered 2 days later. Over 90% of patients received vaginal misoprostol in the study.

Treatment with mifepristone and misoprostol in women with missed miscarriage up to 14 weeks' gestation resulted in a lower failure rate for spontaneously passing the gestational sac within 7 days (17% (59) vs 24% (82), RR 0.73, 95 CI: 0.54, 0.99; p=0.043). Likewise, women who received mifepristone and misoprostol were less likely to require surgical intervention to complete miscarriage up to discharge (17% (62) vs 25% (87), RR 0.71, 95 CI: 0.53, 0.95; p=0.021). If participants passed the gestational sac within 7 days after random assignment, they were asked to do a urinary pregnancy test 3 weeks after random assignment. If the urinary pregnancy test was negative, the participant was discharged from the trial. If participants failed to spontaneously pass the gestational sac within 7 days after random assignment, they were

managed according to local hospital practice, which generally involved offering participants further doses of misoprostol 800 µg or surgical management of miscarriage after appropriate clinical assessment. Participants remained in the trial until they had a negative pregnancy test and were discharged from the early pregnancy unit[28].

A large RCT, Schreiber et al. (2018)[29] provides additional support for the use of mifepristone and misoprostol in the medical management of missed miscarriage, although it is noted that only vaginal misoprostol (following oral mifepristone) was administered in this trial.

Further support to limit the use of MS-2 Step to the medical management of missed miscarriage only comes from results of the submitted network meta-analysis by Ghosh et al. (2021)[30] which was published in the Cochrane database. In the analyses, although the combined regimen of mifepristone and misoprostol was more effective in achieving complete miscarriage compared to expectant management, they noted that this was only applicable to women with missed miscarriage and not incomplete miscarriage. This is likely due to expectant management being a more effective treatment option once the miscarriage process has commenced. Of the 51 trial arms that used misoprostol, the routes of administration used for misoprostol were as follows: 26 of 51 (51%) gave misoprostol vaginally, 19 of 51 (37%) orally, 2 of 51 (4%) vaginally or orally, 2 of 51 (4%) sublingually, and 2 of 51 (4%) did not specify the route of administration. Nineteen of 51 (37%) used 800 µg of misoprostol. The marked heterogeneity within the studies in this analysis for a number of variables is noted.

The recommendations from important national and international clinical guidelines (RANZCOG and NICE) on the management of first trimester miscarriage all support the use of mifepristone and misoprostol (administered buccally or vaginally) in missed miscarriage only. The NICE guidance NG126 on management of miscarriage specifically states under section 1.11.4: 'Do not offer mifepristone as a treatment for incomplete miscarriage'.[20] Therefore, the Sponsor's proposed broad miscarriage indication for MS-2 Step is not supported by the above clinical guidelines. The ACOG's clinical practice guidelines recommend mifepristone and misoprostol in the protocol for the medical management of early pregnancy loss with no miscarriage subtype specified. However, the references supporting the ACOG recommendation are the Schreiber et al. (2018) RCT which only included patients with missed miscarriage and excluded patients with incomplete miscarriage, and studies of medical termination of pregnancy.[21]

It is clear from this submission that miscarriage is a complex condition for which approved safe and effective medicines are needed and there exist long-established data (including RCTs, meta-analyses and Cochrane reviews) and robust clinical guidelines to guide medical management. It is also noted from the Sponsor's submitted real world evidence on off-label use of MS-2 Step that mifepristone and buccal misoprostol are currently being used to a significant degree for the medical management of miscarriage in Australia (although specific uses and patient outcomes are currently unknown). Hence the regulatory decision to approve these medicines would be an important one especially for those patients who would benefit from safe and effective medical management of miscarriage over expectant or surgical management.

Regarding the lack of data related to buccal administration of misoprostol, the Sponsor's rationale for extrapolation of data for vaginal misoprostol to support the use of buccal misoprostol is supported to a large degree. Furthermore, a number of submitted studies, including the key publications of Ghosh et al, (2021)[30] and Chu et al. (2020)[28] do not specify one route of administration of misoprostol over another for use in missed miscarriage despite the overwhelming use of vaginal misoprostol in the studies. Inclusion of oral and sublingual routes of administration for misoprostol in these studies is reassuring.

Taking the published data, real-world data, clinical guidelines and the Sponsor's overall rationale into account, an amended indication of medical management of missed miscarriage up to 70 days of gestation for MS-2 Step may be considered favourable. Limiting use to a specific

type of miscarriage in the indication, along with clear diagnostic requirements, precautions and follow-up instructions would significantly improve the benefit-risk balance for MS-2 Step for use in miscarriage from a regulatory point of view.

