

**Attachment 1: Product information for AusPAR MS-2 Step mifepristone/misoprostol MS Health Pty Ltd PM-2013-01037-1-5 Final 13 October 2014. This Product Information was approved at the time this AusPAR was published.**

## PRODUCT INFORMATION - *MS-2 Step* $\hat{O}$

It is very important that all patients receiving these medications are followed up by a medical 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 14 to 21 days after taking mifepristone. Read the ***SPECIAL WARNINGS AND PRECAUTIONS FOR USE*** carefully.

This document refers to the use of *MS-2 Step*  $\hat{O}$ , which consists of Mifepristone Linepharma 200 mg tablet and GyMiso<sup>®</sup> misoprostol 200 microgram tablets in combination. These medicines are indicated in females of childbearing age for the medical termination of a developing intrauterine pregnancy, up to 63 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).

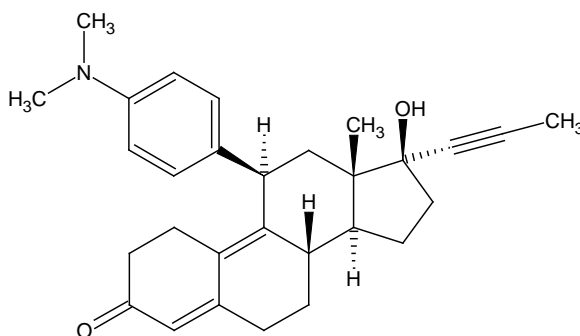
### NAME OF THE MEDICINE

*MS-2 Step*  $\hat{O}$  is a composite pack containing Mifepristone Linepharma 200 mg tablet and GyMiso<sup>®</sup> misoprostol 200 microgram tablets.

### Mifepristone

Australian Approved Name (AAN): Mifepristone

Chemical Structure:



Molecular formula: C<sub>29</sub>H<sub>35</sub>NO<sub>2</sub>

Molecular weight: 429.6

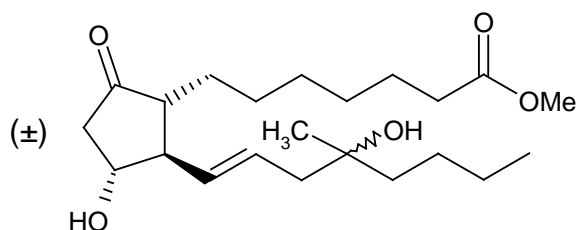
## PRODUCT INFORMATION - MS-2 Step $\hat{O}$

CAS Registry Number: 84371-65-3

### GyMiso<sup>®</sup>

Australian Approved Name (AAN): Misoprostol

Chemical Structure:



Molecular formula: C<sub>22</sub>H<sub>38</sub>O<sub>5</sub>

Molecular weight: 382.5

CAS Registry Number: 59122-46-2

## DESCRIPTION

### Mifepristone Linepharma

White to off-white, round biconvex tablets, diameter 11 mm, with “MF” debossed on one side of the tablet. One pack of Mifepristone Linepharma (green) contains one tablet.

Each tablet contains 200 mg of mifepristone.

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

### GyMiso<sup>®</sup>

White, flat round tablet with “ML” debossed on one side and “200” on the other side. One pack of GyMiso<sup>®</sup> (purple) contains four tablets.

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

GyMiso<sup>®</sup> contains the following excipients: hypromellose, microcrystalline cellulose, sodium starch glycolate type A and hydrogenated castor oil.

## **PRODUCT INFORMATION - MS-2 Step <sup>®</sup>**

### **PHARMACOLOGY**

#### **Pharmacodynamic properties**

##### **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. During the first trimester, pre-treatment with mifepristone allows the dilatation and opening of the cervix uteri. 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 (antiprogestone, antiglucocorticoid and antiandrogenic) activity.

##### **GyMiso<sup>®</sup>**

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

## **PRODUCT INFORMATION - MS-2 Step *Ô***

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.

