AusPAR - MS-2 Step - mifepristone, misoprostol - MS Health Pty Ltd - PM-2025-03355-1-2
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AUSTRALIAN PRODUCT INFORMATION

MS-2-STEP

(Mifepristone and Misoprostol)

Tablets

It is very important that all patients receiving these medications are followed up by a healthcare practitioner, preferably the prescriber, to ensure that the medication has been effective. Even if no adverse events have occurred all patients must receive follow-up up to 21 days after taking mifepristone. Read the **Section *4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE*** carefully*.*

This document refers to the use of ***MS-2 Step***, which consists of Mifepristone Linepharma 200 mg tablet and GyMiso® misoprostol 200 microgram tablets in combination. These medicines are indicated in females of childbearing age for the medical termination of an intrauterine pregnancy or medical management of missed miscarriage, up to 70 days of gestation. The Mifepristone Linepharma 200 mg tablet component of this therapy is also used to treat another condition. For information about the treatment of the other condition, refer to the full Product Information for Mifepristone Linepharma 200 mg tablet individual product (AUST R 175671).

1 NAME OF THE MEDICINE

Mifepristone and Misoprostol

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

MS-2 Step is a composite pack containing:

Mifepristone Linepharma

Each tablet contains 200 mg of mifepristone.

For the full list of excipients, see **Section 6.1 LIST OF**

EXCIPIENTS. **GyMiso®**

Each tablet contains 200 micrograms of misoprostol as a 1% dispersion of misoprostol-hypromellose. Misoprostol is a clear, colourless or yellowish oily liquid.

For the full list of excipients, see **Section 6.1 LIST OF EXCIPIENTS**.

3 PHARMACEUTICAL FORM

Mifepristone Linepharma

White to off-white, round biconvex tablets, diameter 11 mm, with “MF” debossed on one side of the tablet.

GyMiso®

White, flat round tablet with “ML” debossed on one side and “200” on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

- the medical termination of an intrauterine pregnancy, up to 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.

4.2 DOSE AND METHOD OF ADMINSTRATION

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.

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

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

Medical termination of an intrauterine pregnancy up to 70 days of gestation

MS-2 Step should only be prescribed by healthcare practitioners with the appropriate qualifications and training. Ectopic pregnancy should be excluded, an intrauterine device

(IUD) (if present) must be removed, consent must be obtained, and patients must have the ability to access 24-hour emergency care if and when required for incomplete abortion or bleeding.

If little or no bleeding occurs 48 hours after taking ***MS-2 Step*** or when ***MS-2 Step*** does not result in complete expulsion of the intrauterine pregnancy, the patient should return to the treating healthcare practitioner for assessment and discussion of further management options, which may include medical management to complete the expulsion or surgical uterine evacuation.

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

Medical management of missed miscarriage up to 70 days of gestation

Referral to an early pregnancy assessment service should be considered if available. Patients should be counselled on the expectant, medical and surgical management of missed miscarriage. Patients should be counselled on the possible acute effects of ***MS-2 Step***. ***MS-2 Step*** should only be prescribed by healthcare practitioners with the appropriate qualifications and training. Ectopic pregnancy should be excluded, an intrauterine device (IUD) (if present) must be removed, informed consent must be obtained, and patients must have the ability to access 24-hour emergency care if and when required for heavy vaginal bleeding and pain.

If little or no bleeding occurs 48 hours after taking ***MS-2 Step*** or when ***MS-2 Step*** does not result in complete expulsion of the gestational sac, the patient should return to the treating healthcare practitioner for assessment and discussion of further management options, which may include medical management to complete the expulsion or surgical uterine evacuation***.***

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

4.3 CONTRAINDICATIONS

MS-2 Step should not be prescribed in the following situations:

- Lack of access to emergency medical care in the 14 days following start of the treatment (i.e. administration of mifepristone);
- Suspected or confirmed ectopic pregnancy;
- Asthma uncontrolled by therapy;
- Intrauterine device (IUD) in place;
- Uncertainty about gestational age;
- Chronic adrenal failure;
- Concurrent long term corticosteroid therapy;
- Suspected or known haemorrhagic disorders or treatment with anti-coagulants;
- Hypersensitivity to mifepristone, misoprostol (or any prostaglandin), or any of the excipients used in ***MS-2 Step****;*
- Pregnancy not confirmed by an ultrasound or biological test such as urine or serum hCG.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

If applicable, medical practitioner's advice should be sought in the event that further

management of patients with medical comorbidities or adverse events is required.

Take special care in case of suspected acute adrenal failure. In case of suspected acute adrenal failure, dexamethasone administration is recommended (please refer to the dexamethasone Product Information).

Due to the antiglucocorticoid activity of mifepristone, the efficacy of long-term corticosteroid therapy, including inhaled corticosteroids in asthmatic patients, may be decreased during the 3 to 4 days following intake of mifepristone. Therapy should be adjusted.

Rare serious cardiovascular accidents (cardiac arrest, myocardial infarction and/or spasm of the coronary arteries and severe hypotension) have been reported following administration of prostaglandins including misoprostol. For this reason women with risk factors for cardiovascular disease or established cardiovascular disease should be treated with caution.

Although no epileptic seizures have been reported with misoprostol, some have been reported with prostaglandins and other prostaglandin analogues, and therefore this possibility should be borne in mind in patients with a history of epilepsy.

Bronchospasm may occur with some prostaglandins and prostaglandin analogues. The possibility should be borne in mind in patients with a history of asthma.

Severe cutaneous adverse reactions, including toxic epidermal necrolysis and acute generalised exanthematous pustulosis, have been reported in association with mifepristone (see **Section 4.8 ADVERSE EVENTS (UNDESIRABLE EFFECTS))**. In patients who experience severe cutaneous adverse reactions, treatment with mifepristone should be immediately discontinued. Re-treatment with mifepristone is not recommended.

