



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Mifepristone

Proprietary Product Name: Mifepristone
Linepharma

Sponsor: MS Health

October 2012

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- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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I. Introduction to product submission

Submission details

<i>Type of Submission</i>	New Chemical Entity
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	7 August 2012
<i>Active ingredient(s):</i>	Mifepristone
<i>Product Name(s):</i>	Mifepristone Linepharma
<i>Sponsor's Name and Address:</i>	MS Health ¹ , GPO Box 1635, Melbourne VIC
<i>Dose form(s):</i>	Tablet (uncoated, unscored)
<i>Strength(s):</i>	200 mg
<i>Container(s):</i>	Blister pack
<i>Pack size(s):</i>	1 tablet
<i>Approved Therapeutic use:</i>	"Mifepristone Linepharma 200 mg tablet is indicated in females of childbearing age for: 1. Medical termination of a developing intra-uterine pregnancy. In sequential combination with a prostaglandin analogue up to 49 days of gestation. 2. Preparation for the action of registered prostaglandin analogues that are indicated for the termination of pregnancy for medical reasons beyond the first trimester."
<i>Route(s) of administration:</i>	Oral (PO)
<i>Dosage:</i>	1. 200 mg of mifepristone (1 tablet containing 200 mg) orally, followed 36 to 48 hours later by the scheduled prostaglandin analogue administration. 2. 200 mg of mifepristone (1 tablet containing 200 mg) orally, followed 36 to 48 hours later by the scheduled prostaglandin analogue administration, which will be repeated as often as indicated
<i>ARTG Number (s)</i>	175671

Product background

Mifepristone is a new chemical entity in Australia although the drug has been registered overseas for many years. It has progesterone receptor antagonist activity and this provides the rationale of its intended effect as an abortifacient.

¹ The Applicant Marie Stopes International Australia has transferred sponsorship of the registered product to MS Health.

This AusPAR describes the application by Marie Stopes International Australia to register mifepristone for the medical termination of pregnancy in Australia. The proposed treatment regimen involves oral administration of a single 200 mg dose, followed 36–48 h later by a prostaglandin analogue (misoprostol; single or repeated oral (PO) administration). This application is therefore linked to an application to register GyMiso® misoprostol 200 µg tablets. The combination of the two products is essential to achieve an effective termination of pregnancy in women who are up to 49 days of gestation.

The sponsor initially proposed the following indications:

“Mifepristone Linepharma 200 mg tablet is indicated in women and adolescent girls of childbearing age for:

- 1. Medical termination of a developing intra-uterine pregnancy. In sequential combination with a prostaglandin analogue up to 49 days of amenorrhoea (DA).*
- 2. Preparation for the action of prostaglandin analogues during the termination of pregnancy for medical reasons beyond the first trimester.”*

The first part of the indication was later amended to the following²:

“Medical termination of a developing intra-uterine pregnancy In sequential combination with a prostaglandin analogue up to 49 days of gestation.”

The proposed formulation of mifepristone has not been used in any large clinical trial.

Regulatory status

Mifepristone has been registered in China and France since 1988 and subsequently in many countries through Europe during the 1990s and in the USA in 2000. It is also registered in New Zealand (2001).

At the time of application Mifepristone Linepharma had been submitted in the USA and also via the decentralised process in European Union (EU; the reference member state was Sweden). The international regulatory history for Mifepristone Linepharma is summarised in Table 1 below. The status was stated approved in Denmark (7 January 2011), Norway (18 February 2011) and Finland (21 February 2011) and as pending in the United Kingdom (UK), the USA, Canada, Mexico and several countries in Africa including South Africa.

² Note: The indication was amended again before approval (see page 4)

Table 1. International Regulatory history of Mifepristone Linepharma

Country	Marketing Authorisation Holder	Trade name	Strength	Approval date/Status
France	LinepharmaFrance /Linepharma France	Mifepristone Linepharma 200 mg comprimé	200 mg	Pending (Approvable)
Sweden	Linepharma France/ CampusPharma	Mifepristone Linepharma 200 mg Taflette	200 mg	28 January 2011
UK	Linepharma France	Mifepristone	200 mg	Pending (Approvable)
USA	Linepharma France	Mifepristone Linepharma	200 mg	Pending

UK=United Kingdom

Product Information

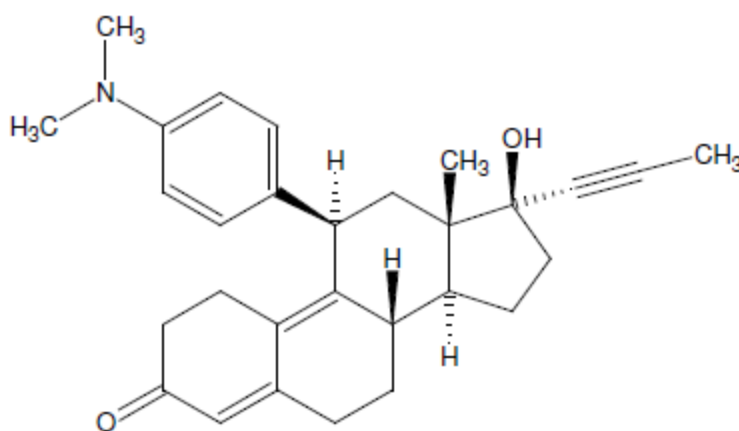
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

Mifepristone is a steroid derivative and the structure is shown in Figure 1 below.

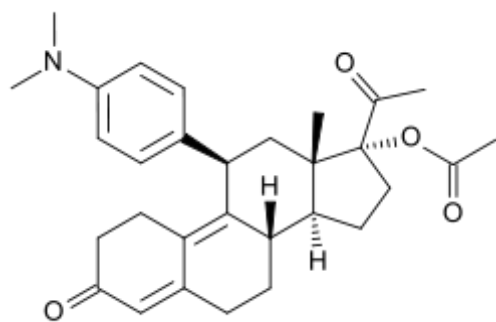
Figure 1. Chemical structure of mifepristone



molecular formula: C₂₉H₃₅NO₂

molecular weight: 429.6

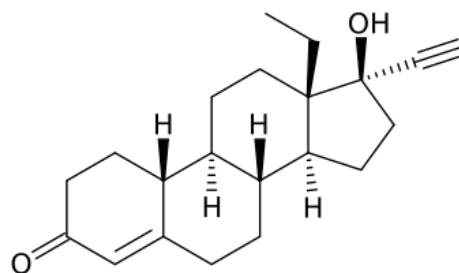
The structure of two related steroidal drugs are shown in Figure 2 below.

Figure 2. Chemical structures of ulipristal acetate and levonorgestrel

ulipristal acetate

ellaOne in EU; *ella* in USA

30 mg tablet [not available in Australia]



levonorgestrel

Levonelle-1/Norlevo 1.5 mg

1.5 mg tablet [Australia]

Mifepristone has multiple chiral centres and it is presented as a single enantiomer as shown. Mifepristone is a crystalline, yellowish powder. It is practically insoluble in water and at intestinal pH. Its solubility is dramatically higher in acid.

Mifepristone is semisynthetic. The drug substance is micronised. The drug substance meets the draft United States Pharmacopeia monograph. Drug substance aspects were considered acceptable.

Drug product

The proposed tablets are “white to off-white, round, biconvex, 11 mm diameter tablet, with ‘MF’ debossed on one side of the tablet.” They are not film-coated. Excipients are conventional. Tablets are not scored.

The formulation proposed for registration was developed to be bioequivalent to overseas mifepristone tablets. The quantitative formulation is a copy of the formulation of *Mifegyne* tablets.

Clinical Trial Formulations

Mifepristone tablets have been commercially available overseas since about 1988. Tablets are supplied in the EU as *Mifegyne*; the *Mifegyne* tablets used in the bioavailability study (see below) are described as coming from France. Tablets are available in the USA as Danco’s *Mifeprex*. The clinical data supporting this application relies heavily on the literature. It is stated that “Most studies reviewed in the application have been performed using either *Mifegyne* or *Mifeprex*”. The application included two bioequivalence studies comparing ‘*Miffée*’ with both *Mifegyne* (Study CAL2015-002) and with *Mifeprex* (CAL2015-001) [*Miffée* is another name for the formulation proposed for registration in Australia].

Manufacture and Control

Mifepristone Linepharma tablets are made by wet granulation. There are no official monographs for mifepristone tablets. Both disintegration and dissolution testing are used.

Mifepristone is somewhat susceptible to oxidative degradation. Degradation in light is plausible but the sponsor has argued that photostability data are not relevant for a single tablet pack. This was considered acceptable given the indication.

Control of the tablets is considered acceptable.

Biopharmaceutics

Because of the international context, this application to register a new chemical entity was not supported by the set of bioavailability studies which would normally be expected. There is, however, information in the literature on mifepristone pharmacokinetics.³

The literature reports that mifepristone is rapidly absorbed. In blood mifepristone is bound to the serum transport protein alpha-1-acid glycoprotein (AAG) but this protein is saturated above doses of about 100 mg. Mifepristone is extensively metabolised by demethylation and hydroxylation, initially by CYP3A4. Most metabolites are active. The half-life is 25 to 30 h. Individual plasma profiles are generally conventional but commonly show a second peak at about 24 h, perhaps due to enterohepatic recycling.

Given the pH dependent solubility of mifepristone it seems possible that bioavailability might be lower in achlorhydric subjects.

Absolute Bioavailability

The submission claims an absolute bioavailability of 69% with a 20 mg dose of mifepristone. This is taken from the literature and is also quoted in the US package insert for *Mifeprex*.⁴ The bioequivalence of *Mifeprex* and *Mifepristone Linepharma* (as 200 mg tablets) has been studied (see below). This was considered sufficient information.

Food Effects

The draft Product Information makes no comment about dosing relative to food. There do not appear to be published studies of the effect of food on bioavailability. Mifepristone may be more extensively dissolved, and thus absorbed, from disintegrated tablets under acidic conditions as noted above. No food directions are given in the overseas product literature. The sponsor makes a clinical argument that even if exposure was reduced this would not affect efficacy, hence directions in relation to dosing are not required.

Formulations

The application included two bioequivalence studies comparing the proposed formulation with the different overseas mifepristone formulations:

Study CAL 052015-001 versus *Mifeprex* tablets (USA)

Study CAL 052015-002 versus *Mifegyne* tablets (France)

These were reasonably large studies (n=48, 50; all female volunteers). They used single fasting doses. There was a significant difference in time to peak plasma concentration (T_{max}) in one study. The *Mifeprex* and *Mifepristone Linepharma* tablets were bioequivalent. In the *Mifegyne* study, the tablets were bioequivalent with respect to exposure (area under the plasma concentration time curve (AUC)) but not peak plasma concentration (C_{max}). The sponsor argues that certain subject results should be treated as outliers, which is generally not considered appropriate in bioequivalence studies. Using all data, the C_{max} results are just outside standard bioequivalence limits (80-125%) in the second study (90 % confidence interval (CI) of the ratio of C_{max} was 103.3 – 126.7%).

The studies were considered to be relevant given the dependence of the application on literature data generated with *Mifeprex* and *Mifegyne* tablets.

³ O. Heikinheimo et al *Clinical Pharmacokinetics*. 33 (1) (pp 7-17), 1997

⁴ http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_mifepristone.cfm

Advisory committee considerations

This application was considered at the 141st meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) (Recommendation No. 2233).

The Committee noted that there was a risk of variable bioavailability with differences in timing of doses in relation to food. The PSC considered that the attention of the Clinical Delegate should be drawn to the absence of data and lack of information on this issue.

The PSC considered that, given the proposed use with *GyMiso* with staggered dosing, this product should be presented as a composite pack with misoprostol. The composite pack should include appropriate and clear warnings and clear instructions on usage.

Quality summary and conclusions

Registration was recommended with respect to chemistry, quality control and bioavailability aspects.

III. Nonclinical findings

Introduction

The nonclinical submission was almost entirely literature based; the sponsor's search strategy was adequate. A copy of the US FDA Summary Basis of Approval for mifepristone was provided as supporting material and offered some additional detail on the studies described in the literature. The nonclinical submission also contained one actual study report (on phototoxicity). The general quality of the nonclinical data set is considered to be high. The sponsor was unable to verify the Good Laboratory practice (GLP) status of the studies from the literature but the evaluator has been able to ascertain such information independently in many cases.

Pharmacology

Mifepristone acts as a progesterone receptor antagonist. *In vitro*, the drug was shown to act with nanomolar potency to competitively inhibit the binding of radioactively labelled (³H)-progesterone to recombinant human progesterone receptors A and B, and to inhibit activation of the receptors in cell-based functional assays. *In vivo*, mifepristone (administered PO) antagonised the actions of exogenously administered progesterone in various assays in rats and rabbits, including the pregnancy maintaining effect of the hormone in ovariectomised rats; complete inhibition was observed at 3–10 mg/kg/day in rats and at 20 mg/kg/day in rabbits. Inhibition of endogenous progesterone activity was evident in numerous studies in which mifepristone was administered at various reproductive stages. Findings included disruption of the oestrus cycle (shown in rats and monkeys), reduction of ovulation (mice, rats and rabbits), inhibition of implantation (mice, rats, guinea pigs and monkeys), and induction of premature labour (mice and rats) or cervical dilation (monkeys). Abortifacient activity was demonstrated in mice (indicative doses, ≥6 mg/kg PO), rats (≥2 mg/kg PO), guinea pigs (≥3 mg/day SC), rabbits (≥0.25 mg/kg/day SC), dogs (5 mg/kg/day PO) and cynomolgus monkeys (≥0.5 mg/kg/day PO). The abortifacient activity of mifepristone in guinea pigs was shown to be enhanced by the administration of a prostaglandin E₂ analogue (sulprostone) on the following day.

Secondary pharmacodynamic studies revealed significant antiglucocorticoid activity, some anti-androgenic activity, very weak oestrogenic activity and no mineralocorticoid activity for mifepristone. In radioligand binding assays, mifepristone's affinity for the human

glucocorticoid receptor was comparable to that for the progesterone receptor. Antagonism of dexamethasone-induced receptor activation was demonstrated with mifepristone *in vitro* at nanomolar concentrations in cell-based experiments and *in vivo* effects of dexamethasone were fully inhibited by mifepristone at 10 or 25 mg/kg PO in rats. Mifepristone's affinity for the androgen receptor (rat prostate) appears to be around 5 times lower than for the human progesterone receptor. Mifepristone (10–100 mg/kg/day PO) was shown to dose dependently inhibit the effect of exogenously administered testosterone in castrated male rats. Uterotrophic activity by mifepristone (assessed in immature mice, rats and rabbits) was at least 10000-times weaker than oestradiol.

The principal metabolites of mifepristone, monodemethylated, didemethylated and hydroxylated derivatives, retain significant anti-progesterone and anti-glucocorticoid activity.

Safety pharmacology studies covered the central nervous system (CNS), autonomic, cardiovascular, respiratory, gastrointestinal, renal, endocrine and haematological systems, with analgesic/anti-inflammatory activity also assessed. Animals were given mifepristone at doses up to 10 or 100 mg/kg. No effects considered to be of clinical importance were identified. Electrocardiography in the 6 month repeat-dose toxicity study in monkeys revealed no treatment-related effects.

Pharmacokinetics

Mifepristone was rapidly absorbed following oral administration in rats and cynomolgus monkeys, with peak plasma concentrations reached at 15 min post dose. Rapid absorption was also evident in women (T_{max} , 45 min at the clinical dose). Rats showed a moderate pre systemic effect, and monkeys a strong pre-systemic effect, associated with lower absolute oral bioavailability compared to humans (39%, 15% and 61% in the respective species). In rabbits, the pre systemic effect was so great that no unchanged mifepristone was detectable following oral administration. The laboratory animal species showed much greater clearance of mifepristone compared with humans (3 L/h/kg in rats and 1.5 L/h/kg in monkeys compared to 0.04 L/h/kg in humans) and significantly shorter plasma half lives (approximately 1 h in rats, 15 h in monkeys and 38 h in women). The volume of distribution was very much lower in women (10% of body weight) than in rats and monkeys (135% and 200% of body weight). Serum protein binding by mifepristone was high in rats, monkeys and humans (97–99%). Saturable high affinity binding to human α_1 -acid glycoprotein, but not animal forms of the protein, was found for mifepristone; this may underlie the differences in clearance and half-life evident in the laboratory animal species compared to humans.

Rapid and extensive extravascular distribution of radioactivity was observed in rats following PO administration of 3H -mifepristone. Outside of the gastrointestinal (GI) tract, the liver displayed the highest levels of radioactivity. Penetration of the blood-brain barrier was modest. Metabolism of mifepristone principally involved sequential demethylation of the 11 β -dimethyl-aminophenyl group and hydroxylation of the 17 α -propynyl group. Formation of metabolites was rapid, and CYP3A4 was identified as the chief mediator. The major plasma metabolites in humans, monodemethylated mifepristone (RU 42633), didemethylated mifepristone (RU 42848) and the hydroxylated alcohol metabolite (RU 42698), were all also identified as major circulating metabolites in rats, dogs and cynomolgus monkeys. Excretion was principally by the faecal route in all species investigated (rats, monkeys and humans), with urine accounting for 3–9% of the dose.

Comparisons of the pharmacokinetic profiles in the laboratory animal species used in the pivotal repeat-dose toxicity studies (rats and cynomolgus monkeys) indicate that sufficient similarities exist to allow them to serve as appropriate models for the assessment of mifepristone toxicity in humans. High mg/kg dose levels and repeat daily

administration in the toxicity studies (compared to single dosing in the clinic) and the metabolites' retention of significant pharmacological activity compensates for the more rapid clearance of the drug in animals compared with humans.

Pharmacokinetic drug interactions

Mifepristone was found to act as a mechanism-based (irreversible) inhibitor of CYP3A4 in experiments with recombinant human enzyme. Based on the kinetic parameters for inhibition (K_i , 4.7 μM ; k_{inact} , 0.089 min^{-1} ; [6 β -hydroxylation of testosterone]) and the peak level of unbound circulating drug in patients, the model of Obach *et al.* (2007)⁵ suggests likely clinically significant inhibition *in vivo*. CYP1A, 2B1 and 2D6 were also shown to be sensitive to inhibition by mifepristone, but significantly less so compared with CYP3A4, and the mode of inhibition was reversible/competitive. Given the major role for CYP3A4 in the metabolism of mifepristone, inducers and inhibitors of this enzyme may alter mifepristone exposure. Furthermore, inhibition of CYP3A4 by mifepristone may affect the kinetics of other drugs that are CYP3A4 substrates.

Toxicology

Acute toxicity

Single dose toxicity studies were conducted in mice, rats and dogs by the PO route and additionally by the intraperitoneal (IP) route in the rodent species. The range of species, routes tested and the duration of the observation period (≥ 14 days) were in accordance with the relevant TGA adopted EU guideline⁶. At 1000 mg/kg PO, mifepristone produced no deaths in mice or dogs, and mortality in 1/20 rats (a male; no deaths in 10 females). This dose in animals is ~ 23 –150-times greater than the clinical dose on a body surface area basis. Abdominal distention, arched back and ambulatory difficulties were observed at this dose in rodents and there was moderate diarrhoea and vomiting in dogs. Overall, the data indicate a low order of acute toxicity for the drug.