Proposed action

For the proposed indication of 'medical termination of an intrauterine pregnancy, up to 70 days gestation', the benefit-risk assessment of MS-Step was favourable. ACM expert advice and discussion was sought regarding the proposed indication of 'medical management of miscarriage up to 70 days of gestation'.

Advisory Committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the Sponsor's response to these documents, advised the following.

Regarding the proposed increase of the current indication for the medical termination of an intrauterine pregnancy from 63 to 70 days of gestation:

1. ***Does the Committee agree that the efficacy and safety of MS-2 Step for the medical termination of intrauterine pregnancy have been satisfactorily demonstrated by the Sponsor for gestations of up to 70 days?***

The ACM considered all the relevant data and advised that the evidence provided from the clinical studies provided by the Sponsor's literature-based submission, supports the efficacy and safety of MS-2 Step for the medical termination of intrauterine pregnancy up to 70 days.

Regarding the proposed indication for the medical management of miscarriage up to 70 days of gestation:

2. ***Does the Committee agree with the wording for the indication and diagnostic, administration and follow-up information I have included in the MS-2 Step PI for prescribers and patients using MS-2 Step for the medical management of missed miscarriage up to 70 days of gestation?***

   The ACM advised that the wording for the indication should state:

   MS-2 Step composite pack indicated for the medical management of missed miscarriage up to 70 days, determined by ultrasound assessment rather than menstrual date/period.

The ACM was satisfied that the data demonstrated a benefit for missed miscarriage only. Additionally, the ACM also advised that the RANZCOG definition of missed miscarriage be included in the product information (PI) and consumer medical information pamphlet (CMI), to avoid confusion. This suggested definition is:

> *Missed Miscarriage: the embryo or foetus has died, but the pregnancy tissue has not passed and is still in the uterus. Women who have had a missed miscarriage may be asymptomatic or have small amount of vaginal bleeding or pain.*

The ACM also considered the suggested changes to the PI and agreed with the inclusion of additional wording with the statement, 'it is recommended that the duration of pregnancy (i.e. up to 70 days gestation) be confirmed by ultrasound.' This is not a contentious issue as, in practice, missed miscarriages are typically confirmed by ultrasound.

Furthermore, the ACM advised replacing the PI wording of the follow-up medical review period after taking Mifepristone, of 'a period of 14 to 21 days' with 'must receive follow-up within 21 days after taking mifepristone'.

Advisory committee conclusion

The ACM considered MS-2 STEP to have an overall positive benefit-risk profile for the proposed extension of indications in females of childbearing age, comprising:

- *an extension of the current indication for the medical termination of an intrauterine pregnancy from up to 63 days' gestation to up to 70 days' gestation; and*
- *a new indication for the medical management of missed miscarriage up to 70 days' gestation, determined by ultrasound equivalence rather than menstrual period.*

Assessment outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register MS-2 Step (mifepristone, misoprostol) for the following extension of indications:

MS-2 Step is indicated in females of childbearing age for:

- *the medical termination of an intrauterine pregnancy, up to 70 days of gestation.*
- *the medical management of missed miscarriage up to 70 days of gestation.*

For the medical termination of an intrauterine pregnancy, it is recommended that the duration of pregnancy (i.e. up to 70 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.

Missed Miscarriage: the embryo or foetus has died, but the pregnancy tissue has not passed and is still in the uterus. Women who have had a missed miscarriage may be asymptomatic or have a small amount of vaginal bleeding or pain. For the medical management of missed miscarriage, it is recommended that the duration of pregnancy (i.e., up to 70 days gestation) and diagnosis of miscarriage be confirmed by ultrasound rather than last menstrual period. Repeat assessments with ultrasound may be needed to confirm the diagnosis.

The safety and efficacy of MS-2 Step in other types of miscarriage, such as incomplete miscarriage has not been established. MS-2 Step is not indicated for threatened miscarriage.

Specific conditions of registration

The MS-2 Step EU-Risk Management Plan (RMP) (version 0.2, dated 23 January 2026, data lock point 19 January 2026), and EU-Risk Management Plan (RMP) (version 1.0, dated 25 March 2026, data lock point 31 January 2026), with Australia- Specific Annex (ASA) (version 1.2, dated 29 June 2026), included with submission PM-2025-03355-1-2, and incorporating any subsequent revisions, or any alternate RMP and incorporating any subsequent revisions, as agreed in writing with the TGA, must be implemented in Australia. This includes implementing any pharmacovigilance activities and risk minimisation measures as documented in the ASA/AU-RMP.

Product Information and Consumer Medicine Information

For the most recent Product Information (PI) and Consumer Medicine Information (CMI), please refer to the TGA PI/CMI search facility.

References/notes

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