Cases of skin rash following misoprostol administration were reported by patients in clinical trials. Angioedema of the face, lips, tongue, and/or larynx, including cases of anaphylaxis have been reported in post-market surveillance with the use of mifepristone and misoprostol, including angioedema occurring within an hour of misoprostol intake. Angioedema associated with upper airway swelling may be life threatening. If the tongue, hypopharynx, or larynx has been involved, appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided**.**

No data is available in patients with inherited porphyria.

In the case of a pregnancy occurring with an intra-uterine device in situ, this device must be removed before administration of Mifepristone Linepharma.

- ***Populations not studied:***

In the absence of specific studies, ***MS-2 Step*** is not recommended in patients with:

- Cardiovascular disease
- Hypertensive disease
- Hepatic disease
- Respiratory disease
- Renal disease
- Diabetes
- Severe anaemia
- Malnutrition

- Heavy smokers

Women who are older than 35 years and who also smoke 15+ cigarettes per day should be treated with caution because such patients were generally excluded from clinical trials of mifepristone.

- ***Specific precautions relating to medical termination of an intra-uterine pregnancy:***
  - Ectopic pregnancy

    Ectopic pregnancy should be excluded and gestation confirmed prior to medical abortion.

  - Rhesus alloimmunisation

    The need for rhesus determination and prevention of rhesus alloimmunisation should be assessed in line with the current clinical guidelines for induced abortions and missed miscarriage.

  - Explanation of requirements for the method

    This method requires the involvement of the woman who should be informed of the requirements of the medical method, which involves:

    - The necessity to take both Mifepristone Linepharma and GyMiso® in sequence according to instructions
    - The need for follow-up up to 21 days after intake of Mifepristone Linepharma in order to confirm that the abortion is complete
    - The non-negligible risk of failure (see **Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical Trials**) of the medical method which may require termination by another method
    - On discharge from the treatment centre, all women should be provided with appropriate medications as necessary and be fully counselled regarding the likely signs and symptoms she may experience and have direct access to the treatment centre by telephone or local access

The expulsion may take place before GyMiso® administration (in about 3% of cases). This does not preclude the need for follow-up to confirm complete expulsion.

The following risks related to the medical method must be taken into account and explained to the woman:

- Failures

The non-negligible risk of failure (including continuing pregnancy and incomplete abortion), which occurs in up to 7.7% of cases prior to 70 days gestation, makes follow up mandatory in order to check that the expulsion is completed. Up to 70 days about 1% women will have continuing pregnancies (in case of medical termination of pregnancy), the rest needing curettage for other reasons.

Exposure of the fetus to misoprostol or mifepristone increases the risk of developing Moebius syndrome and/or an amniotic band syndrome and/or central nervous system anomalies (see **Section 4.6 FERTILITY, PREGNANCY AND LACTATION - Use in Pregnancy**). A second termination of pregnancy procedure shall be considered. In case of continuation of the pregnancy close monitoring by ultrasound scan must be performed in specialised centres.

In cases of non-complete expulsion, a surgical intervention may be necessary.

- Bleeding

The patient must be informed of the occurrence of prolonged vaginal bleeding (an

average of 10 to 16 days after Mifepristone Linepharma and GyMiso® intake) which may be heavy. Bleeding occurs in almost all cases and is not in any way proof of complete expulsion. Persistent bleeding can be the consequence of incomplete expulsion. Bleeding can be large enough to necessitate a blood transfusion, in up to 0.2% of cases up to 70 days gestation, and to lead to a significant decrease in haemoglobin levels.

Since heavy bleeding requiring haemostatic curettage occurs in up to 5 % of cases during the medical method of pregnancy termination, special care should be given to patients with haemostatic disorders with hypocoagulability, or with anaemia. The decision to use the medical or the surgical method should be decided with specialised consultants according to the type of haemostatic disorder and the level of anaemia.

The patient should be informed not to travel far away from the prescribing centre as long as complete expulsion has not been recorded. She will receive precise instructions as to whom she should contact and where to go, in the event of any problems emerging, particularly in the case of very heavy vaginal bleeding.

As per the Royal College of Obstetricians and Gynaecologists guideline, *(The Care of Women Requesting Induced Abortion, November 2011)*, the following is recommended:

> "Following abortion, women should be provided with verbal and written information about:
>
> • symptoms they may experience, emphasising those which would necessitate an urgent medical consultation
>
> • symptoms suggestive of continuing pregnancy.
>
> Independent providers of abortion services should have arrangements in place for referring women to a public hospital emergency department for assessment and admission."
>
> "On discharge, all women should be given a letter providing sufficient information about the procedure to allow another practitioner elsewhere to manage any complications".

Follow-up must take place within a period of up to 21 days after administration of Mifepristone Linepharma to verify by the appropriate means (clinical examination, ultrasound scan, or beta-hCG measurement) that expulsion has been completed and that vaginal bleeding has stopped.

In case of persistent bleeding (even light) beyond this follow-up, the disappearance of bleeding should be checked within a few days.

If an ongoing pregnancy is suspected, a further ultrasound scan may be required to evaluate its viability.

Persistence of vaginal bleeding at this point could signify incomplete abortion, or an unnoticed ectopic pregnancy, and appropriate treatment should be considered. In the event of an ongoing pregnancy diagnosed after follow-up, termination by another method will be offered to the woman.

- Infection

As with other types of abortion, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of mifepristone and

misoprostol. No causal relationship between these events and the use of mifepristone and misoprostol has been established. Treating healthcare practitioners evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event and immediately seek a medical practitioner's (doctors) advice. In particular, a sustained fever of 38ºC or higher, severe abdominal pain, or pelvic tenderness in the days after a medical abortion may be an indication of infection.