Repeat-dose toxicity

Studies of 30 days and 6 months duration were each conducted in rats and cynomolgus monkeys. These involved once daily administration by the clinical route (PO), with animals of both sexes used. The duration of the pivotal studies, the species used and group sizes were consistent with TGA adopted EU guidelines⁷. Three published studies on more specialised aspects of the drug's repeat-dose toxicity (conducted in rats for up to 3 or 4 weeks) were also provided.

Relative exposure

Toxicokinetic data were not obtained in the repeat dose studies nor were AUC values determined in general pharmacokinetic studies in the two species. Exposure ratios have therefore been estimated based on body surface area adjusted doses, as tabulated below. Note that in addition to relative exposure, the assessment of human relevance of the findings in the repeat dose toxicity studies requires consideration of the duration of

⁵ Obach R.S., Walsky R.L. and Venkatakrishnan K. (2007) Mechanism-based inactivation of human cytochrome P450 enzymes and the prediction of drug-drug interactions. *Drug Metab. Dispos.* **35**:246–255.

⁶ Single dose toxicity. 3BS1a. <http://www.tga.gov.au/pdf/euguide/vol3bs1aen.pdf>

⁷ Guideline on repeated dose toxicity. CPMP/SWP/1042/99 Rev 1.

<http://www.tga.gov.au/pdf/euguide/swp104209enrev1.pdf> and

ICH Topic M 3 (R2) Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals. Note for Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals. CPMP/ICH/286/95. <http://www.tga.gov.au/pdf/euguide/ich028695enfinal.pdf>

treatment/pattern of use (that is, subchronic or chronic dosing in animals compared to single clinical administration).

Table 2. Relative exposures

Study; treatment duration		Dose; PO		Exposure ratio
		(mg/kg/day)	(mg/m ² /day)	
Rat (SD)	30 days	8	48	0.4
		40	240	1.8
		200	1200	9
	6 months	5	30	0.2
		25	150	1.1
		125	750	6
Monkey (Cynomolgus)	30 days	4	48	0.4
		20	240	1.8
		100	1200	9
	6 months	5	60	0.5
		15	180	1.4
		45	540	4
Human (women)	single dose	[200 mg]	132	–

Conversion factors for mg/kg to mg/m² doses used for rats, monkeys and humans (50 kg) are 6, 12 and 33, respectively.

Major findings

Effects on reproductive tissues were the most prominent finding. In female rats such effects comprised increased mammary gland secretory activity, blockade of oestrus and ovarian follicular cysts in the 1 month study (at all doses), and inhibition of oestrus cyclicity, decreased number of corpora lutea, increased ovarian cysts, reduction in endometrial stroma and dilatation of endometrial glands, alterations in the epithelial lining of the cervix/vagina, and distension of mammary acini and ducts in the 6 month study (at all dose levels for the most part). Female monkeys displayed changes in the ovaries (dilated follicles and absent corpora lutea), uterus (endometrial thinning, focal mucosal hyperplasia, squamous metaplasia and inflammatory cell infiltration), cervix (mucosal hyperplasia, squamous metaplasia and inflammatory cell infiltration), vagina (moderate keratinisation), fallopian tubes (dilated lumen) and mammary glands (increased development) at all dose levels or from the mid-dose level with treatment for 6 months⁸. In contrast, no histological changes in reproductive tissues were reported for the 1 month monkey study, despite the higher maximum dose level employed. In males, treatment with mifepristone inhibited spermatogenesis in both species (6 month studies only); effects on the prostate and seminal vesicles (atrophy of the epithelium or decreased colloid) were additionally observed in rats. A specialised study in rats established the reversibility of the histological changes in female reproductive tissues.

Other tissues showing microscopic changes were the liver, thyroid, adrenals, kidney and pituitary. In rats, hepatic perilobular fatty degeneration was observed in animals treated with mifepristone at 200 mg/kg/day PO for 1 month (No Observable Effect Level (NOEL) 125 mg/kg/day PO; exposure ratio, 6), and dose related centrilobular enlargement was

⁸ Uterine focal mucosal hyperplasia, squamous metaplasia and inflammatory cell infiltration, and cervical squamous metaplasia and inflammatory cell infiltration in monkeys were not dose-related in incidence however.

seen at ≥ 5 mg/kg/day PO in the 6 month study. In monkeys, no hepatic changes were observed with treatment at up to 100 mg/kg/day PO for 1 month (exposure ratio, 9), while increased lipofuscin (not dose related) was seen at ≥ 5 mg/kg/day PO in the 6 month study. The liver changes observed in the pivotal studies are not considered to be indicative of hepatic damage but rather to reflect altered metabolism.

Thyroid hyperactivity was observed in the 1 month rat study, and increased height of the follicular epithelium was seen at 125 mg/kg/day PO in the 6 month rat study; treatment was also associated with increased thyroid weight in the species. Thyroid findings in monkeys were confined to increased pigmentation (brown; most likely lipofuscin) within the follicular epithelium at 45 mg/kg/day PO for 6 months. Adrenal changes comprised haemosiderosis and increased cortical width in rats (at ≥ 5 mg/kg/day PO in the 6 month study), and increased width and eosinophilia of cells of the zona fasciculata and/or zona reticularis in monkeys (at ≥ 20 mg/kg/day PO in the 1 month study and ≥ 15 mg/kg/day PO in the 6 month study); increased thyroid weight was also observed (6 month studies in both species). No adrenal changes were seen in rats treated with mifepristone at up to 200 mg/kg/day PO in the 1 month study (exposure ratio, 9).

Foci of basophilic/dilated tubules containing colloid were increased at ≥ 5 mg/kg/day PO and interstitial fibrosis was observed at ≥ 25 mg/kg/day PO in the kidneys of rats in the 6 month study. Monkeys treated at ≥ 5 mg/kg/day PO in the 6 month study had increased renal cortical scarring, cortical cysts and subcapsular foci of fibrosis. Treatment produced no renal lesions in either species in the 1 month studies (exposure ratios, ≤ 9).

Diffuse hyperplasia of the pituitary pars anterior was observed in female rats at all dose levels (≥ 5 mg/kg/day PO) in the 6 month study and hypertrophy of the pituitary pars distalis was seen in female rats treated at ≥ 20 mg/kg/day PO for 2 or 4 weeks in a specialised study; pituitary weight was increased. There were, however, no pituitary changes noted in monkeys (exposure ratios, $\leq 4-9$). Pituitary enlargement in rats treated with mifepristone was shown to reflect enhancement of the action of oestrogen.

Various changes in clinical chemistry, urinalysis and haematology were also observed in the repeat dose studies. Findings in female animals in the pivotal rat study comprised increases in serum proteins, cholesterol and plasma calcium and decreases in blood glucose, plasma sodium and serum adrenocorticotrophic hormone (ACTH); increases in urinary volume (and water intake), protein, specific gravity and acidity; and decreases in red blood cell indices, increased platelet counts and decreased clotting time. In the pivotal monkey study, serum ACTH, cortisol, luteinising hormone and (transiently) triglycerides were increased, and serum cholesterol, oestradiol and progesterone were decreased; urinary chloride, potassium and sodium excretion were reduced. No significant haematological changes were found in monkeys treated with mifepristone for 6 months (exposure ratio ≤ 4).

Genotoxicity

The potential genotoxicity of mifepristone was examined in a comprehensive set of tests; all were appropriately validated. These comprised assays for mutagenicity in bacterial, yeast and mammalian cells; gene conversion in yeast; unscheduled deoxyribonucleic acid (DNA) synthesis in HeLa cells; and for clastogenicity in vitro (Chinese hamster ovary cells) and in vivo (mouse bone marrow micronucleus test). All tests returned negative results for mifepristone.

Carcinogenicity

No carcinogenicity studies with mifepristone were submitted. This is acceptable under the relevant TGA adopted EU guideline⁹ considering the pattern/duration of clinical use, the negative results for genotoxicity and the absence of findings in the repeat-dose toxicity studies that would give cause for concern.

Reproductive toxicity

Reproductive toxicity studies with mifepristone covered all stages (fertility and early embryonic development, embryofetal development, and pre-/postnatal development). *In vivo* primary pharmacology studies, discussed above, also provide information relevant to effects on reproductive function.

Placental transfer of mifepristone and/or its metabolites was demonstrated in rats, monkeys and humans. No data on excretion in milk were identified by the sponsor. Such excretion would be expected though based on the drug's structure.

Inhibition of oestrus cycling in rats that had been treated with mifepristone at 0.3 or 1 mg/kg/day PO for 3 weeks was reversed over the following 2–3 weeks. No subsequent effect on reproductive performance (mating, gestation, parturition, litter size, morphology of offspring, body weight change and survival) was found following pairing of the animals with untreated males 5 weeks after the completion of treatment. As well, no subsequent effects on mating performance or fertility were found in rats that had been given a single dose of mifepristone (≤ 100 mg/kg subcutaneously (SC)) at one day of age.

Mifepristone was shown to inhibit blastocyst development *in vitro* in experiments with mouse embryos and fertilised rabbit ova.

Effects on embryofetal development were examined in mice, rats, rabbits and monkeys. In mice and rats, doses of mifepristone that increased fetal loss did not affect body weight or increase abnormalities in surviving fetuses (assessable up to 1 mg/kg/day PO in the two species; complete litter loss at higher doses). In contrast in rabbits, treatment with mifepristone at 2 and 4 mg/kg/day PO (producing approximately one-third and two-thirds fetal loss, respectively) was associated with retardation of ossification of the cranium, sternum and paws in the surviving fetuses. With SC dosing in another rabbit study, malformations (failure of the cranium to close and haemorrhagic destruction of the upper part of the head and brain, no spinal column, no closure of the eyelids) were observed at 0.5 and 1 mg/day (~ 0.17 – 0.33 mg/kg/day). These were considered by the study author to be treatment related on the basis of historical data (30 untreated rabbits of the same strain showing no fetal anomalies in a previous study). Holoprosencephaly was observed in the fetus of a cynomolgus monkey treated with mifepristone at 2.5 mg/kg/day IM on gestational day (GD)15–18; this dose caused early abortions/resorptions in two other animals. The mother of the affected fetus displayed an intrauterine haemorrhage suggestive of impending abortion on GD18 and development of the gestational sac and placenta was subsequently disturbed. While the aetiology of the malformation was not definitively established, the study author did consider a relationship to treatment more likely than the finding representing a spontaneous occurrence. Considering the overall results of the embryofetal development studies, as well as the drug's mechanism of action (antagonism of progesterone), teratogenic potential of mifepristone is deemed plausible and most likely mediated by an effect on the uterus as a consequence of progesterone withdrawal rather than a direct effect of the drug on the fetus.

In a pre-/postnatal development study, slightly increased mortality at birth, delayed development of the righting reflex and slight inhibition of locomotor development were

⁹ The Need for Carcinogenicity Studies of Pharmaceuticals *. 3BS8a. <http://www.tga.gov.au/pdf/euguide/vol3bs8aen.pdf>

observed in the offspring of rats treated with mifepristone at 1 mg/kg/day PO during gestation and lactation. There were no significant effects on pup birth weight or other developmental parameters. Disruption of normal sexual development and reduced adrenal development were observed in male and female neonatal rats repeatedly given mifepristone (1 mg SC every second day for 2 weeks).

Pregnancy classification

No Pregnancy Category has been proposed, as appropriate for an agent indicated only for termination of pregnancy.

Phototoxicity

Mifepristone absorbs ultraviolet (UV) radiation at approximately 300 nm¹⁰ and some (but no particular) distribution of ³H-mifepristone-derived radioactivity to the eyes and skin was noted in rats. A GLP-compliant *in vitro* assay conducted in 3T3 mouse fibroblast cells revealed no phototoxicity for the drug.

Nonclinical Summary, Conclusions and Recommendation

- The nonclinical part of the submission was composed almost entirely of published literature. The search strategy was adequate.
- Mifepristone acts as a progesterone receptor antagonist, displaying nanomolar potency in receptor binding and cell based functional assays *in vitro*. Antagonism of various progesterone mediated activities was shown for mifepristone following administration by the clinical route (PO) in multiple animal species. Abortifacient activity was demonstrated in mice, rats, guinea pigs, rabbits, dogs and cynomolgus monkeys. Enhancement of the abortifacient activity of the drug with subsequent administration of a prostaglandin E₂ analogue was demonstrated in the guinea pig.
- Mifepristone additionally possesses significant antiglucocorticoid activity (comparable in potency to the drug's antiprogestogenic activity) and some antiandrogenic activity. The principal metabolites of mifepristone retain significant anti-progesterone and anti-glucocorticoid activity. Safety pharmacology studies identified no clinically relevant hazards.
- Pharmacokinetic studies indicated rapid absorption in rats, cynomolgus monkeys and humans. Clearance was greater and plasma half-lives were shorter for mifepristone in the laboratory animal species compared to humans. Tissue distribution of ³H-mifepristone-derived radioactivity in rats after PO administration was rapid and wide. Serum protein binding was high in rats, monkeys and humans (97–99%). Principal metabolites of mifepristone are formed by sequential demethylation and hydroxylation, chiefly mediated by CYP3A4. Excretion was mainly by the faecal route in all species examined. Mifepristone was found to act as a mechanism based inhibitor of CYP3A4 in experiments with recombinant human enzyme.
- Mifepristone displayed a low order of acute toxicity in laboratory animal species.
- Repeat-dose toxicity studies of up to 6 months duration were conducted in rats and cynomolgus monkeys. Effects on reproductive tissues were the most prominent finding. Other tissues displaying histological changes were the liver, thyroid, adrenals, kidney and pituitary.
- Mifepristone was examined for potential genotoxicity in assays for mutagenicity in bacterial, yeast and mammalian cells, for gene conversion in yeast, unscheduled DNA

10 Horwitz K.B. (1985) The antiprogestin RU38 486: receptor-mediated progestin versus antiprogestin actions screened in estrogen-insensitive T47Dco human breast cancer cells. *Endocrinology*. 116: 2236–2245.

synthesis in HeLa cells, for clastogenicity *in vitro* and *in vivo*, with universally negative results returned. Carcinogenicity studies have not been performed.

- Placental transfer of mifepristone and/or its metabolites was shown in rats, monkeys and humans. Excretion in milk is not known but suspected. Inhibition of oestrus cycling in rats by mifepristone was shown to be reversible. Embryofetal development studies revealed no treatment-related fetal abnormalities in the surviving fetuses of mice and rats that had been treated at sub abortive doses. Retardation of ossification and malformations were observed in rabbits however, and holoprosencephaly is reported in an exposed monkey fetus. Development was delayed in some respects in a pre-/postnatal study in rats.
- The nonclinical submission contained no major deficiencies.
- Primary pharmacology studies, showing potent anti-progesterone activity, and specifically abortifacient activity in all laboratory animal species tested (which was enhanced in guinea pigs with subsequent administration of a prostaglandin E₂ analogue), support the drug's use for the proposed indication.
- The major role of CYP3A4 in the metabolism of mifepristone and more particularly the drug's ability to act as a mechanism based inhibitor of the enzyme, give rise to concerns for potential interactions with co-administered drugs that are substrates/inducers/inhibitors of this CYP isozyme.
- Toxicological findings in rats and monkeys in repeat dose studies are consistent with the drug's known primary and secondary pharmacological activities (namely, anti-progesterone, anti-glucocorticoid and more limited anti-androgenic actions). They represent subchronic/chronic effects of hormonal disruption and are not considered predictive of similar changes in patients given a single dose.
- Embryofetal development studies suggest some teratogenic potential for the drug, likely to be secondary to effects on the uterus.
- Mifepristone is not genotoxic. The absence of carcinogenicity studies is acceptable under TGA adopted EU guidelines and the product is not considered to pose a particular carcinogenic risk to women.
- There were no nonclinical objections to the registration of Mifepristone Linepharma for the proposed indications.

IV. Clinical findings

Introduction

This was a hybrid application incorporating two bioequivalence studies and a literature-based presentation. The bioequivalence studies compared Mifepristone Linepharma with Mifegyne® and Mifeprex®, products which have been registered in Europe and the USA since 1988 and 2000 respectively for termination of pregnancy indications. Given the lengthy history of registration of mifepristone in many countries and estimates that at least several million women have been treated with mifepristone for abortion in Europe and the USA as well as in many other countries, there is a vast literature both pre registration and post marketing.

Literature references cited (as Studies 501-630) in this clinical evaluation are detailed in Tables 7-11 below and listed under *Appendix 1. Clinical References* at the end of this AusPAR.

Pharmacokinetics

Introduction

This application describes Mifepristone Linepharma as a new chemical entity. While this is so for Australia, it is presented as containing the same active substance as preparations of mifepristone registered in Europe (Mifegyne®) and the USA (Mifeprex®) and the application depends on the published literature relating to these internationally registered preparations.

Bioequivalence studies are pivotal to the application. The demonstration of bioequivalence is a necessary foundation on which to base the use of published literature associated with the reference medicinal products, which comprises a major part of the application.

Two studies were performed, one for each reference product. They were conducted in the same centre, were very similar in design and are presented together in this evaluation, although they were separately described and reported in the application. Individual patient data for both studies were presented in the application. Both studies were open label, randomised, two treatment, two period, two sequence, single oral dose, two-way crossover studies of study product (Mifepristone Linepharma) against reference product.

Study CAL052015-001 (Gujarat, India; Report date 13 November 2009) compared Mifepristone Linepharma (study product) with reference product Mifeprex® (the “Mifeprex® study”) and Study CAL052015-002 (Gujarat, India; Report date 16 February 2010) compared Mifepristone Linepharma with reference product Mifegyne® (the “Mifegyne® study”).

For both studies the primary objective was to compare the bioavailability and characterise the pharmacokinetic profile of Mifepristone Linepharma relative to the reference product in healthy adult women and to assess bioequivalence. The secondary objective was to monitor safety for all participants having at least one dose of study or reference product.

Study CAL052015-001 (Mifeprex® study) was stated to be planned “in accordance with the US guidance requirements ‘Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations’”. Study CAL052015-002 (Mifegyne® study) was stated to be “planned in accordance with the CPMP requirements ‘Note for guidance on the investigation of bioavailability and bioequivalence’ CPMP/EWP/QWP/1401/98 January 2002”. Both studies appear to have been conducted in a manner consistent with the TGA adopted EU guideline “Guideline on the investigation of bioequivalence”¹¹. While the TGA notes that “an application for registration of a generic product in Australia should generally include a bioequivalence study versus a leading brand obtained in Australia”, this is not possible in this instance in the absence of any such product registered in this country.

The two studies reported independent ethics approval and compliance with Indian and international guidelines for medical research, including the International Conference on Harmonization E6 ‘Guideline for Good Clinical Practice’ and the Declaration of Helsinki (Tokyo 2004). They appear to have been conducted consistent with the relevant TGA adopted EU Guideline¹² (annotated with TGA comments).

¹¹ EMEA/CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** *Guideline on the investigation of bioequivalence*
<http://www.tga.gov.au/pdf/euguide/ewp140198rev1.pdf>

¹² Note for guidance on good clinical practice CPMP/ICH/135/95 – Annotated with TGA comments
<http://www.tga.gov.au/pdf/euguide/ich13595.pdf>

Methods

Analytical methods

Mifepristone was assayed using liquid chromatography, tandem mass spectrometry methods. The method and its validation were presented in detail in the sponsor's submission. The methodology was not evaluated by the clinical evaluator.