### **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%.

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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

## **PRODUCT INFORMATION - MS-2 Step $\hat{O}$**

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<sup>®</sup>),  $AUC_{0-t}$  was  $1.9709 \pm 0.8130$  hr.ng/mL,  $AUC_{0-\infty}$  was  $2.0192 \pm 0.8032$  hr.ng/mL and  $C_{max}$  was  $2.6830 \pm 1.2161$  ng/mL. For a single buccal administration of 800 micrograms misoprostol (4 tablets of 200 micrograms GyMiso<sup>®</sup>),  $AUC_{0-t}$  was  $1.9095 \pm 0.2909$  hr.ng/mL,  $AUC_{0-\infty}$  was  $2.0726 \pm 0.3578$  hr.ng/mL and  $C_{max}$  was  $1.3611 \pm 0.3436$  ng/mL. For a single sublingual administration of 800 micrograms misoprostol (4 tablets of 200 micrograms GyMiso<sup>®</sup>),  $AUC_{0-t}$  was  $3.0574 \pm 0.9872$  hr.ng/mL,  $AUC_{0-\infty}$  was  $3.2094 \pm 1.0417$  hr.ng/mL and  $C_{max}$  was  $2.4391 \pm 1.1567$  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.

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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 and excretion**

#### **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

## **PRODUCT INFORMATION - MS-2 Step**

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.

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

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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 37°C. Elimination of misoprostol and its metabolites is also rapid with a plasma elimination half-life of 35 minutes.

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

Misoprostol has no known drug interactions. No induction of the hepatic cytochrome P-450 enzyme system has been observed.

## **CLINICAL TRIALS**

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 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

## **PRODUCT INFORMATION - MS-2 Step *Ô***

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<sup>1</sup> 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 days<sup>2,3,4,5,6</sup>. 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.

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<sup>7</sup> 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

<sup>1</sup> Winikoff B et al. *Obstetr Gynecol* 2008, 1303-10

<sup>2</sup> Chong et al 2012 *Contraception* 86, 251–256

<sup>3</sup> Fjerstad et al 2009 *Contraception* 80, 282-286

<sup>4</sup> Boersma et al 2011 *Eur J of Contraception & Reproductive Health Care* 16, 61-66

<sup>5</sup> Ngoc et al 2011 *Contraception* 83, 410 – 417

<sup>6</sup> Blum et al 2012 *Int J Gynecol Obstetr* 118, 166 - 171

<sup>7</sup> WHO 2000 *Br J Obstetr Gynecol* 107, 524-30

## PRODUCT INFORMATION - *MS-2 Step Ô*

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.

### INDICATION

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

It is recommended that the duration of pregnancy (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.

### CONTRAINDICATIONS

*MS-2 Step Ô* 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;
- 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 Ô*

### PRECAUTIONS

Take special care in case of suspected acute adrenal failure.

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.



## PRODUCT INFORMATION - *MS-2 Step Ô*

Rare serious cardiovascular accidents 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.

No data are available in patients with inherited porphyria.

### SPECIAL WARNINGS AND PRECAUTIONS FOR USE

· ***Populations not studied:***

In the absence of specific studies, *MS-2 Step Ô* 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 a developing intra-uterine pregnancy:***

- **Ectopic pregnancy**

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

- **Rhesus alloimmunisation**

## **PRODUCT INFORMATION - MS-2 Step *Ô***

The use of *MS-2 Step* requires rhesus determination and hence the prevention of rhesus allo-immunisation.

### **o 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 within 14 to 21 days after intake of Mifepristone Linepharma in order to confirm that the abortion is complete
- § The non-negligible risk of failure (see 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:

### **o Failures**

The non-negligible risk of failure, which occurs in up to 7% of cases prior to 63 days gestation, makes follow up mandatory in order to check that the expulsion is completed. Up to 63 days about 1% women will have continuing pregnancies, the rest needing curettage for other reasons.

### **o 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 63 days gestation and to lead to a significant decrease in haemoglobin levels.

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

## **PRODUCT INFORMATION - MS-2 Step *Ô***

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, September 2004*), the following is recommended:

“Following abortion, women must be given a written account of the symptoms they may experience and a list of those that would make an urgent medical consultation necessary. They should be given a 24-hour telephone helpline number to use if they feel worried about pain, bleeding or high temperature. Urgent clinical assessment and emergency gynaecology admission must be available when necessary.”