A high index of suspicion is needed to rule out sepsis (from e.g. *Clostridium sordellii* or other species e.g. Streptococcus) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhoea) more than 24 hours after taking misoprostol. However, the symptoms of *Clostridium sordellii* infection are sometimes not the usual symptoms of sepsis and very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, haemo-concentration, and general malaise. Therefore, the possibility of sepsis should be considered in all women who are undergoing medical termination and who present with nausea, vomiting, or diarrhoea and weakness with or without abdominal pain. These symptoms, even without a fever, may indicate *Clostridium sordellii* infection. Strong consideration should be given to obtaining a complete blood count in these patients. Significant leukocytosis with a marked left shift and haemo-concentration may be indicative of sepsis. Doctors should consider immediately initiating treatment with antibiotics that includes coverage of anaerobic bacteria such as *Clostridium sordellii*. Most of the reported deaths occurred in women who used vaginally administered misoprostol however deaths following other forms of administration have been reported. No causal relationship between mifepristone and misoprostol use and an increased risk of infection or death has been established. *Clostridium sordellii* and other infections such as *Streptococcus* and other bacteria have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynaecologic and non-gynaecologic conditions. Reviews have estimated overall serious infection rates after medical abortion at less than 1%.

Use in hepatic impairment

Mifepristone and its metabolites showed a decrease in both overall peak and exposure in patients with moderate hepatic impairment compared to healthy-matched participants. However, no dose adjustments are recommended in this population (see **Section 5.2 PHARMACOKINETIC PROPERTIES).**

Use in the elderly

There is no relevant use of ***MS-2 Step*** in the elderly population in the indication.

Paediatric use

Limited data are available for use of ***MS-2 Step*** in women under 18 years of age.

There is no relevant use of ***MS-2 Step*** in the prepubertal paediatric population in the indication. Administration to adolescents less than 18 years of age should be undertaken with caution.

Effects on laboratory tests

There are no known effects of mifepristone or misoprostol on laboratory tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Mifepristone

Pharmacokinetic interactions

Effect of other medicinal products on mifepristone

Concomitant administration of mifepristone with CYP3A4 inhibitor itraconazole increased mifepristone AUC by 2.6-fold and its metabolites 22-hydroxy mifepristone and N-demethyl mifepristone exposure by 5.1-fold and 1.5-fold, respectively. C_{max} was increased by 1.5-fold for mifepristone and 1.8-fold for 22 hydroxy mifepristone and decreased to 0.7-fold for N-demethyl mifepristone. No dose adjustment is recommended when mifepristone is given concomitantly with a CYP3A4 inhibitor (e.g. itraconazole, ketoconazole, erythromycin or grapefruit juice), but caution is warranted.

Concomitant administration of mifepristone with CYP3A4 inducer rifampicin was shown to decreased mifepristone AUC by 6.3-fold and its metabolites 22-hydroxy mifepristone and N demethyl mifepristone by 20-fold and 5.9-fold, respectively. Therefore, reduced efficacy may be expected when mifepristone is given concomitantly with a CYP3A4 inducer (e.g. rifampicin, dexamethasone, St. John's Wort and certain anticonvulsants as phenytoin, phenobarbital, carbamazepine).

Therefore, in patients treated with strong or moderate CYP3A4 inducers, a different termination of pregnancy procedure might be warranted. In case of concomitant administration with CYP3A4 inducers, a follow-up appointment with the patient is needed to ensure the pregnancy has completely ended.

Effect of mifepristone on other medicinal products

In vitro and *in vivo* data indicates that mifepristone is an inhibitor of CYP3A4. Co-administration of mifepristone may lead to an increase in serum levels of drugs that are metabolised by CYP3A4. Due to the irreversible nature of the CYP binding and the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP3A4 substrates and have narrow therapeutic range, including some agents used during general anaesthesia.

GyMiso®

Misoprostol has no known drug interactions. No induction of the hepatic cytochrome P-450 enzyme system has been observed. The serum protein binding of misoprostol acid was not affected by indometacin, ranitidine, digoxin, phenylbutazone, warfarin, diazepam, methyldopa, propranolol, triamterene, cimetidine, paracetamol, ibuprofen, chlorpropamide and hydrochlorothiazide. With salicylic acid (300 µg/mL), the protein binding of misoprostol was lowered from 84 to 52% which is not considered clinically significant since the binding of misoprostol acid is not extensive and its elimination half-life is very short.

In laboratory studies, misoprostol has no significant effect on the cytochrome P450 linked hepatic mixed function oxidase system, and therefore should not affect the metabolism of theophylline, warfarin, benzodiazepines or other drugs normally metabolised by this system. No drug interactions have been attributed to misoprostol in extensive clinical trials. As such, other drugs would be unlikely to interfere with misoprostol's metabolism in either normal or hepatically-impaired patients.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

During clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses.

Mifepristone Linepharma

Mifepristone inhibited oestrus cycling in rats at oral doses of 0.3-1 mg/kg/day (less that the clinical dose adjusted for body surface area) in a 3-week study. This was reversed over the following 2-3 weeks and no subsequent effects on reproductive performance were found.

GyMiso®

In fertility studies in rats in which treated females were mated with treated males, increased pre-implantation losses were observed with misoprostol at oral doses greater than 1 mg/kg/day (11 times the recommended human dose, on a mg/m^2 basis). Post-implantation loss was also increased at 10 mg/kg/day (114 times the recommended human dose, on a mg/m^2 basis).

Use in pregnancy

Mifepristone

Linepharma

In animals, the abortifacient effect of mifepristone precludes the proper assessment of any teratogenic effect of the molecule.

Fetal skull/brain malformations, presumed to be related to treatment, have been observed in rabbits and monkeys, but not mice or rats, treated with sub-abortive doses of mifepristone. These most likely occurred secondary to mifepristone's effect on the uterus due to antagonism of progesterone.

Delayed development of the righting reflex and slight inhibition of locomotor development were observed in rats when administered mifepristone at the high-dose level (1 mg/kg/day) from day 15 of gestation to the end of the lactation period (postnatal day 21).