Pharmacokinetic data analysis

Participants were healthy female volunteers aged 18-36 years, appropriate to the proposed indication and purpose of the studies, with other inclusion and exclusion criteria described and reasonable. Attention was paid to contraception and women needed to be not using hormonal contraception during and for at least one month prior to the study. Written informed consent was obtained, with provision for illiterate participants described; this included signature by an impartial witness.

In each study 56 participants were recruited and randomised, with 48 completing the study and having samples analysed for the Mifeprex® study and 50 completing with 49 analysed for the Mifegyne® study; for one completed participant samples were not analysed because of an ensuing pregnancy.

Withdrawals were described and considered appropriately, as were protocol violations, the majority of which related to the precise timing of samples.

The test doses were administered in standardised fasting conditions, with participants given identical meals while in the study centre after dosing. For each participant the two doses (of test and reference product) were given 28 days apart, both to ensure a sufficient washout period and in order that participants were at a similar phase of the menstrual cycle for each dose.

Eighteen venous samples were taken in each period, prior to and then at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 4, 8, 12, 24, 36, 48, 72, 120 and 168 h after each dose.

Sample handling and analytic methods were described in detail. The sample analysts were reported to be blind to whether samples were assessing test or reference product until after assay.

A revision was made to the protocol of the Mifeprex® study in February 2009, after sampling was complete but prior to assay, to clarify the handling of samples of women who withdrew prior to completion of the study and the identification of outliers.

In addition to mifepristone, in both studies the metabolites monodemethylated mifepristone and hydroxylated propynyl mifepristone were assayed. In the Mifeprex® study didemethylated mifepristone was also assayed.

In both studies safety monitoring was appropriate and results reported in detail. It is noted that in both studies a high proportion of included participants had screening haemoglobin levels below the reported normal range (41% for the Mifeprex® and 61% for the Mifegyne® study). All abnormal laboratory results were considered and annotated as not clinically significant (NCS) for continuing participants; in some cases follow up results were included but not those leading directly to withdrawal. Serious adverse events were one pregnancy in each study, resulting in one miscarriage and one elective abortion and a dog bite, all considered unrelated to the study.

Statistical analysis

Standard non-compartmental methods were used to derive the pharmacokinetic parameters. In the Mifeprex® study primary parameters were C_{max} and area under plasma concentration-time curve to last quantifiable concentration (AUC_{0-t}) and to infinity ($AUC_{0-\infty}$) and secondary parameters time to peak plasma concentration (T_{max}), terminal elimination rate constant (λ_z), residual area ($AUC_{\%Extrap_Obs}$) and terminal half-life

($t_{1/2}$). For the Mifegyne® study the same parameters were examined but $AUC_{0-\infty}$ was considered a secondary parameter.

The parameters were derived for each participant from their concentration-time curves and then population statistics calculated.

If the residual area was greater than 20% for any participant, her results would not contribute to population $AUC_{0-\infty}$ values.

Absorption

Bioavailability

After 20 mg mifepristone orally or intravenously, absolute bioavailability is reported as 69% (555).

Bioequivalence

Bioequivalence criteria were defined a priori in the protocol; the 90% confidence intervals for the geometric least squares mean for logarithm-transformed pharmacokinetic parameters C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ were to be within the acceptance range 80.00-125.00%.

For study CAL052015-001 (Mifeprex® study), population parameters for C_{max} and AUC_{0-t} were presented for the 48 participants. The $AUC_{0-\infty}$ value was based on 47 participants after excluding one value in accordance with the pre-defined approach to residual values. Table 3 presents the pharmacokinetic variables for this study and Table 4 presents the primary variables with the calculated parameters for determining bioequivalence.

Table 3: Study CAL052015-001 Pharmacokinetic parameters. Test product B is Mifepristone Linepharma and Reference product A is Mifeprex®.

Parameters	Test product B		Reference product A	
	Mean \pm SD	CV (%)	Mean \pm SD	CV (%)
Primary variables				
C_{max} (ng/ml)	2334.73 \pm 950.38	40.7	2485.83 \pm 788.29	31.7
AUC_{0-t} (ng*h/ml)	62180.94 \pm 26710.21	43.0	66166.52 \pm 27644.79	41.8
$AUC_{0-\infty}$ (ng*h/ml)	66466.49 \pm 29891.66	45.0	70966.62 \pm 31292.71	44.1
Secondary variables				
t_{max} (h)*	0.75 (0.50 – 24.00)	226.9	0.88 (0.50 – 8.00)	111.1
$t_{1/2}$ (h)	36.53 \pm 11.25	30.8	35.88 \pm 10.63	29.6
λ_z (1/h)	0.02 \pm 0.01	28.1	0.02 \pm 0.01	26.4
$AUC_{-}\%$ Extrapol_obs (%)	6.32 \pm 3.36	53.3	6.66 \pm 3.86	58.0

* the median (min-max) value is presented

Table 4. Study CAL052015-001 Bioequivalence values. Test product B is Mifepristone Linepharma and Reference product A is Mifeprex®.

Parameter	Geometric Mean Arithmetic mean (CV %)		Ratio of ln-transformed geometric least squares mean (%) (90% confidence interval)	Power (%)
	Test product B	Reference Product A		
C_{max} (ng/ml)	2122.75 2334.73 (40.7)	2359.31 2485.83 (31.7)	90.1 (83.00 – 97.78)	99.7
AUC_{0-t} (ng*h/ml)	56709.20 62180.94 (43.0)	61059.80 66166.52 (41.8)	93.3 (85.67 – 101.70)	99.5
$AUC_{0-\infty}$ (ng*h/ml)	60279.91 66466.49 (45.0)	65137.66 70966.62 (44.1)	92.9 (84.73 – 101.78)	99.0

Bioequivalence criteria as set in the protocol and consistent with the TGA adopted EU guideline¹¹ are met by these findings, which support the conclusion that Mifepristone Linepharma can be regarded as therapeutically equivalent to Mifeprex®.

For Study CAL052015-002 (Mifegyne® study), both “per protocol” (PP, n=49) and “modified per protocol” (n=48) results were presented, the latter excluding one statistical outlier, who had a very low C_{max} for the reference product (Mifegyne®). No reason was found for this low value. While the exclusion seems reasonable on the face of it, it is outside the TGA adopted Guideline¹¹ which restricts exclusions on a statistical basis to: “A subject with lack of any measurable concentrations or only very low plasma concentrations for reference medicinal product. A subject is considered to have very low plasma concentrations if its AUC is less than 5% of reference medicinal product geometric mean AUC (which should be calculated without inclusion of data from the outlying subject). The exclusion of data due to this reason will only be accepted in exceptional cases and may question the validity of the trial.”

Table 5 presents the pharmacokinetic variables for this study and Table 6 presents the primary variables with the calculated parameters for determining bioequivalence, for both PP and modified PP populations.

Table 5. Study CAL052015-002 Pharmacokinetic parameters. Test product B is Mifepristone Linepharma and Reference product A is Mifegyne®.

Parameters	Test product B		Reference product A	
	Mean ± SD	CV (%)	Mean ± SD	CV (%)
Primary variables				
C_{max} (ng/ml)	2685.64 ± 918.94	34.2	2417.02 ± 923.55	38.2
AUC_{0-t} (ng*h/ml)	72724.64 ± 30233.70	41.6	66124.57 ± 28313.31	42.8
Secondary variables				
$AUC_{0-\infty}$ (ng*h/ml)	78662.12 ± 36006.12	45.8	70238.20 ± 32593.42	46.4
t_{max} (h)*	0.75 (0.50 – 2.00)	42.8	0.75 (0.50 – 8.00)	91.7
$t_{1/2}$ (h)	38.36 ± 12.94	33.7	35.74 ± 11.31	31.6
λ_z (1/h)	0.02 ± 0.01	33.6	0.02 ± 0.01	31.2
AUC %Extrap obs (%)	6.06 ± 4.63	76.5	5.07 ± 3.59	70.8

* the median (min-max) value is presented

Table 6. Study CAL052015-002 Bioequivalence values. Test product B is Mifepristone Linepharma and Reference product A is Mifegyne®.

Parameter	Geometric Mean Arithmetic mean (CV%)		Ratio of ln-transformed geometric least squares mean (%) (90% confidence interval)	Power (%)
	Test product B	Reference Product A		
PP population				
C _{max} (ng/ml)	2542.02 2685.64 (34.2)	2225.37 2417.02 (38.2)	114.4 (103.33 – 126.66)	97.4
AUC _{0-t} (ng*h/ml)	66631.01 72724.64 (41.6)	60249.04 66124.57 (42.8)	110.6 (102.57 – 119.34)	99.9
AUC _{0-∞} (ng*h/ml)	71016.54 78662.76 (45.8)	63217.61 70238.20 (46.4)	112.0 (103.44 – 121.26)	99.8
Modified PP population				
C _{max} (ng/ml)	2521.98 2664.15 (34.4)	2288.66 2455.31 (36.4)	110.4 (101.39 – 120.14)	99.6
AUC _{0-t} (ng*h/ml)	65987.62 72028.15 (41.9)	60857.62 66727.35 (42.4)	108.4 (101.14 – 116.23)	100.0
AUC _{0-∞} (ng*h/ml)	70340.26 77959.59 (46.2)	63887.63 70913.15 (46.0)	109.7 (101.95 – 118.07)	99.9

The case for exclusion of a single value and presentation of a modified Per Protocol (PP) population analysis could be argued despite this being outside the guideline cited; if this were accepted, bioequivalence would be demonstrated according to the protocol and guidelines. The inclusion of this value (PP analysis) results in an upper limit of 90% CI of the relevant peak concentration bioequivalence ratio of 126.66%, which is marginally outside the predefined limit of 125%. The dose of Mifepristone Linepharma proposed in this application and tested in these bioequivalence studies is 200 mg. The dose of mifepristone used in many early studies and registered in several jurisdictions was 600 mg; evolving evidence has demonstrated 200 mg to be adequate, without evidence of harm related to using the higher dose. A marginally high upper limit of the 90% CI of the bioequivalence ratio for peak concentration was considered by this evaluator to be of no clinical relevance. See also the dosage considerations under *Efficacy* below.

The analyses of the metabolites monodemethylated mifepristone and hydroxylated propynyl mifepristone in both studies and of didemethylated mifepristone in the Mifeprex® study were not necessary to establish bioequivalence. They met the bioequivalence criteria for C_{max} and AUC_{0-t} for all metabolites in both studies and for AUC_{0-∞} for all but hydroxylated propynyl mifepristone in the Mifegyne® study, where the 90% CI were 106.28-129.72. These analyses present further support for a conclusion that Mifepristone Linepharma 200 mg tablets can be regarded as therapeutically equivalent to equivalent dose tablets of Mifeprex® and Mifegyne®.

In summary, bioequivalence criteria as set in the protocol and consistent with the TGA adopted EU Guideline¹¹ are met by these findings, with the marginal exception of the upper CI limit for peak concentration ratio. It is nevertheless reasonable to conclude that Mifepristone Linepharma can be regarded as therapeutically equivalent to Mifegyne®.

Influence of food

No studies reported.

Distribution

The volume of distribution is reported to be 8 L after intravenous administration of 280 mg mifepristone; 98% of mifepristone is albumin bound up to concentrations of 0.8 mg/l, principally to alpha-1-acid glycoprotein (AAG). The volume of distribution and plasma clearance are inversely proportional to the plasma concentration of AAG (555).

Elimination***Excretion***

Some 90% of a 600 mg radiolabelled dose of mifepristone was excreted in faeces and 10% in urine, with total plasma clearance estimated at 3 L/hour. Elimination half-life is reported as 18 h (624,625: EU and US product information) or 24-54 h (555), with terminal half-life up to 90 h (624).

Metabolism

The primary metabolic pathway is by N-methylation and terminal hydroxylation of the 17-propynyl chain in the liver. The principal enzyme has been identified as CYP3A4 (556).

Interconversion

Not applicable.

Pharmacokinetics of metabolites

Bioequivalence data were presented in the study reports and briefly considered above. It is unknown whether metabolites contribute to the pharmacological effects of mifepristone (555).

Consequences of possible genetic polymorphism

No information is provided.

Dose proportionality and time dependency***Dose proportionality***

Reference 555 reports little difference in peak concentrations over a range of doses from 100-800 mg and suggests this to be due to saturation of alpha-1-antiglobulin. This is consistent with the observations from clinical research that 200 mg doses are as effective as 600 mg.

Time dependency

Only single dose administration is proposed.

Intra- and inter-individual variability

The coefficients of variation for the population values of C_{max} were around 30-40%.

Pharmacokinetics in target population

The bioequivalence studies were undertaken in healthy volunteer women of reproductive age, which is the target group for the proposed indication. The majority of women in the age group needing to consider abortion are young and well.

Special populations***Children***

Only women who have reached reproductive maturity will need to consider using mifepristone for the proposed indications; this may include adolescents, but not younger children and there are unlikely to be special pharmacokinetic considerations in this group.

Elderly

Not applicable.

Gender

As the drug is to be used for termination of pregnancy, only women will consider using it.

Weight

No information is provided about variations in weight.

Race

No specific information is provided about race but clinical studies have been conducted in many countries and both studies and treatment have involved diverse women around the world. There is no basis to anticipate any particular racial differences.

Impaired renal function

No specific studies are reported, but as mifepristone is largely metabolised in the liver and excreted in the faeces (10% in urine), it is unlikely that renal impairment would be of major importance. Nevertheless, caution is recommended in the presence of renal failure in the proposed PI.

Impaired hepatic function

No specific studies are reported but as mifepristone is largely metabolised in the liver and excreted in the faeces, impaired hepatic function is likely to have a bearing on its elimination. The proposed PI recommends caution with mifepristone in the presence of hepatic failure. This might be better expressed as hepatic impairment.

Evaluator's overall comments on pharmacokinetics in special populations

Given the proposed use of mifepristone in women of reproductive age, the studies undertaken and reported are appropriate. It is reasonable that groups with particular illnesses have not been targeted but it does mean that there is a lack of specific information about the safety and efficacy of mifepristone in the presence of comorbidities. The cautions in the proposed PI are appropriate and sufficient except that caution should be advised in the presence of hepatic impairment rather than failure.

Interactions***In vitro pharmacokinetic interactions***

No studies have been undertaken but CYP3A4 has been identified as the principal enzyme catalysing mifepristone in the liver (556).

In vivo pharmacokinetic interactions

No studies have been undertaken but the role of CYP3A4 suggests that ketoconazole, itraconazole, erythromycin and grapefruit juice may inhibit metabolism and increase mifepristone levels. Similarly rifampicin, dexamethasone and various anticonvulsants (the PI adds St John's Wort to this listing) may induce mifepristone metabolism and lower levels (541). Reference 541 also adds a caution, reflected in the PI, that serum levels of CYP3A4 substrates may be increased, which may be important for agents with a narrow therapeutic range such as some anaesthetic agents.

Evaluator's overall comments on pharmacokinetic interactions

Given the proposed indications for use of mifepristone and the extensive clinical experience to date, it is reasonable that no specific studies have been undertaken. The cautions in the proposed PI are appropriate.

Exposure relevant for safety evaluation

A single dose of 200 mg mifepristone is proposed for the indications which are the subject of this application; there is a vast literature involving clinical experience with

administration of 200 mg and 600 mg doses. There is a smaller literature involving repeated doses for other indications, which are also considered in the safety evaluation in this application.

Evaluator's overall conclusions on pharmacokinetics

In the evaluator's opinion the two studies were appropriately designed and conducted and adequately established bioequivalence between Mifepristone Linepharma and Mifeprex® and Mifegyne®, whether or not the "statistical outlier" value is excluded in calculating C_{max} for Study CAL052015-002.

The mean C_{max} values for all three drugs were in the range 2335-2686 ng/ml (2.3-2.7mg/L), occurring at 0.75-0.88 h, with a half-life of 35.7-38.4 h. These values are consistent with those reported in the literature. For Linepharma's mifepristone the values for C_{max} were 2.3 and 2.7mg/L in the two studies, with peak concentration 0.75 h in both studies and half-life 36.5 and 38.4 h. For Mifeprex® the results were 2.5mg/L, 0.88 and 35.9 h and for Mifegyne® 2.4mg/L, 0.75 and 35.7 h, respectively.

Mifepristone is rapidly absorbed and is metabolised in the liver with largely faecal excretion.

The proposed PI presents a reasonable summary of the pharmacokinetic properties of mifepristone. The higher of the values of C_{max} and half-life from the two bioequivalence studies are used in the product information rather than a mean or range. While some of the parameters are sourced from detailed review studies, the elimination and terminal half-lives of 18 and 90 h, respectively, are sourced from the European and American product information documents.

The sponsor's Clinical Overview presented a reasonable summary of the known clinical pharmacology and the development of Linepharma's mifepristone. It concluded that Linepharma's mifepristone can be regarded as therapeutically equivalent to Mifegyne® and Mifeprex® and that literature data generated during studies with either product can be extrapolated to Linepharma's mifepristone. These are reasonable conclusions.

Pharmacodynamics

Introduction

The material in this section is drawn from a review article (reference 555). It considers a range of laboratory and clinical studies and its conclusions are consistent with those which have been accepted by various regulatory authorities, as evidenced by approved product information (624, 625).

Mechanism of action

Mifepristone is a synthetic steroid with antiprogesterone effects, which competes with progesterone for receptor binding. It also has antigluco-corticoid and weak antiandrogenic activity.

Primary pharmacology

Mifepristone has been shown to antagonise endometrial and myometrial effects of progesterone in women at doses in excess of 1 mg/Kg. During pregnancy mifepristone increases decidual prostaglandin release, sensitizes the myometrium to the contraction-inducing activity of prostaglandins and induces cervical ripening (555).

Secondary pharmacology

Effects of administration to nonpregnant women depend on menstrual cycle phase and may include delaying the midcycle luteinizing hormone surge, inducing mid-luteal phase bleeding or early menstruation. Mifepristone has been demonstrated to be an effective emergency contraceptive and a variety of other gynaecological uses have been suggested and/or examined including treatment of fibroids and endometriosis (554, 555).

Antiglucocorticoid activity results in compensatory elevation of ACTH and cortisol in women with normal adrenal function. Mifepristone has been used in the treatment of meningioma, metastatic breast cancer and Cushing syndrome (555).

Relationship between plasma concentration and effect

A review presented (555) notes that in a study of 17 women having pregnancy termination prior to 56 days gestation, of whom 13 aborted successfully, no correlation was found between clinical efficacy and plasma concentrations of mifepristone or its metabolites, protein binding or plasma AAG.

Pharmacodynamic interactions with other medicinal products or substances

No studies have been reported.

Genetic differences in pharmacodynamic response

No studies reported.

Evaluator's overall conclusions on pharmacodynamics

The pharmacodynamics of mifepristone are well described in the literature and appropriately summarised in the application. In summary, mifepristone is a synthetic steroid with antiprogesterone effects, which competes with progesterone for receptor binding. When administered during pregnancy mifepristone increases decidual prostaglandin release, sensitizes the myometrium to the contraction-inducing activity of prostaglandins and induces cervical ripening. It also has antiglucocorticoid and weak antiandrogenic activity but these are not clinically relevant in women with normal adrenal function at the proposed dosages.

The evaluator could not find support for the statement in the PI that "glucocorticoid bioactivity may be depressed for several days following a single administration of 200 mg mifepristone for termination of pregnancy". Indeed, included in the sponsor's submission is a statement that "In subjects with normal adrenal function, the increase in ACTH produced by mifepristone compensates for its antiglucocorticoid activity and there have been no reports of acute adrenal insufficiency at dosages used to terminate early pregnancy." Other than that observation the statements in the PI concerning pharmacodynamics were considered appropriate.