“On discharge, each woman should be given a letter that gives sufficient information about the procedure to allow another practitioner elsewhere to deal with any complications”

Follow-up must take place within a period of 14 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 extra-uterine 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.

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.

### **o 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 doctors evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event. In particular, a sustained fever of 38°C or

## PRODUCT INFORMATION - *MS-2 Step Ô*

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%.

### Effects on fertility

During clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses. To avoid the potential exposure of a subsequent pregnancy to *MS-2 Step Ô* 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 Ô*.

### Mifepristone Linepharma

Mifepristone inhibited oestrus cycling in rats at oral doses of 0.3-1 mg/kg/day (less than 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.

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## **PRODUCT INFORMATION - MS-2 Step *Ô***

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<sup>2</sup> basis). Post-implantation loss was also increased at 10 mg/kg/day (114 times the recommended human dose, on a mg/m<sup>2</sup> basis).

### **Use in pregnancy**

#### **Mifepristone Linepharma**

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

Foetal 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<sup>8</sup>. 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®**

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<sup>8</sup> Bernard et al 2013 Br J Obstetr Gynecol 120, 568-575

## **PRODUCT INFORMATION - MS-2 Step Ô**

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 foetal 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<sup>2</sup> body surface area basis, respectively).

### **MS-2 Step Ô**

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 foetus, follow-up is very important (see 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.

### **Use during 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 Ô** use should be avoided during breast-feeding.

## PRODUCT INFORMATION - *MS-2 Step Ô*

### Paediatric use

Limited data are available for use of *MS-2 Step Ô* in women under 18 years of age. There is no relevant use of *MS-2 Step Ô* in the prepubertal paediatric population in the indication. Administration to adolescents less than 18 years of age should be undertaken with caution.

### Use in the elderly

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

### 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

## **PRODUCT INFORMATION - MS-2 Step $\hat{O}$**

16 mg/kg/day for 21 months. These doses are at least 27 times the recommended human dose, on a mg/m<sup>2</sup> body surface area basis.

### **Effect on laboratory tests**

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

## **INTERACTIONS WITH OTHER MEDICINES**

### **Mifepristone Linepharma**

No interaction studies have been performed.

On the basis of mifepristone's metabolism by CYP3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum levels of mifepristone). Furthermore, rifampicin, dexamethasone, St. John's Wort and certain anticonvulsants (phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum levels of mifepristone).

Based on *in vitro* information showing that mifepristone acts as a mechanism-based inhibitor of CYP3A4, co-administration of mifepristone may lead to an increase in serum levels of drugs that are CYP3A4 substrates. 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®**

The serum protein binding of misoprostol acid was not affected by indomethacin, 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.



## PRODUCT INFORMATION - *MS-2 Step Ô*

### ADVERSE EFFECTS

The most frequent undesirable effects which are observed during treatment with *MS-2 Step Ô* 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 Ô* pack; vaginal bleeding, sometimes heavy and prolonged (see 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 Ô* 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.

Attachment 1: Product information for AusPAR MS-2 Step mifepristone/misoprostol MS Health Pty Ltd PM-2013-01037-1-5 Final 13 October 2014. This Product Information was approved at the time this AusPAR was published.

## PRODUCT INFORMATION - MS-2 Step $\hat{O}$

<b>MedDRA</b>	<b>Adverse events (frequency)</b>			
<b>System Organ Class</b>	<b>Very common <math>\geq 1/10</math></b>	<b>Common <math>\geq 1/100</math> to <math>&lt; 1/10</math></b>	<b>Uncommon <math>\geq 1/1000</math> to <math>&lt; 1/100</math></b>	<b>Rare <math>\geq 1/10000</math> to <math>&lt; 1/1000</math> and very rare (<math>&lt; 1/10000</math>)*</b>
<b>Infections and infestations</b>			Infection	Toxic shock syndrome
<b>Neoplasms benign, malignant and unspecified</b>				Elevated alpha-foeto protein Elevated carcinoembryonic antigen
<b>Blood and lymphatic system disorders</b>				Thrombotic thrombocytopenic purpura Thrombocytopenia Induced systemic lupus erythematosus
<b>Psychiatric disorders</b>				Mania
<b>Nervous system disorders</b>	Headache			Epilepsy Neurogenic tinnitus
<b>Eye disorders</b>				Ophthalmoplegia
<b>Cardiac disorders</b>				Myocardial infarction Induced Adam-Stokes syndrome
<b>Vascular disorders</b>			Hot flush Hypotension (0.25%)	Superficial thrombophlebitis
<b>Respiratory, thoracic and mediastinal disorders</b>				Bronchospasm Induced bronchial asthma
<b>Gastrointestinal disorders</b>	Nausea Vomiting Diarrhoea Gastric discomfort Abdominal pain	Cramping, light or moderate		Gastric bleeding