A review of births from 105 pregnancies exposed during first trimester of pregnancy to mifepristone alone (46 cases) or to both mifepristone and misoprostol (59 cases) has recently been published. There were 94 live births (90.4%) and 10 (9.6%) miscarriages (including one with major malformation). Elective termination of pregnancy was performed after the subsequent diagnosis of trisomy 21 in one case. The overall rate of major congenital malformations was 4.2% (95% CI: 1.2 – 10.4%), with two cases among 38 patients exposed to mifepristone alone and two cases among 57 patients exposed to both mifepristone and misoprostol. In conclusion, this unique prospective study found that the rate of major malformations after exposure to mifepristone during the first trimester of pregnancy is only slightly higher than the expected 2 – 3% rate in the general population. Nevertheless, data in humans are still too limited to determine whether the molecule is a human teratogen.

GyMiso®

Use of misoprostol has been associated with birth defects. In a few cases where misoprostol was self-administered (orally or vaginally) in order to induce an abortion, the following deleterious effects of misoprostol have been suggested: malformations of

limbs, of fetal movements and of cranial nerves (hypomimia, abnormalities in suckling, deglutition, and eye movements). To date, a risk of malformation cannot be excluded.

Reproductive toxicity studies in animals showed embryotoxicity (increased resorptions) with oral doses of 1 mg/kg/day in rabbits, 10 mg/kg/day in rats, and 20 mg/kg in mice when treatment occurred during the period of organogenesis. An increased incidence of skeletal abnormalities was observed with an oral dose of 1 mg/kg/day in rabbits (possibly due to maternal toxicity) while an increased incidence of cleft palate was seen at a single oral dose of 30 mg/kg in mice (28 and 170 times the recommended human dose, on a mg/m^2 body surface area basis, respectively).

Failure of pregnancy termination (continuing pregnancy)

Use in pregnancy has been associated with an increased risk of birth defects/malformations for ongoing pregnancies exposed to mifepristone and misoprostol or misoprostol alone, compared to control group. In particular, prenatal exposure to misoprostol has been associated with Moebius syndrome (congenital facial paralysis leading to hypomimia, troubles of sucking and deglutition and eye movements, with or without limb defects) and with amniotic band syndrome (limb deformities/ amputations, especially clubfoot, acheiria, oligodactyly, cleft palate inter alia), and central nervous system anomalies (cerebral and cranial anomalies such as anencephaly, hydrocephaly, cerebellar hypoplasia, neural tube defects).

Women considering medical termination of pregnancy should be precisely counselled on the risks to their fetus if an abortion failure occurs and a second termination of pregnancy procedure is not desirable.

MS-2 Step

As a consequence of the above information on mifepristone and misoprostol:

- Women should be informed that due to the risk of failure of the medical method of pregnancy termination and to the unknown risk to the fetus, follow-up is very important (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).
- Should a failure of the medical method be diagnosed at follow-up (viable ongoing pregnancy), and should the patient still agree, pregnancy termination should be completed by another method.

Should the patient wish to continue with her pregnancy, she should be appropriately counselled as to the risk of birth defects. In that event of continuation of the pregnancy, careful ultra-sonographic monitoring of the pregnancy should be carried out.

To avoid the potential exposure of a subsequent pregnancy to ***MS-2 Step*** it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after administration of ***MS-2 Step***.

Use in lactation

Mifepristone is a lipophilic compound and may theoretically be excreted in the mother's breast milk. However, limited data are available. Misoprostol is rapidly metabolised in the mother to misoprostol acid, which is biologically active and is excreted in breast milk. This could cause undesirable effects such as diarrhoea in breast feeding infants. ***MS-2 Step*** use should be avoided during breast-feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most frequent undesirable effects which are observed during treatment with ***MS-2 Step*** are the following:

- Gastrointestinal disorders: nausea (transient and mild), vomiting, diarrhoea, abdominal pain.
- Reproductive system disorders: very frequent uterine contractions observed in the hours following the intake of the misoprostol component of the ***MS-2 Step*** pack; vaginal bleeding, sometimes heavy and prolonged (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).
- General disorders: headache, dizziness, and chills and fever. (Because castor oil is an excipient of the misoprostol component of the ***MS-2 Step*** pack, digestive symptoms (nausea, vomiting, abdominal pain) can be observed).

The adverse events reported with mifepristone and a prostaglandin analogue such as GyMiso®, classified according to frequency and system organ class, are summarised as shown in Table 1.

Table 1: **Adverse Events for the Combined Use of Mifepristone and Misoprostol**

MedDRA	**Adverse events (frequency)**				
System Organ Class	**Very common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1000 to < 1/100**	**Rare ≥ 1/10000 to < 1/1000 and very rare (< 1/10000)***	**Unknown frequency**
Infections and infestations			Infection	Toxic shock syndrome	
Neoplasms benign, malignant and unspecified				Elevated alpha-foeto protein Elevated carcinoembryonic antigen	
Blood and lymphatic system disorders				Thrombotic thrombocytopenic purpura Thrombocytopenia Induced systemic lupus erythematosus	
Psychiatric disorders				Mania	
Nervous system disorders	Headache Dizziness			Epilepsy Neurogenic tinnitus	

Table 1: **Adverse Events for the Combined Use of Mifepristone and Misoprostol**

MedDRA	**Adverse events (frequency)**				
System Organ Class	**Very common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1000 to < 1/100**	**Rare ≥ 1/10000 to < 1/1000 and very rare (< 1/10000)***	**Unknown frequency**
Eye disorders				Ophthalmoplegia	
Cardiac disorders				Cardiac arrest Myocardial infarction and/or spasm of the arteries Induced Adam-Stokes syndrome Arrhythmia	
Vascular disorders			Hot flush Hypotension (0.25%)	Superficial thrombophlebitis	
Respiratory, thoracic and mediastinal disorders				Bronchospasm Induced bronchial asthma	
Gastrointestinal disorders	Nausea Vomiting Diarrhoea Gastric discomfort Abdominal pain	Cramping, light or moderate		Gastric bleeding Necrotising pancreatitis	
Hepatobiliary disorders				Abnormal liver function tests Hepatic failure Hepatorenal failure	
Skin and subcutaneous tissue disorders			Skin rash / pruritus	Urticarial reaction Toxic epidermal necrolysis Erythema nodosum Angioedema*	Acute generalized exanthematous pustulosis
Musculoskeletal and connective tissue disorders				Limb spasm	
Renal and urinary disorders				Renal failure	