Efficacy**Introduction**

The application and the evaluation base the assessment of efficacy entirely on literature reports. The vast majority of these reports are based on studies in Europe, where Mifegyne® is registered or the USA where Mifeprex® is registered. A small number report on studies conducted in Asian countries where other preparations may have been used.

Background

Any medical treatment must be preceded by proper assessment of the clinical problem and informed consideration of relevant treatment options, followed by informed consent for the chosen path. For a woman who has come to the difficult decision to have an abortion, when choice of method is available this is a separate and subsequent decision.

For a woman the choice between surgical and medical abortion involves balancing the pros and cons of surgery and anaesthesia against those of a treatment with a slightly lower efficacy, involving more pain and bleeding, which allows some women to feel more in control but is perceived as more unpleasant by others. There is good evidence that satisfaction with treatment is greater when women are able to have their preferred method.

In the United Kingdom (UK), where mifepristone has been registered for termination of pregnancy indications since 1991, routinely kept abortion statistics record the increase in proportions of abortions undertaken medically as compared to surgically. In Scotland, where active research into medical abortion was undertaken prior to registration, uptake was prompt and has increased steadily from 16% in 1992 to over 70% of abortions in 2010, regardless of gestation; in 2010 82% of all abortions under 9 weeks gestation were done medically¹³. In England and Wales the uptake was much slower until around 2000 when the proportion was 12%; by 2010 43% of all abortions were undertaken medically¹⁴.

As indicated in the application, mifepristone was first registered in France and China, then in many countries through Europe and a little later in the USA; it is registered in many other countries including New Zealand. The use of mifepristone in medical abortion regimens is standard practice when it is available, because of the well established efficacy of combination regimens of mifepristone and prostaglandins.

Many of the studies which established the place and dosage of mifepristone used different prostaglandins and dosage regimens from those currently recommended by respected authorities based on evolving evidence. The vast majority of recent research uses combined regimens of 200 mg doses of mifepristone with misoprostol, with the aim of refining misoprostol regimens, by focusing on aspects such as:

- interval between mifepristone and misoprostol
- route of administration of misoprostol, which may be oral, sublingual, buccal or vaginal
- variations and refinements of misoprostol dosage regimens
- variation of regimens for different gestations
- side effect profiles and satisfaction with different regimens.

The literature search strategy

The methodology of the literature search strategy for efficacy and safety was developed in consultation with the TGA.

It is reported that 435 English language articles were retrieved in the efficacy and safety search. Some 104 articles remained for efficacy and safety evaluation after excluding a large number *“for the following reasons:*

- *No relation with early pregnancy termination;*

13 Abortion Statistics Year ending 31st December 2010. NHS National Services Scotland. 2011. Available from: <http://www.isdscotland.org/Health-Topics/Sexual-Health/Abortions/> Accessed July 2011

14 Abortion statistics, England and Wales, 2009. Department of Health. 2010. Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsStatistics/DH_116039 Accessed July 2011

- *Not an original clinical trial (that is, review, commentary and lecture);*
- *No detailed data recorded about side-effects during mifepristone treatment;*
- *Study of other medications (that is, methotrexate, herbal medications), with no data about mifepristone alone;*
- *Unreliable data source (that is, fake data or other forms of fraudulent action, special in Chinese papers, a few authors published the same data in different journals)*
- *Impossibility to obtain a copy of the whole article"*

This seems a reasonable approach to this vast literature except for point 3. Studies which are informative on efficacy should not have been excluded from consideration solely on the basis of lack of detailed data on mifepristone side effects, assuming some safety information was included. There may have been none of these, but this is not clear.

For the evaluation of efficacy, the remaining 104 articles were classified as follows:

For first-trimester pregnancy termination (28 articles):

- *Prospective clinical trial assessing efficacy (information on pregnancy outcome) of mifepristone alone or in combination with a prostaglandin analogue*
- *Mifepristone dose 600 mg or 200 mg, alone, or in combination with either gemeprost vaginally or misoprostol at any dose, via oral (including sublingual and buccal) route.*
- *Administration of the prostaglandin analogue 24 to 48 h after mifepristone.*
- *This review excluded studies where there was no group receiving mifepristone alone or followed by the prostaglandin analogues at the dosage regimen defined above.*

For pregnancy termination beyond the first trimester (10 articles):

- *Prospective clinical trials assessing efficacy (information on pregnancy outcome) of mifepristone followed by a prostaglandin analogue*
- *Mifepristone dose 600 mg or 200 mg, followed by any prostaglandin (any dosage regimen) allowed in this indication.*

This strategy has yielded a manageable volume of data including sufficient good quality material to make a judgment about the place of mifepristone in combined regimens for pregnancy termination.

The exclusion of studies involving vaginal administration of misoprostol in the first trimester results in the omission of some studies reporting medical abortion in routine clinical practice. These outcomes are more important to the consideration of prostaglandin regimens, which are not the focus of this application, than of mifepristone itself. The point needs making that prostaglandin regimens have not been systematically examined in the application.

For the second trimester studies, it is unclear why at least one large case series reporting prospectively collected data appears to have been excluded, while others which are not necessarily clinical trials appear to have been included.

None of the studies has been identified in the application as pivotal.

Approach to efficacy evaluation

The evaluation separates the two indications which are the subject of the application and considers them under separate headings below.

In general, the literature reports included well women at least 18 years old and noted their requests for termination of pregnancy and informed consent. Ethical approval was reported for research studies. The vast majority of the studies were randomised

controlled trials conducted to evaluate various components of mifepristone/prostaglandin regimens such as dose of mifepristone, interval between mifepristone and prostaglandin, different prostaglandins and various routes and dosages of misoprostol. Some were pilot studies to examine a particular regimen, usually prospective cohorts and there is a small number of studies described as consecutive cohorts which report on prospectively collected data in routine care. Inclusion/exclusion criteria were described and participant flow presented for most studies including explanation of any exclusions from analysis.

The evaluator considered all the studies included in the submission which are informative for efficacy for the indications which are the subject of the application and have highlighted in the tables those included in the sponsor's efficacy evaluation. The evaluator omitted 4 papers which were considered in the sponsor's evaluation: two papers because they related to gestational bands outside the proposed indications, one paper because it was a study of bleeding rather than efficacy and another paper which appears to report a subset of another study. The evaluator included some additional (unhighlighted) papers in the tables; these mainly include mifepristone dosages or mifepristone/prostaglandin intervals outside the sponsor's proposed range or perhaps most commonly administration of misoprostol by the vaginal route. The evaluator included them as they were believed to be informative about the overall body of research and clinical questions being addressed in this area.

In each table except Table 10 the papers are listed in chronological order, to demonstrate the unfolding research agenda in this area.

The provenance of mifepristone in each study is indicated in the tables as follows:

- Mifegyne® (MG)
- Mifeprex® (MP)
- Post registration (PR): where the study was conducted after registration in a country where Mifegyne® or Mifeprex® is registered
- Abortion Rights Mobilization (ARM): a non-profit advocacy organization with FDA approval to manufacture mifepristone for research
- Roussel-Uclaf (RU)
- World Health Organization Geneva (WHO)
- Not specified (NS): where the provenance was not specified and the post registration category above did not apply.

Dose-response studies and main clinical studies

Indication 1: mifepristone for medical abortion up to 49 days gestation

Medical termination of a developing intra-uterine pregnancy, in sequential combination with a prostaglandin analogue up to 49 days of amenorrhoea (DA)

While the evaluator used the sponsor's abbreviation DA (for days of amenorrhoea), this was taken to mean the period of gestation. The duration of amenorrhoea is not always an accurate predictor of gestation, so it is appropriate to accept an accurate dating method such as ultrasound examination in determining clinical decisions based on gestation. Forty-nine days is equivalent to 7 weeks (and 0 days) gestation, or 21 days after the first missed period based on a normal 28 day menstrual cycle.

Endpoints for efficacy of first trimester pregnancy termination

The application and most of the included studies use the conventional primary endpoint of achieving abortion without surgical intervention, as avoiding surgery is a major reason for

choosing the method. The point at which surgical intervention is considered and the reasons for intervention vary enormously between studies.

Surgery would routinely be performed because of ongoing heavy vaginal bleeding and in most studies on a woman's request if she did not wish to wait any longer for cessation of bleeding or passage of a gestation sac.

Ultrasound examination may be performed routinely at variously timed follow up points such as 24 h, one, two or three weeks or not at all. It has become clear that ultrasound examination will frequently identify some intrauterine "debris" after medical abortion, which will usually pass spontaneously and does not itself mandate surgical evacuation of the uterus.

As clinicians become more experienced and familiar with medical abortion, they tend to become more conservative about ultrasound examination, which is then likely to be performed only if indicated by symptoms, including the possibility of ongoing pregnancy. They also become less likely to recommend uterine evacuation solely on the basis of an ultrasound diagnosed incompletely emptied uterus.

Clearly these varying clinical approaches will result in differing surgical intervention rates independent of the direct effects of the medications used. For this reason, the evaluator used "complete abortion" meaning abortion without surgical intervention as the summary endpoint, without distinguishing assessments and timepoints. In many studies this was judged clinically.

Variation of clinical practice was discussed in many studies; the following quotes are illustrative:

Reference 506 (WHO 1993):

"Doctors' anxiety and lack of experience were probably the reasons for the higher incidence of curettage for 'incomplete' abortion in (some centres) than in (others)."

Reference 528 (Winikoff 2008):

"The consideration of provider practice is particularly relevant because most of the mifepristone-misoprostol regimens tested in randomised trials are highly effective (greater than 90% overall efficacy). Moreover management disparities may help to explain inconsistencies among randomised controlled trials, especially those done in one or only a few sites. The effect of provider practices may be unavoidable, costly to measure, and difficult to interpret, but if trial results should guide real-world practice, there is benefit to a protocol that does not overregulate clinical management."

Variations were also described in the sponsor's submission:

"Efficacy rates for a given pregnancy age vary largely between investigational centers (520, 522, 527). This could be due to extrinsic factors such as different knowledge on the method (less trained investigators tend to conclude to a failure earlier than experienced investigators and to perform a surgical procedure, identified as a failure, more often); different environment (e.g. access to ultrasonography), or home or clinic follow-up (527) might also account for the observed efficacy rate variations."

In most studies at least some women and in some studies the majority of women having early medical abortion aborted at home, especially prior to 7 weeks gestation. Apart from a handful of very small studies there was always a loss to follow up, both in the studies and in routine care. Some studies reported considerable effort taken to contact non-attenders or obtain follow up information from their community practitioners; most non-attenders appear to have aborted and not wanted further follow up, being satisfied that the treatment has been effective. However a small proportion have sought further care elsewhere, some with complications, so effectiveness of treatment cannot be assumed in the absence of confirmation.

Some studies express the complete abortions as a proportion of all women entered, while others express them as a proportion of all analysed (participant number in brackets in the tables) that is those for whom outcomes are known. While the latter proportions are likely to be appropriate, the former are likely to be underestimates of the complete abortion rate. One study (590) did report that longer follow up, after two weeks, might reveal a slight increase in numbers requiring late surgical intervention, with a slight reduction in complete abortion rates, although this effect is likely to be small.

Regimens for early medical abortion.

Mifepristone alone

Reference 552 reports a 1986 study in which 100 women at less than 5 weeks gestation (35DA) were given doses of 400-800 mg mifepristone over 2-4 days and 85 of the women aborted (similar proportions over the three different dosage regimens). Although all women had vaginal bleeding within 4 days of starting mifepristone, 15 women had curettage performed at 13 days after the start of treatment because of non-response (absence of conceptus expulsion and elevated human chorionic gonadotropin (hCG) concentration on day 6), that is 15% failure rate.

Reference 561 (1990) also reports a small study in which maximal abortion rates of 80% were achieved with a single dose of 450 mg mifepristone.

Reference 554 is a 1997 review which cites 552 and two other reports from 1987 and 1992, concluding that maximal efficacy was achieved with single oral dosage of 600 mg up to 42 days gestation but that the complete abortion rates of 80% achieved were insufficient given 95% efficacy of suction curettage methods at the same gestation. Some of the same and some different studies were reviewed in reference 555, which came to the same conclusion regarding failure rates with mifepristone alone.

Reference 501 noted internal Roussel Uclaf data that 9% of woman had an ongoing pregnancy after 600 mg of mifepristone and 26% after 200 mg.

Many of the studies included in the application report rates of abortion within 48 h of mifepristone dosage, that is prior to planned prostaglandin administration, of around 2-3% in early pregnancy, confirming a low short term abortion rate.

These studies and reviews support a conclusion that mifepristone alone is not sufficiently effective to be used to induce abortion.

Alternatives to mifepristone: prostaglandin alone or after methotrexate

Reference 566 (Table 7) reports a 2002 randomised double-blind trial comparing 200 mg mifepristone with placebo, both followed by 800 µg misoprostol vaginally for early abortion, in 250 women at ≤56 days gestation. 114/119 (95.7%) aborted without surgery after mifepristone and misoprostol, compared with 110/125 (88.0%) after misoprostol alone ($p < 0.05$). This study noted that abortion rates of 88.0% could be clinically acceptable if alternative regimes were not available and also that abortion rates of 92-96% could be achieved with regimens using methotrexate in combination with misoprostol, although it might take 2-3 weeks for abortion to occur. No other direct comparisons of mifepristone with prostaglandin and prostaglandin alone in the first trimester are included in the application.

The reviews 554 (1997) and 555 (1993) express the early conviction that regimens of mifepristone in combination with prostaglandin would be optimal for early medication abortion.

Reference 572 (2003, not tabulated) reports the experience of an American private practice with concurrently offered mifepristone/misoprostol and methotrexate/misoprostol regimens. They found that despite the greater cost to women (US\$430 compared with \$350) "*patients quickly adapted their preference to the newer*

mifepristone/misoprostol regimen, which provides more rapid expulsion and a greater gestational age range for effective use."

Dose of mifepristone (Table 7)

The 600 mg dose of mifepristone is registered in France, UK, USA and many other countries.

Several large well conducted studies (506, 507, 509) have since demonstrated 200 mg mifepristone to be of equivalent efficacy to 600 mg doses when combined with a variety of regimens of vaginal gemeprost or oral misoprostol. Study 511 compared 50 mg and 200 mg doses of mifepristone followed by two gemeprost regimens and concluded that the 50 mg dose was significantly less effective than 200 mg in these regimens. Reference 562 suggested that 100 mg mifepristone might be adequate but that further studies are needed to resolve this question.

Studies 506, 507 and 511 refer to pharmacokinetic studies which demonstrate a non-linear dose-peak concentration relationship at doses above 100 mg, with linear response at doses in the 2-25mg range; this explains why there may be no advantage in increasing the dose above 100-200 mg.

These studies support the conclusion that 200 mg mifepristone is adequate in combination with prostaglandin to induce first trimester abortion. It can be seen from the tables that virtually all studies published from 2001 onwards report on 200 mg doses of mifepristone.

Table 7 summarises the studies which examined dose of mifepristone, including one which compared 200 mg mifepristone with placebo.

Table 7. Dose of mifepristone (highlighted studies included in sponsor's efficacy evaluation).

Reference number	Design	Gestation	Mifepristone dose and interval to PG (Source of mifepristone)	PG regimen miso= misoprostol gema= gemprost	Participants entered (analyzed)	Complete abortion (95% CI)	Continuing pregnancies
First author	No. of centres						
Year published	Location						
506	RCT	≤ 56DA	200mg +48h		393 (388)	93.8% (91.4-96.2%)	0.5% (0-1.2%)
WHO Task Force	11 centres		400mg +48h	1mg gema PV	393 (391)	94.1% (91.8-96.5%)	0.5% (0-1.2%)
1993	7 countries		600mg +48h (Roussel-Uclaf)		396 (389)	94.3% (92.0-96.7%)	0.3% (0-0.8%)
507	RCT	≤ 63DA	200mg +48h	600µg miso PO	110	93.6%	
McKinley	1 centre		600mg +48h (Mifegyne®)		110	93.6%	
1993	Scotland						
509	RCT	≤ 63DA	200mg +48h	400µg miso PO	792	89.3% (86.9-91.3%)	2.8% (1.8-4.2%)
WHO Task Force	17 centres		600mg +48h (Roussel-Uclaf)		797	88.1% (85.6-90.2%)	1.9% (1.9-4.4%)
2000	International						
511	RCT	≤ 56DA	50mg +48h	0.5mg gema	249	84.7%	4.4%
WHO Task Force	13 centres		50mg +48h	1mg gema	325	89.8%	2.2%
2001	International		200mg +48h	0.5mg gema	325	91.7%	0.6%
			200mg +48h	1mg gema	325	92.9%	0.6%
			50mg (pooled)	Both		87.6% (84.6-90.2%)	
			200mg (pooled) (Roussel-Uclaf)	Both		92.3% (90.0-94.2%)	
562	RCT	≤ 49DA	100mg +48h	400µg miso PO	40	85% (71-94%)	
Creinin	1 centre		(ARM)	800µg miso PO	40	100% (91-100%)	
2001	USA						
566	RCT	≤ 56DA	200mg +48h	800 µg miso PV, rpt daily up to 3	125 (119)	95.7%	
Jain	3 centres		placebo +48h (ARM)		125	88.0%	
2002	USA					p<0.05	

RCT: randomized controlled trial

ARM: Abortion Rights Mobilization

Interval between mifepristone and misoprostol (Table 8)

The conventional interval between mifepristone and prostaglandin was 36-48 h, based on the understanding that this time was required for the antiprogesterone effects to enhance the response to prostaglandins. Schaff in reference 504 presented a systematic review (of papers included in the application as 584, 502, 519, 563 and one other), concluding that the interval between mifepristone and misoprostol 800 µg vaginally could be reduced from 48 h to 24 h without loss of efficacy but that a one day interval was less effective when oral misoprostol was used. These and the additional studies (568, 596, 594, 503, 557 and 579) summarised in Table 8 support this conclusion but suggest that shorter intervals (6-8 h or immediate administration of misoprostol) may have acceptable efficacy at some gestations with some regimens, 800 µg vaginal misoprostol being the main one studied to date.

Table 8. Mifepristone prostaglandin interval (highlighted studies included in sponsor's evaluation).