## PRODUCT INFORMATION - MS-2 Step $\hat{O}$

MedDRA	Adverse events (frequency)			
System Organ Class	Very common $\geq 1/10$	Common $\geq 1/100$ to $< 1/10$	Uncommon $\geq 1/1000$ to $< 1/100$	Rare $\geq 1/10000$ to $< 1/1000$ and very rare ( $< 1/10000$ )*
<b>Hepatobiliary disorders</b>				Abnormal liver function tests Hepatic failure Hepatorenal failure
<b>Skin and subcutaneous tissue disorders</b>			Skin rash / pruritus	Urticarial reaction Toxic epidermal necrolysis Erythema nodosum Angioedema*
<b>Musculoskeletal and connective tissue disorders</b>				Limb spasm
<b>Renal and urinary disorders</b>				Renal failure
<b>Pregnancy, puerperium and perinatal conditions</b>	Very common 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.		Hydatiform mole Ectopic pregnancy Amniotic band syndrome Gestational trophoblastic tumor Uteroplacental apoplexy
<b>Reproductive system and breast disorders</b>	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
<b>General disorders and administration site conditions</b>	Fatigue Chill / fever Dizziness	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

## PRODUCT INFORMATION - MS-2 Step $\hat{O}$

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 **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 takes place approximately 14 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 **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.

## DOSAGE AND ADMINISTRATION

MS-2 Step  $\hat{O}$  is indicated for medical termination of developing intra-uterine pregnancy, up to 63 days of gestation.

## **PRODUCT INFORMATION - *MS-2 Step O***

The method of administration is as follows:

**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) buccally, i.e: kept between the cheek and the gum for 30 minutes before any fragments being swallowed with water.

When *MS-2 Step O* fails to cause termination of intra-uterine pregnancy, the patient should return to the treating doctor for assessment and discussion of treatment options, which may include pregnancy termination by surgery.

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 O* should be taken 2 hours before or 2 hours after a meal.

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

*MS-2 Step O* should only be prescribed by doctors with the appropriate qualifications and certified training. Ectopic pregnancy should be excluded, an 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.

## **OVERDOSAGE**

### **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.

## **PRODUCT INFORMATION - MS-2 Step Ô**

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 foetal 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 13 11 26 (Australia).

## **PRESENTATION AND STORAGE CONDITIONS**

Each *MS-2 Step Ô* 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. Store below 25°C, keep in original container to protect from light.
- 1 purple carton containing GyMiso<sup>®</sup> misoprostol 200 microgram tablet packaged in a dual-faced Aluminium blister. Pack size of 4 tablets (2 tablets per blister). Store below 25°C, keep in original container to protect from light.

Keep out of reach of children.

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

### **Mifepristone Linepharma**

PVC/PVDC/Aluminum blister of 1 tablet

Pack size of 1 tablet

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

### **GyMiso<sup>®</sup>**

Dual-faced aluminium blisters of 2 tablets per blister

**Attachment 1: Product information for AusPAR MS-2 Step mifepristone/misoprostol MS Health Pty Ltd PM-2013-01037-1-5 Final 13 October 2014. This Product Information was approved at the time this AusPAR was published.**

## **PRODUCT INFORMATION - MS-2 Step Ô**

Pack size of 4 tablets

Keep in the original purple carton

### **Poison schedule of the medicines**

Schedule 4

### **Name and address of the sponsor**

MS Health  
Suite 129, 135 Cardigan Street  
Carlton VIC 3053 Australia.

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### **Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG)**

4 June 2014

### **Date of most recent amendment**

The prescriber must ensure that consent and treatment of the patient is in accordance with the appropriate state or territory legislation.