Table 1: **Adverse Events for the Combined Use of Mifepristone and Misoprostol**

MedDRA	**Adverse events (frequency)**				
System Organ Class	**Very common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1000 to < 1/100**	**Rare ≥ 1/10000 to < 1/1000 and very rare (< 1/10000)***	**Unknown frequency**
Pregnancy, puerperium and perinatal conditions	Uterine contractions or cramping (10 to 45%) in the hours following prostaglandin intake.	Heavy bleeding occurs in about 5% of the cases and may require haemostatic curettage in up to 1.4% of the cases. Fetal malformations		Hydatiform mole Ectopic pregnancy Amniotic band syndrome Gestational trophoblastic tumor Uteroplacental apoplexy	
Reproductive system and breast disorders	Vaginal bleeding Uterine spasm	Prolonged post-abortion bleeding Spotting Severe haemorrhage Endometritis Breast tenderness Heavy bleeding	Haemorrhagic shock Salpingitis	Bilateral adnexal mass Intrauterine adhesion Ovarian cyst rupture Breast abscess Haematosalpynx Uterine rupture	
General disorders and administration site conditions	Fatigue Chill / fever	Fainting		Anaphylaxis Periorbital edema Vagal symptoms	

*Including occasional case reports

- Post-marketing experience indicates that death can occur as a result of medical termination of pregnancy (although this is a very rare outcome, <1 in 100,000). The reported deaths were due to sepsis (fatal toxic shock syndrome) associated with *Clostridium sordellii*, which also occurs in association with childbirth and spontaneous termination. The symptoms of *Clostridium sordellii* infection are sometimes not the usual symptoms of sepsis. Therefore, the possibility of sepsis should be considered in all women who are undergoing medical termination and who present with nausea, vomiting, or diarrhoea and weakness, with or without abdominal pain. These symptoms, even without a fever, may indicate *Clostridium sordellii* infection. Strong consideration should be given to obtaining a complete blood count in these patients. Significant leukocytosis with a marked left shift and haemo-concentration may be indicative of sepsis. Doctors should consider immediately initiating treatment with antibiotics that includes coverage of anaerobic bacteria such as *Clostridium sordellii*. Refer to **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**.

- Bleeding is an almost constant part of the procedure, whatever the prostaglandin analogue used, and at any pregnancy term, although it is usually more abundant when pregnancy age increases. It can occur after mifepristone alone. When heavy, it usually reflects incomplete abortion and is observed in approximately 3 to 12% of cases, depending on the pregnancy age and the prostaglandin analogue used, and needs specific treatment. It can necessitate a blood transfusion in up to 0.2% of cases. It can be prolonged for several days after prostaglandin analogue administration and sometimes leads to a decrease in haemoglobin levels. This potentially severe complication justifies that after intake (i) follow-up should take place up to 21 days after Mifepristone Linepharma administration to ensure that expulsion is complete with no persisting bleeding and (ii) until follow-up has taken place, the woman remains close to a facility where she can be treated at any moment in case of severe or prolonged bleeding. Refer to **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**.

The issue of the outcome of persisting pregnancy in the case of failure of the medical method remains incompletely solved; a risk of malformation attributable to mifepristone or to prostaglandin analogues such as misoprostol cannot be excluded, and women should be adequately counselled in such a situation. Another fact to take into consideration is the possibility of a pregnancy persisting in the form of an ectopic pregnancy, since evidence suggests that the method does not appear able to terminate an ectopic pregnancy.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems and to MS Health at 1300 515 883.

4.9 OVERDOSE

Mifepristone Linepharma

No case of overdose has been reported.

In the event of massive ingestion signs of adrenal failure might occur. Signs of acute intoxication may require specialist treatment including the administration of dexamethasone.

GyMiso®

The toxic dose of misoprostol in humans has not been determined. Cumulative total daily doses of 1600 micrograms have been tolerated, with only symptoms of gastrointestinal discomfort reported.

Clinical signs that may indicate an overdose are sedation, tremor, convulsions, dyspnoea, abdominal pain, diarrhoea, fever, palpitations, hypotension or bradycardia. Hypertension and tachycardia have also been reported following overdoses. Overdose in pregnancy has resulted in uterine contractions with fetal death.

There is no specific antidote. Treatment should be symptomatic and supportive. Consider administration of activated charcoal in the event of a potentially toxic ingestion.

Activated charcoal may reduce absorption of misoprostol if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action Mifepristone

Linepharma

Pharmacotherapeutic group: Other Sex Hormone and Modulator of the Reproductive function/ Antiprogestogen. ATC code: GO3XB01

Mifepristone is a synthetic steroid with an antiprogestational action as a result of competition with progesterone at the progesterone receptors.

Mifepristone binds to human progesterone receptors with nanomolar affinity. In animals, oral administration was shown to inhibit the action of endogenous or exogenous progesterone in multiple species (rat, mouse, rabbit, dog and monkey). This action is manifested in the form of pregnancy termination.

In women at doses of greater than or equal to 1 mg/kg, mifepristone antagonises the endometrial and myometrial effects of progesterone. During pregnancy it sensitises the myometrium to the contraction inducing action of prostaglandins. While clinical data have demonstrated that mifepristone facilitates dilatation of the cervix, no data are available to indicate that this results in a lowering of the rate of early or late complications to the dilatation procedure.

In the event of an early termination of pregnancy, the combination of a prostaglandin analogue used in a sequential regimen after mifepristone leads to an increase in the success rate and accelerates the expulsion of the conceptus.