Reference number First author Year published	Design No. of centres Location	Gestation	Mifepristone dose and interval to PG (Source of mifepristone)	Prostaglandin (PG) regimen miso= misoprostol geme= gemeprost	Participants entered (analyzed)	Complete abortion (95% CI)
584 Schaff 2000	RCT 16 centres USA	≤ 56DA	200mg + 1D 200mg + 2D 200mg + 3D (ARM)	800µg miso PV	745 (734) 778 (766) 772 (755)	98% (97-99%) 98% (97-99%) 96% (95-97%)
519 Schaff 2001	RCT 15 centres USA	≤63DA	200mg + 24h (Not specified)	400µg miso PO +400µg at 2h 800µg miso PV	548 596	*90% *97% X ² =23.95, p=0.001
502 Creinin 2001	RCT 1 centre USA	≤ 49DA	600mg + 6-8h 600mg + 48h (Not specified)	400µg miso PO repeated after 48h if needed 400µg miso PO	43 (42) 44 (44)	50% (35-65%) at 24h; 95% at 2 weeks 91% (82-99%) at 24h; 98% at 2 weeks
568 Pymar 2001	Pilot study 1 centre USA	≤ 49DA	200mg + 6-8h (Not specified)	800µg miso PV	40	98% (86-100%)
563 Creinin 2004	RCT Multicentre USA	≤ 63DA	200mg + 6-8h 200mg + 23-5h (Post registration)	800µg miso PV, rpt at 7D	540 (525) 540 (531)	95.8% (93.7-97.3%) 98.1% (96.6-99.1%)
596 Murthy 2005	Pilot study 1 centre USA	≤ 49DA	200mg + immed (Post registration)	800µg miso PV	40	90% (80-99%)
594 Li 2006	Prospective study 1 centre Taiwan	≤ 49DA	200mg + immed (Not specified)	800µg miso PV	90	97.8%
503 Guest 2007	RCT 1 centre Scotland	< 63DA	200mg + 6h 200mg + 36-48h (Post registration)	800µg miso PV 800µg miso PV	225 (210) 225 (215)	89% 96%; RR 0.92 (95%CI 0.84-0.98)
557 Creinin 2007	RCT 4 centres USA	≤ 63DA	200mg + immed 200mg + 24h (Post registration)	800µg miso PV, rpt at 7D	567 (554) 561 (546)	95.1% (93.0-96.8) 96.9% (95.1-98.2)
579 Lohr 2007	Pilot study 1 centre USA	≤ 49DA 50-56DA 57-63DA	200mg + immed (Post registration)	800µg miso BU	40 40 (39) 40	72.5% (56.1-85.4%) 69.2% (52.4-83%) 72.5% (56.1-85.4%)

RCT: randomized controlled trial

ARM: Abortion Rights Mobilization

Which prostaglandin?

Some of the earliest studies used sulprostone as the prostaglandin to follow mifepristone, but there were several case reports of serious cardiovascular complications including a fatal myocardial infarction (501). Other early studies demonstrated that gemeprost is a safe and effective option but very few studies using gemeprost have been reported in the last 10 years since it was established that misoprostol regimens produced equivalent outcomes. Misoprostol is preferred by most clinicians and researchers because unlike gemeprost it is stable at room temperature and can be administered by several different routes; it is also more cost effective. The gemeprost studies have not been separately tabulated in this evaluation.

Prostaglandin regimens

The application proposes the use up to 49DA of three oral dosages of misoprostol: 600µg,

800µg or 400µg repeated after 2 h, although the 600µg option is not included in the PI. Other routes of administration were not considered apparently because they have not been registered anywhere, although many of the included papers report on the use of sublingual, buccal and/or vaginal routes.

In this evaluation Table 9 lists in chronological order summary data for all the included studies reporting adequate outcome information for early medical abortion. Those considered in the sponsor's efficacy evaluation are highlighted. Most of them extend beyond the 49DA of the proposed indication, so Table 10 lists the data for those studies either limited to ≤49DA or including a subanalysis for this gestational group as well as those for which such outcomes could be derived by the evaluator. Table 10 is grouped by misoprostol regimen (dose and route).

Although many of the studies go beyond 49DA and many regimens were found to have lesser efficacy beyond 49 or 56DA, efficacy beyond 49DA was not evaluated, as it is outside the proposed indication. Although the literature search strategy excluded vaginal administration of misoprostol, many of the studies included at least one arm in which vaginal misoprostol was a comparator and the outcomes of these study arms have been included in the tabulations. Because of the repeated studies demonstrating equivalent efficacy of 600 mg and 200 mg mifepristone, the evaluator retained regimens using both doses in the tables.

Scanning the tables in chronological order, the reducing frequency of studies using 600 mg doses of mifepristone and prostaglandins other than misoprostol is apparent, as is the increasing use of non-oral routes of administration of misoprostol.

Table 9. Prostaglandin in regimens (highlighted studies included in sponsor's efficacy evaluation).

Reference number First author Year published	Design No. of centres Location	Gestation	Mifepristone dose and interval to PG (Source of mifepristone)	Prostaglandin (PG) regimen miso-misoprostol gemo-gemeprost	Participants entered (analyzed)	Complete abortion (% CI)
604 Hill 1989	Prospective study 1 centre UK	≤63DA	600mg + 48h (Not specified)	1mg gemo PV	100	95%
601 Peyron 1993	2 cohort studies 25 centres France 1 centre France	≤49DA	600mg + 2D (Post registration)	400µg miso PO 400µg miso PO + 200µg at 4h	505 (488) 390 (385)	96.9% (94.1-97.7%) 98.7% (96.8-99.5%)
517 Sang 1994	RCT 5 centres China	≤49DA	200mg + 2D Not specified	600µg miso PO Sulprostone arm not shown	150 (149)	94.6% (89.5-97.6%)
524 El-Refaey 1994	RCT 1 centre Scotland	≤56DA	200mg + 36-48h (Mifegyne®)	800µg miso PO 400µg miso PO + 400µg at 2h	75 75	95% 92%
515 Baird 1995	RCT 1 centre Scotland	≤63DA	200mg + 48h (Mifegyne®)	0.5mg gemo PV 600µg miso PO	400 (391) 400 (386)	96.7% (94.9-98.5) 94.6% (92.3-96.9)
578 El Refaey 1995	RCT 1 centre Scotland	≤63DA	600mg + 36-48h (Post registration)	800µg miso PO 800µg miso PV	135 (130) 135 (133)	87% (78% within 4 h) 95% (93% within 4h)
571 UK Multicentre Study Group (Urquhart) 1997	Prospective study 13 centres UK	≤63DA	600mg + 48h (Roussel Uclaf)	1mg gemo PV	1018 (957)	94.8% (93.4-96.2)
539 Spitz 1998	Prospective study 17 centres USA	≤49DA 50-56DA 57-63DA	600mg + 2D (Not specified)	400µg miso PO	859 (827) 722 (678) 540 (510)	*92% (90-94) *83% (80-86) *77% (74-81)
577 Schaff 1999	Prospective trial 7 centres USA	≤56DA	200mg + 48h (ARM)	800µg miso PV	933	97%
574 Guengant 1999	Prospective study 1 centre Guadeloupe	≤49DA	600mg + 48h (Post registration)	400µg miso PO + 200µg at 6-12h	92 (88)	95.40%
588 Schaff 2000	Prospective trial 16 centres USA	≤49DA 50-56DA 57-63DA	200mg + 48h (ARM)	800µg miso PV	578 251 308	97% 96% 94%
523 Bhattacharya 2000	RCT 10 centres India	≤63DA	200mg + 2D (WHO Geneva)	Meteneprost arm not shown 600µg miso PO	450 (440)	87.70%
513 Bartley 2001	RCT 1 centre Scotland	≤63DA	200mg + 48h (Mifegyne®)	0.5mg gemo PV 800µg miso PV	499 (453) 497 (457)	96.20% 98.70%
519 Schaff 2001	RCT 15 centres USA	≤63DA	200mg + 24h (Not specified)	400µg miso PO + 400µg at 2h 800µg miso PV	548 596	*90% *97% X ² =23.95, p=0.001
525 Elul 2001	Prospective trial 2 centres International	≤56DA	200mg (Not specified)	400µg miso PO	120 (112) centre 1 195 (191) centre 2	93% 91%
575 Knudsen 2001	Consecutive cohort 1 centre Denmark	≤56DA	600mg + 36-48h (Mifegyne®)	400µg miso PO	100	93%
597 Bhorge 2001	Prospective study 1 centre Norway	≤63DA	600mg + 48h (Post registration)	800µg miso PV	226 (219)	95%
518 Schaff 2002	RCT 14 centres USA	≤63DA	200mg + 2D (Post registration)	400µg miso PO 400µg miso PO + 400µg at 2h 800µg miso PV	228 (220) 279 (269) 538 (522)	84% 92% 96% p<0.001
600 Tang 2002	Pilot study 2 centres China	≤63DA	200mg + 48h (Mifegyne®)	800µg miso SL	100	94%
582 Tang 2003	RCT 1 centre Hong Kong	≤63DA	200mg + 48h (Mifegyne®)	800µg miso SL 800µg miso PV	112 112	98.2% (93-99%) 93.8% (88-97%)
522 WHO 2003	RCT 15 centres International	≤63DA	200mg + 2D (WHO Geneva)	800µg miso PO + 400µg PO BD 7D 800µg miso PV + 400µg PO BD 7D 800µg miso PV	740 741 738	92.3% (90.1-94.1) 94.7% (92.9-96.2) 93.5% (91.5-95.2)
526 Middleton 2005	RCT 2 centres USA	≤56DA	200mg + 1-2D (Post registration)	800µg miso BU 800µg miso PV	223 (216) 219 (213)	95% 93% NS
521 Shannon 2005	Prospective trial 5 centres USA	≤49DA	200mg + 2D (Post registration)	400µg miso PO	376 (354)	91.5% (88.2-94.0)
520 Shannon 2006	RCT 3 centres Canada	≤56DA	200mg + 24-48h (Mifeprex®)	400µg miso PO ± repeat 24h 600µg miso PO ± repeat 24h 800µg miso PV ± repeat 24h	319 319 318	94.7% (92.4-97.1) 93.4% (91.1-95.8) 94.3% (92.0-96.7)
516 Coyaji 2007	RCT 2 centres India	≤56DA	200mg + 48h (Not specified)	400µg miso PO 400µg miso PO repeated at +3h	150 (149) 150 (148)	86% 92% (NS) OR 1.81 (0.85-3.86)
528 Winikoff 2008	RCT 7 centres USA	≤63DA	200mg + 24-36h (Mifeprex®)	800µg miso BU 800µg miso PO	484 (421) 482 (426)	*96.2% (93.9-97.8) *91.3% (88.2-93.8)

RCT: randomized controlled trial

ARM: Abortion Rights Mobilization

* significantly different

Table 10. Gestation ≤ 49 DA

Reference number	Data type	Mifepristone dose and interval to PG (source of mifepristone)	Prostaglandin (PG) regimen miso = misoprostol gemo = gemeprost	Participants entered (analyzed)	Complete abortion (95% CI)
400µg misoprostol orally					
601	Study ≤ 49 DA	600mg + 2D (PR)	400µg miso PO	505 (488)	96.9% (94.1-97.7%)
601	Study ≤ 49 DA	600mg + 2D (PR)	400µg miso PO + 200µg at 4h	390 (385)	98.7% (96.8-99.5%)
539	Subanalysis	600mg + 2D (NS)	400µg miso PO	859 (827)	92% (90-94)
574	Study ≤ 49 DA	600mg + 48h (PR)	400µg miso PO + 200µg at 6-12h	92 (88)	95.40%
518	Subanalysis	200mg + 2D (PR)	400µg miso PO	(143)	*89%
502	Study ≤ 49 DA	600mg + 48h (NS)	400µg miso PO	44 (44)	^91% (82-99%) at 24h; 98% at 2 weeks
521	Study ≤ 49 DA	200mg + 2D (PR)	400µg miso PO	376 (354)	91.5% (88.2-94.0)
520	Calculated	200mg + 24-48h (MP)	400µg miso PO + repeat 24h	(268)	95.1%
600µg misoprostol orally					
507	Calculated	200mg + 48h (MG)	600µg miso PO	61	96.7%
507	Calculated	600mg + 48h (MG)	600µg miso PO	58	98.3%
517	Study ≤ 49 DA	200mg + 2D (NS)	600µg miso PO	150 (149)	94.6% (89.5-97.6%)
515	Calculated	200mg + 48h (MG)	600µg miso PO	(154)	96.1%
520	Calculated	200mg + 24-48h (MP)	600µg miso PO + repeat 24h	(258)	95.0%
800µg misoprostol orally divided dose					
519	Subanalysis	200mg + 24h (NS)	400µg miso PO + 400µg at 2h	348	#90% (86.7-93.3%)
518	Subanalysis	200mg + 2D (PR)	400µg miso PO + 400µg at 2h	(176)	*93%
524	Subanalysis	200mg + 36-48h (MG)	800µg miso PO 400µg miso PO + 400µg at 2h	65 (pooled)	95%
800µg misoprostol orally single dose					
522	Calculated	200mg + 2D (WHO)	800µg miso PO + 400µg PO BD 7D	236	93.6%
528	Calculated	200mg + 24-36h (MP)	800µg miso PO	(205)	96.1%
Other non-vaginal routes					
582	Calculated	200mg + 48h (MG)	800µg miso SL	29	100%
528	Calculated	200mg + 24-36h (MP)	800µg miso BU	(213)	97.2%
Vaginal misoprostol					
577	Calculated	200mg + 48h (ARM)	800µg miso PV	660	97%
588	Study ≤ 49 DA	200mg + 48h (ARM)	800µg miso PV	571	97%
519	Subanalysis	200mg + 24h (NS)	800µg miso PV	383	#97% (95.3-98.7%)
513	Calculated	200mg + 48h (MG)	800µg miso PV	(233)	99.6%
566	Subanalysis	200mg + 48h (ARM)	800µg miso PV, rpt daily up to 3 doses	(75)	96%
518	Subanalysis	200mg + 2D (PR)	800µg miso PV	(349)	*97%
582	Calculated	200mg + 48h (MG)	800µg miso PV	26	96.2%
522	Calculated	200mg + 2D (WHO)	800µg miso PV + 400µg PO BD 7D	240	94.6%
522	Calculated	200mg + 2D (WHO)	800µg miso PV	223	95.1%
520	Calculated	200mg + 24-48h (MP)	800µg miso PV + repeat 24h	(252)	95.2%
<24h interval mifepristone-misoprostol					
502	Study ≤ 49 DA	600mg + 6-8h (NS)	400µg miso PO repeated after 48h if needed	43 (42)	^50% (35-65%) at 24h; 95% at 2 weeks
568	Study ≤ 49 DA	200mg + 6-8h (NS)	800µg miso PV	40	98% (86-100%)
596	Study ≤ 49 DA	200mg + immed (PR)	800µg miso PV	40	90% (80-99%)
594	Study ≤ 49 DA	200mg + immed (NS)	800µg miso PV	90	97.8%
579	Subanalysis	200mg + immed (PR)	800µg miso BU	40	72.5% (56.1-85.4%)
Gemeprost regimens					
515	Calculated	200mg + 48h (MG)	0.5mg gemo PV	(170)	95.9%
571	Calculated	600mg + 48h (RU)	1mg gemo PV	(337)	95.8%
513	Calculated	200mg + 48h (MG)	0.5mg gemo PV	(252)	97.6%

Study ≤ 49 DA: only these gestations included
 Subanalysis: these results presented in reference
 Calculated: derived by evaluator from data presented

MG: Mifegyne®
 MP: Mifeprex®
 PR: post registration in country where MP or MG registered
 NS: not specified
 ARM: Abortion Rights Mobilization
 RU: Roussel-Uclaf
 WHO: World Health Organization

^, *, #: significantly different

Almost all regimens reported had complete abortion rates in excess of 90%. When populations ≤ 49 DA were examined, all regimens with an interval between mifepristone and misoprostol >24 h and a dose of misoprostol ≥ 600 µg (including 800 µg in divided doses 2 h apart) had complete abortion rates of at least 93%. For two of the “split dose” studies (400 µg twice 2 h apart) there were statistically higher complete abortion rates using 800 µg misoprostol vaginally.

The proposed doses of oral misoprostol are adequate for induction of abortion up to 49DA. Other routes of administration of misoprostol have not been systematically considered in this application or evaluation. While efficacy rates are similar, in clinical practice side effect profiles play a substantial role in decision-making (see below).

Doses of 0.5 or 1 mg gemeprost 48 h after 200 mg mifepristone are adequate for the induction of abortion up to 49DA, with complete abortion rates reported from 95.8-97.6% (see bottom panel of Table 10).

In general, the evolving evidence should be considered in choosing a prostaglandin regimen; see below.

Indication 2: mifepristone for medical abortion in the second trimester

Preparation for the action of prostaglandin analogues during the termination of pregnancy for medical reasons beyond the first trimester.

Prior to the development of mifepristone, a range of methods of second trimester termination included surgical methods such as hysterotomy or dilatation and evacuation and medical methods including extraamniotic and intraamniotic prostaglandins. More recently prostaglandins have been used vaginally, these now constituting the main alternative to surgery when second trimester termination is needed. Because surgical abortion in the second trimester requires particular surgical expertise and training, in many centres there is limited or even no availability of this option, which is increasingly the case with advancing gestation.

Endpoints for second trimester termination of pregnancy

The main endpoints relate to the induction-abortion interval, that is the time from first prostaglandin dose until delivery of the fetus. Most studies include median intervals and proportion aborted within 24 h. Most protocols include strategies for failed induction after 24 h, which may include a repeat course of the same regimen or a variety of other options including surgery. Outcomes beyond 24 h are not considered in this evaluation.

A secondary endpoint often presented is the proportion of women having manual removal of the placenta and/or uterine evacuation in the operating theatre. As with first trimester endpoints, this one varies with local clinical practice for instance whether intervention is routine after a certain time or based only on bleeding and so on. Summary figures are included when provided.

Because second trimester procedures are routinely conducted within a healthcare facility, these times are generally reasonably accurately available.

Studies relevant to this indication are listed in Table 11; the highlighted studies are those included in the sponsor's evaluation.

Table11. Second trimester abortion

Reference number First author Year published	Design No. of centres Location	Gestation	Mifepristone dose and interval to PG regimen (Source of mifepristone)	Prostaglandin (PG) regimen miso- misoprostol gem- gemeprost	Participants entered (analyzed)	Induction-abortion interval	Aborted within 24 hours	Retained placenta and/or evacuation
532 Thong 1992	RCT 1 centre Scotland	12-18 weeks	Nil Nil (Dilapan) 200mg +36h (Not specified)	1mg gem PV 6hrly up to 4 doses	58 (standard treatment) 20 (randomized) 20 (randomized)	15.7h 15.6h 6.6h p<0.0001	72% within 24h 85% within 24h 95% within 24h	
512 Webster 1996	RCT 1 centre Scotland	13-20 weeks	200mg +36-48h 600mg +36-48h (Mifegyne®)	800µg miso PV + up to 4 doses 400µg PO	35 35	6.86h (5.78-8.15) 6.94h (5.75-8.37)	97.10% 94.30%	3 (8.6%) 5 (14.3%)
534 Ho 1996	RCT 1 centre Hong Kong	14-20 weeks	200mg +36-48h (Not specified)	400µg miso PO 3hrly up to 5 doses 1mg gem PV 6hrly up to 4 doses	25 25	11.8h±9 12.2h±7.1 NS	92% within 24h 88% within 24h NS	5 (20%) 10 (40%) NS
535 Ho 1997	RCT 1 centre Hong Kong	14-20 weeks	200mg +36-48h (Not specified)	200µg miso PV 3hrly up to 5 doses 200µg miso PO 3hrly up to 5 doses	49 49	9.0h 13.0h p<0.001	89.8% within 24h 69.4% within 24h p<0.05	26.5% 40.8% NS
570 UK Multicentre Study Group 1997	Prospective study 20 centres UK	12-24 weeks	600mg +36-48h (Mifegyne®)	1mg gem PV 3hrly up to 5 doses	267 (261)	7h	Not reported	53.2%
530 Ngai 2000	RCT 1 centre Hong Kong	14-20 weeks	200mg + 36-48h (Not specified)	400µg miso PO 3hrly up to 5 doses 200µg miso PV 3hrly up to 5 doses	70 69		81.4% within 24h 84.0% within 24h NS	18.6% 24.6%
537 Tang 2001	Consecutive cohort 1 centre Scotland	12-24 weeks	200mg +36h (Mifegyne®)	1mg gem PV 6hrly up to 4 doses	956	7.8h	96.4% within 24h	11.5%
529 Bartley 2002	RCT 1 centre Scotland	12-20 weeks	200mg +36h (Mifegyne®)	1mg gem PV 6hrly up to 4 doses 800µg miso PV + up to 4 doses 400µg PO 3hrly	50 50	6.6h 6.1h NS	96% 94% NS	6 (12%) 5 (10%)
531 Tang 2005	RCT 1 centre Hong Kong	12-20 weeks	200mg +36-48h (Not specified)	400µg miso SL 3hrly up to 5 doses 400µg miso PO 3hrly up to 5 doses	(60) 58 60	5.5h 7.5h p=0.009	91.4% (81.0-96.7%) within 24h 85% (73.7-92.1) within 24h NS	17.2% 11.7%
592 Goh 2006	Consecutive cohort 1 centre Scotland	12-20 weeks	200mg +36-48h (Post registration)	800µg miso PV + up to 4 doses 400µg PO 3hrly	386	6.7h%	97.9% within 24h	5%
533 Kapp 2007	RCT 1 centre USA	18-23 weeks	200mg + 20-24h Placebo (Post registration)	400µg miso then 200µg 6hrly all	32 32	10h (8-12) 18h (15-22) p<0.01	97% within 24h 72% within 24h p<0.01	3.1% 6.3% NS

Medical regimens for second trimester termination of pregnancy**Place of mifepristone**

Mifepristone alone has not been examined for termination of pregnancy in the second trimester. Reference 532 compared gemeprost after 200 mg mifepristone, Dilapan or no pretreatment (only the first two randomised) and found a significantly reduced induction-abortion interval. Reference 522 reported a small randomised study of a misoprostol regimen which resulted in significantly lower median induction-abortion intervals at 18-23 weeks gestation (10 compared with 18 h, p<0.01) and significantly higher proportions aborted within 24 h (97% compared with 72%, p<0.01) when 200 mg mifepristone was given 20-24 h before misoprostol began.

These studies found that a lower total dosage of prostaglandin was required after mifepristone and support the use of mifepristone prior to prostaglandin for second trimester termination of pregnancy.

Dose of mifepristone

Reference 512 reported a randomised controlled trial comparing 200 mg with 600 mg doses of mifepristone prior to a standard misoprostol regimen in women from 13-20 weeks gestation and found equivalent abortion-induction intervals (6.86 and 6.94 h) and proportions aborting within 24 h (97.1% and 94.3%). The large cohorts reported in references 537 and 570 report similar induction-abortion intervals with 200 mg and 600 mg mifepristone regimens (7.8 and 7 h), despite different gemeprost regimens.

These results together with the pharmacokinetics referred to above support 200 mg as the appropriate dose of mifepristone for use in second trimester termination of pregnancy.

Interval between mifepristone and prostaglandin

All the included studies report the use of a 36-48 h interval between mifepristone and prostaglandin in the second trimester, except one (reference 533) which used 20-24 h in 64 women. In the absence of other evidence, it is appropriate to recommend the 36-48 h interval.

Which prostaglandin?

The earlier studies examined gemeprost; regimens of 1 mg 3 hourly for up to 5 doses (reference 570) and 1 mg 6 hourly for up to 4 doses (references 529, 532, 534 and 537) were found to be effective. More recent studies report on misoprostol for the reasons identified above.

Gemeprost is registered in Australia for therapeutic termination (second trimester of pregnancy) at a dosage of 1 mg vaginally 3 hourly to a maximum of 5 administrations.

Misoprostol dosage regimens

These have not been systematically considered in this application and no particular regimen is recommended. The table shows that several regimens have been associated with median induction-abortion intervals in the range of 5-8 h. These include 800 µg misoprostol vaginally followed by up to 4 doses of 400 µg orally 3 hourly (references 512, 529 and 592) and 400 µg misoprostol sublingually or orally 3 hourly for up to 5 doses (531). Some studies (534, 535, 530, 533) using 400 µg or 200 µg doses have had longer induction-abortion intervals and/or lower rates of abortion within 24 h.

In general the evolving evidence should be considered in choosing a prostaglandin regimen; see *Analysis performed across trials (pooled analyses and meta-analysis)* below.

Clinical studies in special populations

Reference 576 reports a study in 28 young women aged from 14-17, at ≤56DA who had abortion induced with 200 mg mifepristone and 800 µg misoprostol PV after 48 h (with consent of at least one parent). The method was found to be safe, effective and acceptable for “minors” with appropriate support.

The sponsor also reports clinical experience in 121 Australian women aged under 18 years, with comparable outcomes to older women.

Analysis performed across trials (pooled analyses and meta-analysis)

This section reproduces the main results and authors’ conclusions of the Cochrane reviews of “Medical methods for first trimester abortion”¹⁵ and “Medical methods for mid-

¹⁵Kulier R, Kapp N, Gülmezoglu AM, Hofmeyr GJ, Cheng L, Campana A. Medical methods for first trimester abortion. Cochrane Database of Systematic Reviews 2004, Issue 1. Art. No.: CD002855. DOI: 10.1002/14651858.CD002855.pub3.

trimester termination of pregnancy”¹⁶ as well as the recommendations of the Royal College of Obstetricians and Gynaecologists (RCOG) Evidence-based Clinical Guideline “The Care of Women Requesting Induced Abortion”¹⁷ concerning early medical abortion and mid-trimester medical abortion. The RCOG recommendations are supported by a detailed review of available evidence, which is presented in the guideline.

These references were not included with the application but are included here because they are systematic reviews of high quality. The RCOG recommendations cover licensed UK regimens and alternative evidence based regimens. An earlier version of the first trimester Cochrane review was picked up in the literature search but not included in the current submission.

Mifepristone in the first trimester

Cochrane review: Main results and authors' conclusions (3)

“Fifty-eight trials were included in the review. The effectiveness outcomes below refer to ‘failure to achieve complete abortion’ with the intended method unless otherwise stated.

1. Combined regimen mifepristone/prostaglandin: Mifepristone 600 mg compared to 200 mg shows similar effectiveness in achieving complete abortion (4 trials, RR 1.07, 95% CI 0.87 to 1.32). Misoprostol administered orally is less effective (more failures) than the vaginal route (RR 3.00, 95% CI 1.44 to 6.24) and may be associated with more frequent side effects such as nausea and diarrhoea. Sublingual and buccal routes were similarly effective compared to the vaginal route, but had higher rates of side effects.
2. Mifepristone alone is less effective when compared to the combined regimen mifepristone/prostaglandin (RR 3.76 95% CI 2.30 to 6.15).
3. Five trials compared prostaglandin alone to the combined regimen (mifepristone/prostaglandin). All but one reported higher effectiveness with the combined regimen. The results of these studies could not be combined but the RR of failure with prostaglandin alone is reportedly between 1.4 to 3.75 with the 95% confidence intervals indicating statistical significance.
4. In one trial comparing gemeprost 0.5 mg with misoprostol 800 mcg, misoprostol was more effective (failure with gemeprost: RR 2.86, 95% CI 1.14 to 7.18).
5. There was no difference in effectiveness with use of a divided dose compared to a single dose of prostaglandin.
6. Combined regimen methotrexate/prostaglandin demonstrates similar rates of failure to complete abortion when comparing intramuscular to oral methotrexate administration (RR 2.04, 95% CI 0.51 to 8.07). Similarly, day 3 vs. day 5 administration of prostaglandin following methotrexate administration showed no significant differences (RR 0.72, 95% CI 0.36 to 1.43). One trial compared the effect of tamoxifen vs. methotrexate and no statistically significant differences were observed in effectiveness between the groups.

Authors' conclusions

Safe and effective medical abortion methods are available. Combined regimens are more effective than single agents. In the combined regimen, the dose of mifepristone can be lowered to 200 mg without significantly decreasing the method effectiveness.

¹⁶ Wildschut H, Both MI, Medema S, Thomee E, Wildhagen MF, Kapp N. Medical methods for mid-trimester termination of pregnancy. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD005216. DOI: 10.1002/14651858.CD005216.pub2.

¹⁷ Royal College of Obstetricians and Gynaecologists. The care of women requesting induced abortion. London: RCOG; 2004. <http://www.rcog.org.uk/index.asp?PageID=662>

Vaginal misoprostol is more effective than oral administration, and has less side effects than sublingual or buccal. Some results are limited by the small numbers of participants on which they are based. Almost all trials were conducted in settings with good access to emergency services, which may limit the generalizability of these results.

2004 RCOG guideline, page 52 (5)

“Early medical abortion (gestations up to 9 weeks)

RECOMMENDATION 39

Medical abortion using mifepristone plus prostaglandin is the most effective method of abortion at gestations of less than 7 weeks.

RECOMMENDATION 40

Medical abortion using mifepristone plus prostaglandin continues to be an appropriate method for women in the 7–9 week gestation band.

RECOMMENDATION 41

* For early medical abortion a dose of 200 mg of mifepristone in combination with a prostaglandin is appropriate.

RECOMMENDATION 42

* Misoprostol (a prostaglandin E1 analogue) is a cost-effective alternative for all abortion procedures for which the E1 analogue gemeprost is conventionally used (that is, early medical abortion, cervical priming, mid-trimester medical abortion).

RECOMMENDATION 43

Based on available evidence, the following regimen appears to be optimal for early medical abortion up to 9 weeks (63 days) of gestation. This advice is based on considerations of efficacy, adverse-effect profile and cost:

- *mifepristone 200 mg orally followed 1–3 days later by misoprostol 800 micrograms vaginally. The misoprostol may be administered by a clinician or self-administered by the woman. For women at 49–63 days of gestation, if abortion has not occurred 4 h after administration of misoprostol, a second dose of misoprostol 400 micrograms may be administered vaginally or orally (depending upon preference and amount of bleeding).

The following regimen is licensed within manufacturer’s summary of product characteristics and is also appropriate for early medical abortion up to 9 weeks (63 days) of gestation:

- mifepristone 600 mg orally followed 36–48 h later by gemeprost 1mg vaginally.
- * This regimen is unlicensed.”

There have been some changes to the licensed regimens in the UK and the RCOG guideline is undergoing revision following an updated review of the evidence. Based on a draft published temporarily for consultation early this year there are likely to be some changes to the recommended regimens but combinations of 200 mg mifepristone with misoprostol continued to be recommended in the draft, consistent with established evidence. Vaginal, buccal and sublingual routes of administration were addressed and in the draft oral misoprostol was considered an option prior to 49DA. If the new edition is available prior to final consideration of this application, the relevant sections should be considered.

Mid-trimester medical abortion

Cochrane review: Main results and authors’ conclusions (4)

“Fourty (sic) RCTs were included, addressing various agents for pregnancy termination

and methods of administration. When used alone, misoprostol was an effective inductive agent, though it appeared to be more effective in combination with mifepristone. However, the evidence from RCTs is limited.

Misoprostol was preferably administered vaginally, although among multiparous women sublingual administration appeared equally effective. A range of doses of vaginally administered misoprostol has been used. No randomised trials comparing doses of misoprostol were identified; however low doses of misoprostol appear to be associated with fewer side-effects while moderate doses appear to be more efficient in completing abortion. Four RCTs showed that the induction to abortion interval with 3-hourly vaginal administration of prostaglandins is shorter than 6-hourly administration without an increase in side-effects.

Many studies reported the need for surgical evacuation. Indications for surgical evacuation include retained products of the placenta and heavy vaginal bleeding. Fewer women required surgical evacuation when misoprostol was administered vaginally compared with women receiving intra-amniotic PGF_{2a}. Mild, self-limiting diarrhoea was more common among women who received misoprostol compared to other agents.

Authors' conclusions

Medical abortion in the second trimester using the combination of mifepristone and misoprostol appeared to have the highest efficacy and shortest abortion time interval. Where mifepristone is not available, misoprostol alone is a reasonable alternative. The optimal route for administering misoprostol is vaginally, preferably using tablets at 3-hourly intervals. Apart from pain, the side-effects of vaginal misoprostol are usually mild and self limiting. Conclusions from this review are limited by the gestational age ranges and variable medical regimens, including dosing, administrative routes and intervals of medication, of the included trials."

2004 RCOG guideline, page 56 (5)

"Mid-trimester medical abortion

RECOMMENDATION 45

For mid-trimester abortion (13–24 weeks of gestation) medical abortion with mifepristone followed by prostaglandin is an appropriate method and has been shown to be safe and effective.

RECOMMENDATION 46

For mid-trimester medical abortion, a dose of *200 mg of mifepristone is adequate.

RECOMMENDATION 47

Surgical evacuation of the uterus is not required routinely following mid-trimester medical abortion. It should only be undertaken if there is clinical evidence that the abortion is incomplete.

RECOMMENDATION 48

Based on available evidence, the following regimen appears to be optimal for mid-trimester medical abortion. This advice is based on considerations of efficacy, adverse-effect profile and cost:

- *Mifepristone 200 mg orally, followed 36–48 h later by misoprostol 800 micrograms vaginally, then misoprostol 400 micrograms orally, 3-hourly, to a maximum of four oral doses.

The following regimen is licensed within manufacturer's summary of product characteristics and is also appropriate for mid-trimester medical abortion:

- Mifepristone 600 mg orally, followed 36–48 h later by gemeprost 1 mg vaginally every 3 h to a maximum of five pessaries.

*This regimen is unlicensed.”

As indicated above this guideline is being revised.

Supportive studies: Mifepristone in Australia

Experience with mifepristone in Australia

Several publications report the use of mifepristone in Australia for abortion indications under section 19(5) of the Therapeutic Goods Act (the authorised prescriber program).

de Costa et al¹⁸ reported that ten Queensland women at <63DA had abortion successfully induced by 200 mg mifepristone orally, followed 48 h later by 800 µg misoprostol intravaginally.

Mulligan and Messenger¹⁹ reported on South Australian experience with 947 medical abortions up to 9 weeks gestation resulting in 5.6% having surgical intervention within the ensuing 28 days. Details of loss to follow up were not provided. The regimen was 200 mg mifepristone orally, followed by 800 µg misoprostol vaginally, sublingually or buccally after 0-72 h, with further doses of 200µg misoprostol vaginally, sublingually or buccally three times daily if cramping or heavy bleeding persisted. There were 4 haemorrhages >1000 ml, 1 failed abortion and 2 admissions with sepsis.

The same authors reported on 49 second trimester medical abortions, with median 10 h and mean 17 h induction to abortion interval (range 3-55 h); 3 women had abortion completed by surgical dilatation and evacuation, 10 had manual removal of the placenta, 2 had postpartum haemorrhage, one of whom was transfused, 4 had curettage for retained products of conception and one had infection identified on vaginal culture. The regimen used was mifepristone 200 mg orally followed by admission 0-72 h later for 800 µg misoprostol vaginally and up to 4 further doses of 400 µg every 3 h.

Dickinson et al²⁰ reported on two successive temporal cohorts of West Australian women having second trimester termination of pregnancy from 14-24 weeks gestation. The first group comprised 189 women treated with misoprostol alone, 400 µg misoprostol vaginally 6 hourly for a maximum of 48 h. The second group comprised 199 women treated with mifepristone after it became available under the authorised prescriber scheme. The regimen was 200 mg mifepristone, with admission 24-48 h later for 800 µg misoprostol vaginally followed by 400 µg orally every 3 h for a maximum of 5 doses. The median induction –abortion interval was 15.5 h (interquartile range 11.2-22.7) for the misoprostol alone group and 8.6 h (5.6-13.8) for the mifepristone/misoprostol group; p<0.001. The period of hospitalisation was significantly reduced in the mifepristone/misoprostol group, with no change in haemorrhage (10% >500 ml) or removal of placenta in the operating room (approximately 25%).

The submission included reports of the sponsor’s Australian experience (between 9 August 2009 and 8 August 2010) of 5730 medication abortions at up to 63 DA. The regimen used was 200 mg mifepristone followed at 24-48 h by 800 µg misoprostol buccally. They report 3.5% requiring surgical intervention but do not include details of loss to follow up. The result is presented as 96.4% complete success without need for surgical intervention.

¹⁸ de Costa CM, Russell DB, de Costa NR, Carrette M, McNamee HM. Early medical abortion in Cairns, Queensland: July 2006 – April 2007. Medical Journal of Australia 2007; 187 (3): 171-173.

¹⁹ Mulligan E and Messenger H. Mifepristone in South Australia: the first 1343 tablets; Australian Family Physician 2011; 40 (5) p342-5.

²⁰ Dickinson JE, Brownell P, McGinnis K and Nathan EA. Mifepristone and second trimester pregnancy termination for fetal abnormality in Western Australia: worth the effort. Australian and New Zealand Journal of Obstetrics and Gynaecology 2010; 50 (1) p60-64.

Commentary on Australian experience

The three reports of first trimester abortion included women up to 63DA with outcomes consistent with those in the literature presented in this application; with surgical intervention rates of around 5% although details of follow up were not provided except for the smallest group. In each case the dose of mifepristone used was 200 mg with an initial dose of 800µg misoprostol. In one study this was administered vaginally, in another any of vaginal, sublingual or buccal routes and in the sponsor's report the buccal route was used.

The two reports of second trimester termination of pregnancy both used 200 mg mifepristone orally followed by an initial dose of 800 µg misoprostol vaginally after 24-48 h or 0-72 h and further doses of 400 µg orally 3 hourly. Rates of surgical intervention were high at 33% and 25%. Dickinson et al²⁰ draw comparisons with the previous cohort in which the doses and frequency of misoprostol used were lower, so it is uncertain to what extent the differences are due to the addition of mifepristone rather than the misoprostol regimen. Nevertheless the difference in median induction-abortion interval is similar to those observed in the randomised controlled trials reported in references 532 and 533 (see above)

None of the studies reported oral administration of misoprostol, nor use of gemeprost; their regimens were consistent with the findings of the Cochrane reviews and RCOG guidelines cited above.

Evaluator's overall conclusions on clinical efficacy

Mifepristone used together with prostaglandins has a higher efficacy in the induction of abortion with more rapid effect than mifepristone alone (up to 80%), prostaglandins alone (up to 88%) or prostaglandins with methotrexate (up to 2-3 weeks for effect).

Several large, well conducted studies have demonstrated a single dose of 200 mg mifepristone to be of equivalent efficacy to 600 mg (the dose registered in several countries) when combined with a variety of prostaglandin regimens to induce early medical abortion. A 50 mg dose has a lower efficacy than 200 mg (87.6% compared with 92.3%) and 100 mg doses have not been adequately investigated.

Many prostaglandin regimens have been studied. They were not systematically examined in this application which focused on oral misoprostol regimens up to a gestation of 49 days. It was nevertheless clear from the material in the application that efficacy of the proposed prostaglandin regimens is likely to be less after 49 days, that is outside the proposed indication.

An interval of 36-48 h between mifepristone and misoprostol is conventionally used. Several studies have examined shorter intervals but intervals of 24 h or less have a lower efficacy than 36-48 h intervals for the oral misoprostol regimens proposed in the application (90% versus 97%, 50% versus 91%). Some shorter intervals appeared to hold promise for regimens including vaginal administration of misoprostol.