Mifepristone binds to the glucocorticoid receptor with affinity comparable to that for the progesterone receptor. Full inhibition of the action of dexamethasone was evident in rats at oral doses 0.5-1.1 times the human dose adjusted for body surface area. In man the antiglucocorticoid action is manifested at a dose equal to or greater than 4.5 mg/kg by a compensatory elevation of ACTH and cortisol.

Mifepristone also has some anti-androgenic activity. In toxicological studies in rats and monkeys up to a duration of 6 months, mifepristone produced effects related to its antihormonal (antiprogesterone, antiglucocorticoid and antiandrogenic) activity.

GyMiso®

Pharmacotherapeutic group: Other gynecological medicines – prostaglandins. ATC code: G02AD06

Misoprostol is a synthetic analogue of prostaglandin E1. At the recommended dosages, misoprostol induces contractions of the smooth muscle fibers in the myometrium and

relaxation of the uterine cervix. The uterotonic properties of misoprostol should facilitate cervical opening and evacuation of intrauterine debris.

In the event of an early termination of pregnancy, the combination of GyMiso® used in a sequential regimen after mifepristone leads to an increase in the success rate and accelerates the expulsion of the conceptus.

Pharmacodynamic studies in early pregnancy have found an increase in uterine tone around 8 minutes after oral and 40 minutes after buccal misoprostol, with sustained contractions achieved by a mean of around 90 minutes and uterine activity peaking prior to 5 hours. Following oral administration uterine activity rises earlier than other routes, but is lower overall. Pretreatment with mifepristone has previously been shown to increase uterine contractility in response to misoprostol.

Clinical trials

Medical termination of pregnancy

Clinical efficacy of early medical abortion is defined as complete abortion without surgical intervention, regardless of the reason for the intervention, which may include continuing pregnancy, missed or incomplete abortion, prolonged or heavy vaginal bleeding or a woman's request.

An observational cohort study of 18,018 women attending one of 16 Australian clinics for MTOP (gestational age ≤ 63 days) was conducted. Patients were administered 200 mg mifepristone orally in-clinic, followed 24-48 hours later by 800 micrograms of misoprostol buccally, self-administered at home. Method success was defined as complete abortion not requiring surgical intervention. Follow up information was available for 15,565 (86.4%) of the total cohort. At least one adverse event was reported in 2,914 (16.2%) people, including 789 (4.4%) patients with at least one serious adverse event. Method failure was recorded in 749 (4.2%) patients, while heavy vaginal bleeding was reported by 573 (3.2%) of patients. The prevalence of serious infection was 0.2% (n=37), and proportion of patients requiring blood transfusion was 0.1% (n=18). One death was recorded (<0.01%); however, an association between MTOP and cause of death, necrotising pneumonia, was not established.

An open-label single-group prospective trial performed in Mexico by Gynuity Healthcare, USA, involving 971 women available for efficacy treated with 200 mg mifepristone followed by 800 micrograms misoprostol administered buccally indicated that efficacy was 98.0, 96.8 and 95.9% for women with gestational age 49 days and below, 50-56 days and 57-63 days, respectively. In these 3 gestational age groups, the rate of surgical evacuation was 2.0, 3.2 and 4.1% respectively. In this study 25 women received a second dose of misoprostol, in each case, a dose of 800 micrograms by the buccal route. Of those 25, 20 had a successful outcome with medication alone, 4 had a surgical intervention and 1 woman did not return for follow up. In this study, bleeding occurred in all women independent of outcome, and was judged as more than expected in 27.1% of the women.

In an Authorised Prescribers Program in Australia in 2012 that included 7,166 women, efficacy was 97.4% for women with gestational age <49 days, and 95.2% for women with gestational age of 49-63 days. The rate of incomplete termination requiring aspiration was: <49 days: 2.3%; 49-63 days: 4.8%. The rate of ongoing pregnancies was: <49 days: 0.3%; 49-63 days: 0.6%. Bleeding was considered as an adverse event in 0.24% of women, independent of pregnancy age.

Studies published in the literature have reported mifepristone and oral or buccal

misoprostol regimens. In one study of 966 patients[1] with pregnancies up to gestational age of 63 days, randomised to 200 mg mifepristone followed 24-36 hours later by 800 micrograms of misoprostol orally or buccally, reported efficacy rates were 91.3% for the oral and 96.2% for the buccal group (RR 0.95, 95% CI 0.92-0.98, p=0.003).

Studies published on the combination of mifepristone 200 mg and misoprostol 800 micrograms buccally, and reporting outcomes by gestational age, encompass 399 women with gestational ages 50 – 56 days and 344 women with gestational ages 57 – 63[2][3][4][5][6][7] days. Efficacy ranged from 86.5 to 98.5% in women with gestational age 50 – 56 days and from 93.0 to 100% in those with gestational age 57 – 63 days. In these studies, the rate of ongoing pregnancies ranged from 0 to 7.1% in women with gestational age 50 – 56 days and from 0 to 2.3% in those with gestational age 57 – 63 days.

Additional literature includes women with gestational ages up to 70 days. A large retrospective cohort study evaluated outcomes following mifepristone 200 mg and misoprostol 800 micrograms administered buccally or vaginally through 70 days of amenorrhoea. Of 14,504 encounters, follow-up data were available for 8,825 patients. Among those at 64–70 days, complete abortion occurred in 92.7% of patients using vaginal misoprostol and 93.2% of those using buccal misoprostol, with no clinically meaningful difference between routes of administration.[8]

A prospective, comparative, open-label trial enrolling women 57–70 days Last Menstrual Period (LMP) across six U.S. clinics evaluated the efficacy and acceptability of medical abortion using
200 mg oral mifepristone followed by 800 micrograms buccal misoprostol. Among 629 analysable cases, success rates were similar between gestational age groups (57–63 days: 93.5%; 64–70 days: 92.8%). Ongoing pregnancy rates were also comparable (3.1% and 3.0%). Acceptability was high in both groups, with most women reporting their experience as satisfactory or very satisfactory.[9]

Literature data provides information on the bleeding and expulsion pattern after termination of pregnancy with mifepristone and misoprostol: approximately half of women start to bleed before prostaglandin administration. Median bleeding time is 10 to 16 days. Bleeding is judged more or much more abundant than usual menses for 2 to 3 days after prostaglandin. In studies where it was measured, there was a slight but significant decrease in haemoglobin level after compared to baseline. In one study blood loss was quantified: the median blood loss was 83 mL and 5.4% of women had a blood loss above 200 mL. Expulsion usually takes place within
3 hours after misoprostol in approximately half of the women, and within 4 hours after misoprostol in approximately 50 to 90% of women.