While gemeprost was demonstrated to be a safe and effective option recent studies have largely examined misoprostol, which is associated with equivalent outcomes, is stable at room temperature, can be administered by several different routes and is more cost effective.

The proposed regimens of oral misoprostol, 800µg in single or divided doses or 600 µg administered 36-48 h after 200 mg mifepristone result in complete abortion rates of 93-98%, with the lowest lower 95% CI, where reported, of 89%.

For the second trimester, two small studies found significantly reduced induction-abortion intervals with mifepristone pretreatment compared to none or Dilapan. A randomised controlled trial found equivalent abortion-induction intervals and abortion rates within 24

h with 600 mg and 200 mg mifepristone doses prior to vaginal misoprostol in the second trimester.

Several studies reported prostaglandin regimens used in the gestation range of 12-24 weeks associated with median induction-abortion intervals in the range of 5-8 h and over 90% of women aborting within 24 h. Surgical evacuation was needed in 10-12%, with some studies reporting rates as high as 20-30%.

Second trimester prostaglandin regimens were not systematically examined in the application and no regimen is recommended.

In general the evolving evidence should be considered in choosing a prostaglandin regimen.

In summary, 200 mg mifepristone is the recommended dose prior to prostaglandin regimens for medical abortion up to a gestation of 49 days and in the second trimester. Up to 49 days the proposed regimens of 600 µg oral misoprostol or 800 µg in single or divided doses administered 36-48 h after mifepristone result in a complete abortion rate of 93-98%. In the second trimester the addition of 200 mg mifepristone prior to prostaglandin regimens reduces the induction-abortion interval and the total dose of prostaglandin required.

Commentary on efficacy assessment in the sponsor's Clinical Overview

The evidence and recommendations for a 200 mg dose of mifepristone and a 36-48 h interval between mifepristone and misoprostol are appropriate for both early and second trimester termination of pregnancy. Overall the review of mifepristone/prostaglandin regimens and its conclusions are reasonable apart from the exclusion from consideration of vaginal administration of misoprostol. There is no detailed consideration of buccal and/or sublingual routes. The recommended regimens for 800 µg (in single or divided doses) or 600 µg oral misoprostol for early medical abortion up to 49DA are reasonable as is the statement that gemeprost 1 mg vaginally may be used. The observation that different regimens may be needed after 49DA is appropriate; these are outside the proposed indications and are not examined in detail.

The descriptions of expected bleeding patterns are appropriate.

The evaluator noted that several of the reference numbers in the sponsor's submission (including Tables 7-10) appeared to be incorrect.

Safety

Introduction

There are several components to the assessment of safety and adverse events in the use of mifepristone for abortion:

- Abortion by any method carries risks and complications although overall there are greater risks associated with childbirth at term.
- Pain and bleeding are part of the procedure of medical abortion; it is not really appropriate to consider them as adverse events per se although women need to have realistic expectations of what is involved and their symptoms need to be managed in the course of providing care. Clinicians and women need to be able to assess when pain or bleeding are excessive or exceptional.
- Mifepristone is almost universally used together with a prostaglandin for this purpose, so it can be difficult to determine whether particular symptoms, side effects or adverse events are due to one or the other drug.

While separating these components is to some extent academic, it can be important in advising women about what to expect and sometimes in selecting abortion methods or regimens for particular women.

Some events may vary in frequency with gestation at which abortion occurs.

Analysis is further complicated by the fact that some of the common adverse events such as nausea, vomiting, dizziness and breast tenderness are common in normal pregnancy.

Many of the common adverse events are highly subjective and both perceptions and ascertainment methods vary greatly. Some studies have attempted to separate events occurring between mifepristone and prostaglandin from those following prostaglandin. Where consistent differences in timing have been reported they are commented upon in the evaluation but by and large the adverse events are considered regardless of timing, that is, associated with medical abortion rather than specifically with mifepristone.

For this application, safety information was sought from the literature studies analysed for efficacy, from a commissioned literature review of the Chinese and English language literature and from relevant information available in "literature official reports". The literature search strategy included searching for case reports and for studies in which mifepristone was used long term for a range of gynaecological and non-gynaecological conditions, including Cushing syndrome and meningioma.

The approach to the evaluation was to focus on the failed procedures (requiring surgical intervention), serious adverse events (haemorrhage requiring surgery and/or transfusion, serious infections, uterine rupture, myocardial infarction) and deaths. For the milder events, which are mainly self limiting and to which mifepristone is generally of doubtful causal relationship, safety and adverse event reports in the references provided were considered against the frequency listings in the summary table and the reviews listed under *Patient Exposure* (see below) with a view to identifying any important inconsistencies. Brief commentary is provided under *Adverse Events* (below).

Safety data were appropriately recorded and examined in the bioequivalence studies.

Patient exposure

Many millions of women have been treated with mifepristone in single doses of 600 mg or 200 mg with prostaglandin for termination of pregnancy in the 23 years since it was first registered in France. Shannon (628) reports that 15 million women were treated in China by 2002 and the most recent FDA Postmarketing Adverse Events Summary for mifepristone²¹ estimates that approximately 1.52 million women have used mifepristone in the USA to April 2011.

Over 25,000 mifepristone recipients are listed in the First trimester efficacy below and 2,200 in the Second trimester efficacy table below. The application safety review presents tables reported to represent 190,000 women exposed to mifepristone, mainly in 200 mg doses.

Several reviews addressing safety were included in the current submission:

- reference 501, reporting on 16,173 early medical abortions in France
- reference 593, reporting on 95,163 procedures in the USA
- reference 543, reviewing 227,823 procedures in the USA
- reference 546, reporting on adverse events notified from around 80,000 procedures in the USA

²¹ FDA Postmarketing Adverse Events Summary for mifepristone.
<http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM263353.pdf> Accessed July 2011

- reference 541, a review addressing complications and safety
- reference 628, which considers 46,421 medical abortions in reviewing infection

These large studies provide information on rare and serious events.

It was appropriate to consider the long term administration of mifepristone for the safety review. In general, the findings were not relevant to the single dose use and indications which are the subject of this application. The analysis and conclusions presented in the sponsor's submission are appropriate, with many of the adverse events related to the often serious underlying conditions which were being treated. The adverse events from long term use of mifepristone are briefly addressed below under *Adverse events* and otherwise not considered further in this evaluation.

Adverse events

General comments

Adverse events are tabulated in Table 12 (also presented in the proposed product information). This is an appropriate summary of the safety information ascertained in the literature review and presented both in summaries and in the references included in the sponsor's submission.

The majority of the data and information relate to early medical abortion; specific comments are made under each heading about mid trimester abortion when relevant differences are identified.

Ulmann (501) reported that 8.5% of over 16,000 women had at least one "notified side effect", most of which were benign, including symptoms such as malaise and headache. Hausknecht (546) reported in 2003 on 139 adverse events notified to the FDA from an estimated 80,000 cases in the first 18 months of registration of mifepristone in the USA; the denominator was of necessity inexact and only the more serious events were likely to have been reported in this study. Henderson et al (593) reported a complication rate of 2.2:1,000, most commonly heavy bleeding, from systematic data collection on over 95,000 cases in a large American service system. This study did not examine adverse events such as gastro-intestinal symptoms.

There were variations in the reporting and recording of safety aspects, probably most clearly delineated in the infection review (628) which considered differences in local clinical practices.

For the gastrointestinal and other non-serious adverse events, there were apparently well conducted studies with quite different rates, which may have to do with women's expectations, how and when questions were asked, how events were recorded and possibly cultural and other differences. In the evaluator's opinion there are no particular landmark studies and it is not fruitful to try to narrow down these rates although some of the randomised controlled trials provide useful data comparing side effect profiles of different regimens, mainly of prostaglandins.

As far as the more serious adverse events are concerned, in the evaluator's opinion the data set as a whole is likely to be highly sensitive to the detection of safety signals. It is reassuring that rates of 'serious infection' assessed in various ways, were remarkably consistent at less than 1%. The picture in respect of haemorrhage requiring blood transfusion was also quite consistent. The scale of clinical experience over two decades is such that there is a realistic expectation that even very rare events will have been reported, which in the evaluator's opinion is evidenced by the included case reports, which are diverse and mostly singular, often of doubtful relationship to the drugs used. Given the rarity of serious events, the evaluator remained of the view that searching all of the material provided, including case reports and large postmarketing series, was more appropriate than seeking probably unattainable precision in a small number of highly

documented studies. The safety review considered additional material on another 160,000 odd cases.

Table 12. Adverse events reported after the use of mifepristone, single administration, alone, or followed by a prostaglandin analogue for the termination of pregnancy (first or second trimester).

Medra 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)*
Gastrointestinal disorders	Nausea Vomiting Diarrhea Dizziness Gastric discomfort Abdominal pain			Gastric bleeding
Nervous system disorders	Headache			Epilepsy Neurogenic tinnitus
Reproductive system and breast disorders	Vaginal bleeding Uterine spasm	Prolonged post-abortion bleeding Spotting Severe hemorrhage Endometritis Breast tenderness Heavy bleeding	Hemorrhagic shock Salpingitis	Bilateral adnexal mass Intrauterine adhesion Ovarian cyst rupture Breast abscess Hematosalpinx Uterine rupture
General disorders and administration site conditions	Fatigue Chill / fever	Fainting		Anaphylaxis Periorbital edema
Infections and infestations			Infection	Toxic shock syndrome
Vascular disorders			Hot flush	Superficial thrombophlebitis Hypotension
Cardiac disorders				Myocardial infarction Induced Adam-Stokes syndrome
Respiratory, thoracic and mediastinal disorders				Bronchospasm Induced bronchial asthma

Table 12. continued

Medra 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)*
Skin and subcutaneous tissue disorders			Skin rash / pruritus	Urticarial reaction Toxic epidermal necrolysis
Pregnancy, puerperium and perinatal conditions				Hydatiform mole Ectopic pregnancy Amniotic band syndrome Gestational trophoblastic tumor Uteroplacental apoplexy
Hepatobiliary disorders				Abnormal liver function tests Hepatic failure Hepatorenal failure
Blood and lymphatic system disorders				Thrombotic thrombocytopenic purpura Thrombocytopenia Induced systemic lupus erythematosus
Renal and urinary disorders				Renal failure
Neoplasms benign, malignant and unspecified				Elevated alpha-feto protein Elevated carcinoembryonic antigen
Musculoskeletal and connective tissue disorders				Limb spasm
Eye disorders				Ophthalmoplegia
Psychiatric disorders				Mania

* Including occasional case reports

MedDRA = Medical Dictionary for Regulatory Activities

Adverse events intrinsic to the procedure of medical abortion***Abdominal pain and uterine spasm***

These symptoms are appropriately considered together and reflect the uterine contractions intended to be induced in order to expel the pregnancy. These are almost universal but analgesia requirements vary enormously; in some studies the majority of women use no analgesia, while in others a majority will use oral analgesia. It appears that few women prior to 49DA will need parenteral analgesia but analgesia requirement does

appear to increase with advancing gestation. In many centres medical abortion, particularly up to 49DA may be very acceptable when prostaglandin is self administered at home (525, 527, 574, 577). Suitable analgesia must be available whether abortion is conducted at home or in a health care facility. Up to about a third of women are reported to experience some abdominal pain or cramping after mifepristone and before prostaglandin.

Second trimester: pain is universal as uterine contractions must be induced for successful abortion to occur. The need for parenteral analgesia is more frequent in second trimester terminations; when this was reported most studies indicated that half or more women needed parenteral analgesia but one study reported 28-31% requirement (531).

Vaginal bleeding

Vaginal bleeding is also intrinsic to the process of abortion. Up to 30-50% of women will have some spotting or bleeding after mifepristone and before prostaglandin, with up to about 3% of women in the first trimester aborting during this phase; most of those who have not already bled will have some bleeding within a few hours of prostaglandin administration. Most studies report a median duration of bleeding of around 12 days, with a range up to 60 days, some of which may be spotting. Some studies have reported that it is usual for 2-3 days of bleeding to be considered heavier than normal menses.

Assessment of what comprises excessive or prolonged bleeding may be subjective but symptomatic bleeding is a common reason for surgical intervention. Sitruk-Ware's review (541) estimated that bleeding is considered to be excessive in about 10% of women but only 0.33-2.6% will have curettage because of this.

Prolonged post abortion bleeding, spotting, heavy bleeding and severe haemorrhage are listed as common with frequencies of 1-10%. Heavy and prolonged bleeding are considered further below, together with haemorrhagic shock, which is listed as uncommon (0.1-1%) and second trimester haemorrhage.

Women need to be advised about expected bleeding and about indicators that they should seek advice or emergency care.

Gastrointestinal side effects

Nausea is reported at rates from around 20-60%: it is not always clear whether this is a new symptom following mifepristone or is a pre existing pregnancy symptom.

Vomiting is reported in up to around 40% of women undergoing medical abortion; the rates seem to be lower before than after prostaglandin but again this may be a pre existing pregnancy symptom.

Diarrhoea is also reported in up to around 30-40% of women undergoing medical abortion with most studies reporting low rates prior to prostaglandins.

Gastric discomfort is also reported to be very common.

Studies which have directly compared the administration of misoprostol by different routes consistently find the lowest rates of gastrointestinal side effects after vaginal administration, with higher rates after sublingual or buccal administration and the highest rates with oral administration. This is one important consideration in choice of misoprostol regimen due to the unpleasant if transient nature of these symptoms.

Infection

Infection has been extensively reviewed (628, 541, 543). In the table of adverse events endometritis is listed as common (1-10%), salpingitis and infection as uncommon (0.1-1%) and toxic shock syndrome as very rare (<0.1%). Case definition and ascertainment are very variable, particularly for mild infections, with a review by Shannon reporting a 10 fold difference between reported infection rates after mifepristone and vaginal misoprostol in the UK (2.2%) and elsewhere (0.25%). This difference was thought to be

due to differences in local therapeutic practice rather than real differences in incidence. Although mild infections may be common, there is a lack of systematic information about them, many studies noting that milder infections and for that matter other mild adverse events are likely to be under reported. Serious infections are considered further below.

Other adverse events

Headache, fever, chills, dizziness and fatigue are all listed as very common, with frequencies greater than 10%. In the studies reviewed rates of headache ranged from 1-49%, in most studies around 10-25%. The range was even greater for fatigue, which was less consistently reported. For fever, warmth and chills, in which there was some overlap, the range was from 0.3-50%; there may also have been some overlap with hot flushes, listed as an uncommon adverse event. These are recognised adverse effects of prostaglandins. Dizziness was reported in these studies at rates up to around 40%. Breast tenderness and fainting are listed as 1-10% and were reported less consistently in the studies.

Skin rashes and pruritus are listed with a frequency of 0.1-1%.

Rare and very rare events and case reports.

Most of the events listed in this column are based on case reports; while many are serious most are unlikely to be causally related to mifepristone and given the now vast international experience with mifepristone there is a reasonable level of confidence that they are indeed very rare.

Adverse events in the bioequivalence studies

These were generally minor and transient and they were appropriately considered and consistent with the overall safety findings. There was no pattern to suggest a difference between the test and reference products. There were three serious adverse events, none caused by the studies. One was an animal bite and the other two were accidental pregnancies, one of which resulted in elective abortion and the other in miscarriage.

Adverse events after long term use of mifepristone

The sponsor's safety review reported adverse events after use of mifepristone, usually for at least several months, for a range of conditions including breast cancer, meningioma, Cushing syndrome and endometriosis. The following listing is of adverse events additional to those reported in the summary table for single dose mifepristone, where estimated frequency was at least 1%; many frequencies were determined on the basis of very small studies, often reflecting only one event (adapted from sponsor's table). The number of events and study size are indicated in brackets as numerator and denominator respectively.

Adverse events reported in more than one study:

- anorexia (16/27)
- amenorrhoea (21/44)
- hot flushes (32/69)
- gynaecomastia/breast tenderness (14/54)
- skin rash (10/53)
- adrenal insufficiency (3/36)

Adverse events reported in only one study:

- weight loss (10/11)
- endometrial hyperplasia (6/57)

- somnolence (4/11)
- depression (6/25)
- pedal oedema (3/25)
- partial alopecia (3/25)
- thinning of hair (3/28)
- increase in eosinophil count (not recorded)
- seizure (grand mal) (2/21)

Adverse events reported in one participant in one study:

- acute exanthema with fever
- joint pain
- hypoglycaemic episodes
- severe hypokalaemia
- increased bilirubin
- acute myocardial infarction
- sudden asystole
- impotence
- decreased libido
- peritoneal carcinoma
- hypothyroidism
- increase in TSH (thyroid stimulating hormone)

These events are considered unlikely to be of any relevance to single dose use of mifepristone as proposed in the application.

Serious adverse events and deaths

Failed early medical abortion: surgical intervention

Failure rates of up to around 7% requiring surgical intervention at gestations up to 49DA are reported with the proposed regimens. Most of the studies evaluated report continuing pregnancy rates around 1% or less for these early pregnancies, although Shannon et al (521) reported a 3.6% continuing pregnancy rate with a regimen using 400 µg oral misoprostol. Suction curettage will usually be undertaken for these pregnancies at a varying interval after the attempted medical abortion. Review is recommended within 2 weeks to ensure that a continuing pregnancy can be diagnosed and dealt with.

A small number of surgical procedures will be done on an urgent basis because of heavy bleeding.

The remainder of the surgical interventions comprise a combination of cases where there is prolonged and/or heavy bleeding following medical abortion, which may or may not be associated with evidence of retained products of conception. Some programs routinely conduct ultrasound examination to identify missed abortion or retained products of conception; these are likely to have higher intervention rates.

Surgical intervention and second trimester abortion

Uterine evacuation for manual removal of retained placenta, for retained products of conception or for heavy or prolonged bleeding is commoner after second than first

trimester medical abortion, most studies reporting around 10-20%. One multicentre study reported over 50% of cases having surgical evacuation but it was noted that this was routine practice in many of the participating centres.

All studies report a proportion of women who do not abort within 24 h of starting prostaglandin after mifepristone for termination of second trimester abortion, usually around 5% with established optimal prostaglandin regimens. Repeat or alternative regimens then need to be considered.

Deaths from infection

After an estimated 1.52 million medical abortions in the USA, the recent FDA Postmarketing Adverse Events Summary²¹ notes 14 deaths associated with mifepristone, including 8 from sepsis, 7 positive for *Clostridium sordellii* and 1 positive for *Clostridium perfringens*. All but one of these followed the use of vaginal misoprostol, the other buccal misoprostol. They note only one *Clostridium sordellii* death reported from other countries, presumably the Canadian case (520). This appears to add 3 more recent sepsis deaths to those reported in the sponsor's submission and discussed in the literature (520, 541, 543, 549).

Fatal toxic shock syndrome associated with *Clostridium sordellii* has also been reported in association with childbirth, miscarriage and several other medical and surgical conditions²².

Although some have postulated a link with vaginal administration of misoprostol, this is not established (543,628).

Other deaths

The same FDA report²¹ includes 2 deaths from ectopic pregnancy, 2 from drug overdoses, a suspected homicide and a case of delayed toxic shock-like syndrome with an apparently infected fibroid. The ectopic pregnancy deaths are likely to result from failure to diagnose them rather than medical abortion treatment per se.

Reference 501 notes a death from myocardial infarction after injection of sulprostone.