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[1] Winikoff B et al. Obstetr Gynecol 2008, 1303-10
[2] Chong et al 2012 Contraception 86, 251-256
[3] Fjerstad et al 2009 Contraception 80, 282-286
[4] Boersma et al 2011 Eur J of Contraception & Reproductive Health Care 16, 61-66
[5] Ngoc et al 2011 Contraception 83, 410-417
[6] Blum et al 2012 Int J Gynecol Obstetr 118, 166-171
[7] WHO 2000 Br J Obstetr Gynecol 107, 524-30
[8] Young et al 2022 Contraception 115, 62-66
[9] Winikoff et al 2012 Obstetr Gynecol 120,1070-1076
[10] 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.

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

Medical management of missed miscarriage

MifeMiso was a large UK multicentre RCT that included women aged ≥16 years old with a diagnosis of missed miscarriage on pelvic ultrasound 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.

Around 90% of patients received vaginal misoprostol in the study. Of note, 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.[10]

In a network meta-analysis which was published in the Cochrane database, the combined regimen of mifepristone and misoprostol was more effective in achieving complete miscarriage compared to expectant management for women with missed miscarriage.[11]

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Mifepristone Linepharma

After oral administration of a single dose of 200 mg, mifepristone is rapidly absorbed. The peak concentration of 2.3 to 2.7 mg/L is reached after 0.75 hours (mean of 49 subjects). The half-life of mifepristone is 36.5 to 38.3 hours.

Mifepristone shows non-linear pharmacokinetics. Following the distribution phase the elimination is at first slow, with a half-life of approximately 12 to 72 hours, and then the concentration is more rapidly reduced with a half-life of 18 hours. With radio-receptor analysis, the final half-life is shown to be up to 90 hours, including all mifepristone metabolites that can bind to progesterone receptors.

After administration of low doses of mifepristone (20 mg orally or intravenously), the absolute bioavailability is 69%.

GyMiso®

When administered orally, misoprostol is rapidly absorbed and metabolised. Peak concentrations around 1.1 ng/mL were reached about 15 minutes after a 400 µg dose in the fasting state. Plasma concentrations of its main degradation metabolite, misoprostol acid, reach their peak of 2 - 2.5 ng/mL after a 2 µg/kg oral dose within approximately 30 minutes and rapidly decline thereafter. As a result, uterine contractility increases and then plateaus after about one hour. Absorption is almost complete, measured at levels between 64 - 73% from urinary data.

For a single oral administration of 800 micrograms misoprostol (4 tablets of 200 micrograms GyMiso®), AUC_{0-t} was 1.9709 ± 0.8130 hr.ng/mL, $AUC_{0-\infty}$ was 2.0192 ±

0.8032 hr.ng/mL and C_{max} was 2.6830 ± 1.2161 ng/mL. For a single buccal administration of 800 micrograms misoprostol (4 tablets of 200 micrograms GyMiso®), AUC_{0-t} was 1.9095 ± 0.2909 hr.ng/mL, $AUC_{0-\infty}$ was 2.0726 ± 0.3578 hr.ng/mL and C_{max} was 1.3611 ± 0.3436 ng/mL. For a single sublingual administration of 800 micrograms misoprostol (4 tablets of 200 micrograms GyMiso®), AUC_{0-t} was 3.0574 ± 0.9872 hr.ng/mL, $AUC_{0-\infty}$ was 3.2094 ±1.0417 hr.ng/mL and C_{max} was 2.4391 ± 1.1567 ng/mL. For log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}, there were statistically significant differences between 3 treatment groups (p = 0.0159, 0.0162 and 0.0083, respectively). Sublingual administration of misoprostol had a higher $AUC_{0-\infty}$ compared with buccal and oral administration which indicated bioavailability was higher by the sublingual route. Misoprostol sublingual and oral administration resulted in higher C_{max} compared with buccal. The C_{max} of buccal administration was achieved later compared with other routes of administration. No difference was found when comparing oral, sublingual and buccal half-lives (p= 0.4495).

Distribution

Mifepristone Linepharma

In plasma, mifepristone is 98% bound to plasma proteins: albumin and principally alpha-1-acid glycoprotein (AAG), to which binding is saturable. Due to this specific binding, the volume of distribution and plasma clearance of mifepristone are inversely proportional to the plasma concentration of AAG.

GyMiso®

Serum protein binding of labeled misoprostol acid was studied in man and was similar in young (81-88%) and elderly (81-89%) subjects. Accumulation in erythrocytes was not seen.

Metabolism

Mifepristone Linepharma

N mono- and di-demethylation and terminal hydroxylation of the 17-propynyl chain are primary metabolic pathways of hepatic oxidative metabolism. Metabolites are detectable in plasma 1 hour after ingestion of mifepristone. Plasma AUC for the dominant metabolite, monodemethylated mifepristone, is approximately double that of the unchanged mifepristone at the clinical dose, and this metabolite retains significant affinity for the progesterone receptor. The other metabolites also display some progesterone receptor affinity (approximately 10 to 15% that of mifepristone). The metabolites may contribute to the pharmacological effects of mifepristone.

In vitro CYP3A4 appears as the isoenzyme primarily responsible for mifepristone demethylation and hydroxylation in human liver microsomes. CYP3A4 substrates progesterone and midazolam inhibited metabolite formation by up to 77%. Other isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1) had apparently no action on mifepristone metabolism.

GyMiso®

Metabolism of misoprostol to misoprostol acid is rapid with no intact misoprostol found in plasma consistent with an *in vitro* half-life of 6.4 minutes for de-esterification of misoprostol in human plasma at 37ºC. Elimination of misoprostol and its metabolites is also rapid with a plasma elimination half-life of 35 minutes.

Excretion

Mifepristone Linepharma

After administration of 600 mg radiolabelled mifepristone, 10% of the total radioactivity was recovered in urine and 90% in faeces.

GyMiso®

The liver is the primary site of metabolism and between 1-4% of misoprostol acid is excreted in the urine.

Characteristics in specific groups of subjects or patients

Hepatic impairment

A study of 8 women with moderate hepatic impairment and 8 women with normal hepatic function (median age 61 years), treated with a single oral dose of mifepristone 200 mg assessed the pharmacokinetics of mifepristone and its metabolites (N-demethylated metabolite, hydroxylated metabolite and di-demethylated metabolite). The total C_{max} of mifepristone and its metabolites were reduced by half in patients with moderate hepatic impairment compared to normal hepatic function participants. Similarly, the total AUC_{∞} was reduced by 43% and 50% for mifepristone and N-demethylated metabolite in patients with moderate hepatic impairment compared to normal hepatic function participants.

Considering the above, the clinical consequences of 200 mg mifepristone administration in patients with moderate hepatic impairment are unknown.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Mifepristone

Linepharma

Mifepristone has been evaluated in tests for mutagenicity in bacterial, yeast and mammalian cells; gene conversion in yeast; unscheduled DNA synthesis in HeLa cells; and for clastogenicity *in vitro* (Chinese hamster ovary cells) and in vivo (mouse bone marrow micronucleus test). No evidence of genotoxicity was observed.

GyMiso®

Misoprostol has been evaluated in tests for mutagenicity in bacterial, yeast and mammalian cells; and for clastogenicity *in vitro* (Chinese hamster ovary cells) and *in vivo* (mouse bone marrow micronucleus test). No evidence of genotoxicity was observed.

Carcinogenicity

Mifepristone

Linepharma

No long-term animal carcinogenicity studies have been conducted with mifepristone. Based on the negative genotoxicity results, findings in general repeat-dose toxicity studies and considering the pattern of clinical use, mifepristone is not predicted to pose a particular carcinogenic risk.

GyMiso®

The potential carcinogenicity of misoprostol has been evaluated in both mice and rats. There was no evidence of an effect of misoprostol on tumour occurrence or incidence in rats receiving oral doses up to 2.4 mg/kg/day for 24 months. Similarly, there was no effect of misoprostol on tumour occurrence or incidence in mice receiving oral doses up to 16 mg/kg/day for 21 months. These doses are at least 27 times the recommended human dose, on a mg/m^2 body surface area basis.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mifepristone Linepharma 200 mg tablet contains the following excipients: maize starch, povidone, microcrystalline cellulose, colloidal anhydrous silica and magnesium stearate.

GyMiso® contains the following excipients: hypromellose, microcrystalline cellulose, sodium starch glycollate type A and hydrogenated castor oil.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Do not use after the expiry date printed on the carton labels of the composite pack and the individual components.

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C, keep in the original container to protect from

light. Keep out of reach of children.

Mifepristone Linepharma

Keep in the original green carton in order to protect from light

GyMiso®

Keep in the original purple carton

6.5 NATURE AND CONTENTS OF CONTAINER

Each ***MS-2 Step*** composite pack consists of:

- 1 green carton containing Mifepristone Linepharma 200 mg tablet packaged in a PVC/PVDC/Aluminium blister. Pack size of 1 tablet.
- 1 purple carton containing GyMiso® misoprostol 200 microgram tablet packaged in a dual-faced Aluminium strip or blister. Pack size of 4 tablets (2 tablets per blister).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

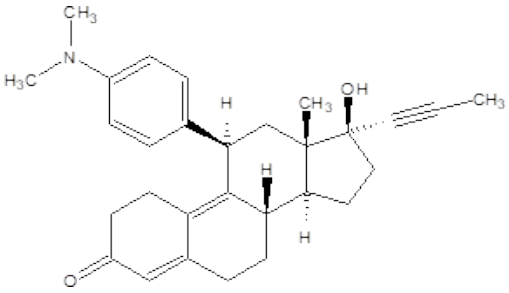
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Mifepristone

Chemical

structure



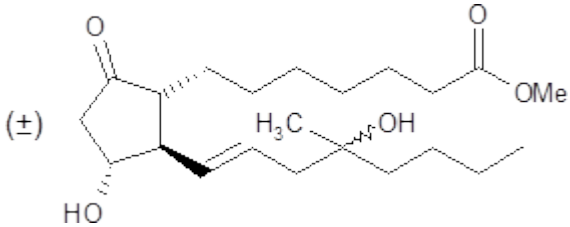
Molecular formula: $C_{29}H_{35}NO_2$ Molecular weight: 429.6

CAS number

CAS Registry Number: 84371-65-3

GyMiso®

Chemical Structure



Molecular formula:$C_{22}H_{38}O_5$ Molecular weight: 382.5

CAS number

CAS Registry Number: 59122-46-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8 SPONSOR

MS Health Pty
Ltd Ground
Floor East, 678
Victoria Street,
Richmond, VIC, Australia,

3121 Ph: 1300 515 883

MS-2 Step® is a registered trademark of MSI Reproductive Choices (UK). Mifepristone Linepharma and GyMiso® are licensed from Linepharma International Limited (UK).

9 DATE OF FIRST APPROVAL

4 June 2014

10 DATE OF REVISION

XXXXX

11 SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.1	Extension of indication

4.2	Editorial updates; clarifications in line with the indications
4.4	Updated frequency of risk of failure and bleeding in line with the extension of indications
5.1	Included additional clinical trial data for extension of indications