Serious infections

A number of reviews have considered infection rates in large treatment populations, generally found to occur at rates less than 1% (501, 543, 593, 628). Some explicitly focussed on serious infections (variously defined) while Shannon et al's international review (628) found an overall infection rate of 0.92% after 46,421 medical abortions with a range of 0.00-6.11%. They attributed the variation to local practices and considered it unlikely that there was a meaningful difference in infection rates by route of administration of misoprostol. Fjerstad et al (543) reported a reduction in identified serious infection rates associated with changing from vaginal to buccal misoprostol and the introduction of routine antibiotic prophylaxis. They noted that this was not evidence of cause and effect.

"FDA does not have sufficient information to recommend the use of prophylactic antibiotics for women having a medical abortion"²³ because of the rarity of fatal sepsis, the individual and resistance risks posed by routine prophylaxis and because of uncertainty about which antibiotic regimen to use.

²² Aldape MJ, Bryant AE and Stevens DL. *Clostridium sordellii* Infection: Epidemiology, clinical Findings and Current Perspectives on Treatment. Clinical Infectious Diseases 2006; 43, p1436-46.

²³ Mifeprex (mifepristone) Information (FDA)
<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111323.htm>
 Accessed July 2011

Heavy bleeding, severe haemorrhage, and haemorrhagic shock

There is no clear definition of these terms but blood transfusion may be considered a surrogate for haemorrhagic shock. Some cases of severe haemorrhage and heavy or prolonged bleeding may have resulted in blood transfusion, while others may have been treated with curettage and are considered under the heading of unsuccessful medical abortion.

Blood transfusions were reported after first trimester abortions as follows: x/n (reference number) where x is the number of cases and n is the number of participants in the study:

11/16173 (501), 3/1182 (506), 0/220 (507), 2/896 (508), 7/1224 (511), 2/999 (513), 1/800 (515), 0/150 (517), 0/738 (518), 0/1144 (519), 2/2219 (522), 2/893 (523), 1/442 (525), 7/1018 (571), 1/2030 (588), 0/90 (594), 0/226 (597), 1/505 (601), 0/390 (601), 0/105 (604).

Overall this amounts to 40/31,484 cases, or 0.12%. The early French study (all ≤ 49 DA) reported a rate of $<0.1\%$ and the remaining studies, many of which included some later gestations, had a total rate of 29/15,331 or 0.19%.

In the second trimester transfusions similarly counted in the evaluated studies yielded a total rate of 8/1856 or 0.43%, suggesting that transfusion rates do increase somewhat with gestation. The raw figures are as follows, including studies where transfusions were mentioned or “no serious complications” were specified:

2/70 (512), 0/50 (534), 0/98 (535), 2/261 (570), 0/139 (530), 1/956 (537), 2/100 (529), 0/118 (531), 1/64 (533).

Acute myocardial infarction

One cardiac death and two other acute myocardial infarctions occurred in Europe after sulprostone injection (501, 553). A further non fatal coronary artery occlusion was reported in the USA after misoprostol (546).

Pregnancy complications

Several ectopic pregnancies have been reported with some fatalities. These were likely missed diagnoses at the time of planning medical abortion; an attempted medical abortion of a presumed intrauterine pregnancy may cloud the assessment of subsequent symptoms. It is important to confirm intrauterine pregnancy prior to embarking on medical abortion as the usual regimens are not appropriate to treat ectopic pregnancy.

Gestational trophoblastic tumour is listed as a very rare event. This is also likely to be a missed diagnosis rather related to medical abortion regimens.

Term pregnancy after mifepristone is very rare because of the high efficacy of medical abortion regimens and because the majority of women with failed medical abortion will proceed to complete it by other means. However, there are some case reports of fetal anomalies following mifepristone, of doubtful but nevertheless possible aetiological relationship.

Uterine rupture

This is a serious complication of second trimester medical abortion listed as a rare or very rare adverse event. It seldom occurs prior to 18 weeks gestation except in the presence of a uterine scar for instance following previous caesarean section. It most likely relates to the selected prostaglandin regimen rather than to mifepristone itself. One case was reported in reference 570.

Laboratory findings

No specific studies have been done on single dose mifepristone for termination of pregnancy.

Although some studies noted a small average fall of haemoglobin following medical abortion this was considered to be related to blood loss rather than any direct drug effect.

Safety in special populations

No specific studies have been done.

Immunological events

No information is available.

Safety related to drug-drug interactions and other interactions

No specific studies have been undertaken but the likely issues related to the metabolism of mifepristone by the CYP3A4 enzyme have been identified (see PK above) and are addressed in the proposed product information.

Discontinuation due to Adverse Events

These indications require single dose use with no discontinuation due to adverse events reported.

Post marketing experience

Most of the literature reported is post marketing in the countries where the studies were undertaken. Findings are included under earlier headings.

Evaluator's overall conclusions on clinical safety

The safety of mifepristone in medical abortion regimens has been well established in extensive international clinical use, with the issues of concern well identified. The safety of mifepristone needs to be considered in the context that abortion by any method carries a degree of risk as does pregnancy and childbirth.

Abdominal pain and vaginal bleeding are intrinsic to the procedure and vaginal bleeding may result in a need for surgical evacuation of the uterus, occasionally urgently. This rarely but occasionally happens beyond 2-3 weeks after the procedure. There is a recognised failure rate of the procedure, which means that follow up is essential to ensure that abortion has been successful. Up to around 7% of women will need surgical intervention after medical abortion up to 49 days gestation and 10-20% will need uterine evacuation following second trimester medical abortion.

Common adverse events are uncomfortable but self limiting and not serious, many likely related to prostaglandin rather than mifepristone itself. These include nausea, vomiting, diarrhoea, fever, chills, dizziness and headache.

More serious complications such as need for blood transfusion occur in around 1-2:1,000 prior to 49 days gestation and more frequently, around 4:1,000 in the second trimester.

Uterine rupture has been rarely reported in second trimester abortion and clinicians should consider individual risk factors and pay careful attention to appropriate prostaglandin regimens to minimise this risk.

Serious infection is very rare but deaths have occurred in North America following toxic syndrome associated with *Clostridium sordellii*. It has been suggested but not confirmed that this may be related to vaginal administration of misoprostol.

There is no information about overdosage but this is unlikely to be an issue given the proposed single tablet use and packaging.

In assessment prior to medical abortion and in symptomatic women afterwards, the possibility of ectopic pregnancy needs to be considered as rupture and deaths have occurred when this diagnosis has been missed.

Fetal adverse effects are possible in continuing pregnancy after failed medical abortion.

Women need to be given information about what to expect and when and how to obtain both routine follow up and urgent care after medical abortion either in the first 49 days of gestation or in the second trimester.

The sponsor's Clinical Safety Overview including the summary of clinical safety and the summary of the Chinese literature are appropriate subject to the following minor points:

- The transfusion rate is quoted as 0.5-1%. This seems high for medical abortion up to 49 days gestation although it may be reasonable for second trimester termination of pregnancy. The evaluator recommended separating them out for the two gestational periods (1-2:1,000 up to 49DA and around 4:1,000 in the second trimester). A rate of 0.1-0.2% was quoted in another part of the sponsor's submission.
- The statement that patients must remain within access of the treatment facility for 2-3 weeks after the procedure seems unrealistic and perhaps unnecessary. The experience recorded in the literature with loss to follow up suggests remaining nearby to be an unrealistic request. While women should certainly be encouraged to keep in touch with the treatment facility, they need good information about what to expect, how to get advice at any time of day or night and to be provided with information that will assist their usual health professional to provide ongoing care as necessary. The complications which may arise unexpectedly can usually be managed by any facility which can provide care for early pregnancy and miscarriage.
- Avoiding the unlabeled vaginal route of administration may or may not reduce risk the risk of *Clostridium sordellii* infection. The further comment in the sponsor's submission that antibiotic prophylaxis may reduce risks is hypothetical in respect of *Clostridium sordellii*.

List of questions

Efficacy

The sponsor was asked to provide a listing of any studies excluded from the efficacy and safety evaluation solely because of "No detailed data recorded about side-effects during mifepristone treatment" (sponsor's submission)

Clinical summary and conclusions

Clinical aspects

Pharmacokinetics

In the evaluator's opinion the two studies were appropriately designed and conducted and adequately established bioequivalence between Mifepristone Linepharma and Mifeprex® and Mifegyne®, whether or not the "statistical outlier" value is excluded in calculating C_{max} for Study CAL052015-002.

Mean C_{max} for all three drugs was in the range 2335-2686 ng/ml (2.3-2.7mg/L), occurring at 0.75-0.88 h, with a half-life of 35.7-38.4 h. These values are consistent with those reported in the literature. For Linepharma's mifepristone the values for C_{max} were 2.3 and 2.7 mg/L in the two studies, with the peak concentration detected at 0.75 h in both studies and half-life 36.5 and 38.4 h. For Mifeprex® the results were 2.5 mg/L, 0.88 and 35.9 h and for Mifegyne® 2.4 mg/L, 0.75 and 35.7 h, respectively.

Mifepristone is rapidly absorbed and is metabolised in the liver with largely faecal excretion.

The proposed product information presents a reasonable summary of the pharmacokinetic properties of mifepristone. The higher of the values of C_{\max} and half-life from the two bioequivalence studies have been used in the product information rather than a mean or range. While some of the parameters are sourced from detailed review studies, the elimination and terminal half-lives of 18 and 90 h, respectively, are sourced from the European and American product information documents.

Pharmacodynamics

The pharmacodynamics of mifepristone are well described in the literature and appropriately summarised in the application. In summary, mifepristone is a synthetic steroid with antiprogesterone effects which competes with progesterone for receptor binding. When administered during pregnancy mifepristone increases decidual prostaglandin release, sensitises the myometrium to the contraction inducing activity of prostaglandins and induces cervical ripening. It also has antiglucocorticoid and weak antiandrogenic activity but these are not clinically relevant in women with normal adrenal function at the proposed dosages.

Clinical efficacy

Mifepristone used together with prostaglandins has a higher efficacy in the induction of abortion with more rapid effect than mifepristone alone (up to 80%), prostaglandins alone (up to 88%) or prostaglandins with methotrexate (up to 2-3 weeks for effect).

Several large well-conducted studies have demonstrated a single dose of 200 mg mifepristone to be of equivalent efficacy to 600 mg (the dose registered in several countries) when combined with a variety of prostaglandin regimens to induce early medical abortion. This conclusion is also supported by the Cochrane review¹⁵. A 50 mg dose has a lower efficacy than 200 mg (87.6% compared with 92.3%) and 100 mg doses have not been adequately investigated.

Many prostaglandin regimens have been studied. They were not systematically examined in this application which focused on oral misoprostol regimens up to a gestation of 49 days. It was nevertheless clear from the material in the sponsor's application that efficacy of the proposed prostaglandin regimens is likely to be less after 49 days, that is outside the proposed indication.

An interval of 36-48 h between mifepristone and misoprostol is conventionally used. Several studies have examined shorter intervals but intervals of 24 h or less have a lower efficacy than 36-48 h intervals for the oral misoprostol regimens proposed in the application (90% versus 97%, 50% versus 91%). Some shorter intervals appeared to hold promise for regimens including vaginal administration of misoprostol.

While gemeprost was demonstrated to be a safe and effective option, recent studies have largely examined misoprostol, which is associated with equivalent outcomes, is stable at room temperature, can be administered by several different routes and is more cost effective.

The proposed regimens of oral misoprostol, 800 µg in single or divided doses or 600 µg, administered 36-48 h after 200 mg mifepristone result in complete abortion rates of 93-98%, with the lowest lower 95% CI, where reported, 89%.

For the second trimester, two small studies found significantly reduced induction-abortion intervals with mifepristone pretreatment compared to none or Dilapan. A randomised controlled trial found equivalent abortion-induction intervals and abortion rates within 24 h with 600 mg and 200 mg mifepristone doses prior to vaginal misoprostol in the second trimester.

Several studies reported prostaglandin regimens used in the gestation range of 12-24 weeks associated with median induction-abortion intervals in the range of 5-8 h and over 90% of women aborting within 24 h. Surgical evacuation was needed in 10-12%, with some studies reporting rates as high as 20-30%.

Second trimester prostaglandin regimens were not systematically examined in the application and no regimen is recommended.

In general, the evolving evidence should be considered in choosing a prostaglandin regimen.

In summary, 200 mg mifepristone is the recommended dose prior to prostaglandin regimens for medical abortion up to a gestation of 49 days and in the second trimester. Up to 49 days the proposed regimens of 600 µg oral misoprostol or 800 µg in single or divided doses, administered 36-48 h after mifepristone result in a complete abortion rate of 93-98%. In the second trimester the addition of 200 mg mifepristone prior to prostaglandin regimens reduces the induction-abortion interval and the total dose of prostaglandin required.

Clinical safety

The safety of mifepristone in medical abortion regimens has been well established in extensive international clinical use, with the issues of concern well identified. The safety of mifepristone needs to be considered in the context that abortion by any method carries a degree of risk, as does pregnancy and childbirth; to some extent in the consideration of mifepristone and prostaglandin the risks and complications of the procedure of medical abortion are being attributed to the drugs used. The main alternative way of achieving early abortion, that is surgery, also carries risks and is generally subject to less systematic scrutiny.

Abdominal pain and vaginal bleeding are intrinsic to the procedure and vaginal bleeding may result in a need for surgical evacuation of the uterus, occasionally urgently. This rarely but occasionally happens beyond 2-3 weeks after the procedure. There is a recognised failure rate of the procedure, which means that follow up is essential to ensure that abortion has been successful. Up to around 7% of women will need surgical intervention after medical abortion up to 49 days gestation. This should be considered against the 100% surgical intervention rate of the main alternative to early medical abortion. It should also be noted that the rates of surgical intervention after medical abortion depend very much on the clinical timelines and endpoints chosen. Around 10-20% of women will need uterine evacuation following second trimester medical abortion.

Common adverse events are uncomfortable but self limiting and not serious, many likely to be related to prostaglandin rather than mifepristone itself. These include nausea, vomiting, diarrhoea, fever, chills, dizziness and headache.

More serious complications such as need for blood transfusion occur in around 1-2:1,000 prior to 49 days gestation and more frequently, around 4:1,000 in the second trimester.

Uterine rupture has been rarely reported in second trimester abortion and clinicians should consider individual risk factors and pay careful attention to appropriate prostaglandin regimens to minimise this risk.

Serious infection is very rare but deaths have occurred in North America following toxic syndrome associated with *Clostridium sordellii*. It has been suggested but not confirmed that this may be related to vaginal administration of misoprostol.

There is no information about overdosage but this is unlikely to be an issue given the proposed single tablet use and packaging.

In assessment prior to medical abortion and in symptomatic women afterwards, the possibility of ectopic pregnancy needs to be considered as rupture and deaths have occurred when this diagnosis has been missed.

Fetal adverse effects are possible in continuing pregnancy after failed medical abortion.

Women need to be given information about what to expect and when and how to obtain both routine follow up and urgent care after medical abortion either in the first 49 days of gestation or in the second trimester.

Benefit risk assessment

Benefits

Mifepristone is well established as an essential component of medical abortion regimens, including up to 49 days gestation and in the second trimester. This application establishes the bioequivalence of Mifepristone Linepharma with Mifeprex® and Mifegyne® which have been registered for at least one and two decades respectively and with which there is extensive international experience.

In the first 49 days of pregnancy a 200 mg dose of mifepristone followed 36-48 h later by a suitable misoprostol regimen results in at least 93% complete abortions without a need for surgical intervention, thus avoiding surgery and analgesia for those women who prefer this method. It can be acceptable for prostaglandin to be self administered and the abortion to take place at home if this is the woman's preference and there is adequate support and access to emergency care if needed.

In the second trimester, treatment with 200 mg mifepristone 36-48 h prior to an evidence based course of prostaglandins decreases the induction-abortion interval, reducing prostaglandin dosage required and increasing the proportion of women who will abort inside 24 h.

Risks

Pain and bleeding are to be expected as part of any abortion procedure: they are managed by providing adequate information and analgesia as needed.

The risk of ongoing pregnancy is up to around 1% in most studies prior to 49 days gestation; follow up must be planned and undertaken to ensure that any continuing pregnancies are identified and women are offered an alternative method of abortion. If a woman then decides to continue with her pregnancy, she needs to be advised to have the pregnancy monitored, as fetal adverse effects of mifepristone and prostaglandins are possible; the evidence does not support termination for that reason alone.

When the misoprostol regimens proposed in this application are used after mifepristone up to 49 days gestation, up to around 7% of women will need surgical evacuation of the uterus, mostly because of prolonged or heavy bleeding, this proportion tending to fall with increasing experience of the practitioners. A minority of these procedures will be needed on an urgent basis because of heavy bleeding, usually within the first two weeks after the procedure but occasionally later. Women need to be informed about what to expect and when and how to seek assistance at any time of day or night.

Some 10-20% of women may need manual removal of the placenta or surgical evacuation of the uterus after second trimester termination of pregnancy.

Approximately 0.1-0.2% of women will have enough bleeding to require blood transfusion after early medical abortion, up to around 0.5% in the second trimester.

The risk of serious infection after medical abortion is less than 1%, most infections being treated with complete recovery. There are very rare case reports of fatal toxic shock syndrome.

There are several case reports of ectopic pregnancy including deaths due to rupture of ectopic pregnancy; while not caused by medical abortion, the evolution of symptoms and rupture in these cases follows failure to recognise ectopic pregnancy during the pre-abortion assessment. The best prevention is confirmation of intra-uterine pregnancy prior to abortion by any means.

Overall mortality after early medical abortion is likely of the order of 1:100,000 (9, 557), which compares with around 12.9:100,000 for term delivery (626). Mortality after surgical abortion in the first trimester is likely similar to that for medical abortion or possibly lower, based on very rare events.

Adverse events including nausea, vomiting, diarrhoea, headache, fever, chills and fatigue are very common (>10%) during medical abortion. Most of these are more common after prostaglandin than mifepristone in studies which have separately assessed them; they vary according to route of administration of misoprostol. They are usually transient and self-limiting, although of course unpleasant for women.

Commentary on prostaglandin regimens

The prostaglandin regimens proposed in this application are reasonable and have established efficacy up to 49 days gestation. However, they are not the only evidence based regimens and they are not appropriate after 49 days when alternative evidence-based regimens should be used, for example as recommended by the RCOG¹⁷ or evaluated by the Cochrane reviews^{15, 16}.

It is noted that Gemeprost (Cervagem®) is a prostaglandin registered for use for “therapeutic termination in patients in the second trimester of gestation” and therefore currently available to be used with mifepristone in Australia. Current evidence would suggest that alternative regimens to the approved dosage scheme could be considered.

While a number of prostaglandin regimens were considered in the application, it did not systematically examine all options including buccal, sublingual or vaginal routes of administration nor did it examine regimens suitable for gestations beyond 49 days.

It is likely that evidence will continue to evolve and prostaglandin regimens will continue to be refined, more rapidly than can reasonably be explicitly defined in regulatory information. Those clinicians already prescribing mifepristone have demonstrated their preference to use misoprostol in current evidence based protocols, rather than necessarily those registered in other countries^{18,19,20}. They are likely to continue this practice, which is appropriate to this clinical problem.

In the opinion of the evaluator, for these reasons prostaglandin regimens should not be fixed and clinicians should be encouraged to use current evidence based regimens as recommended and updated by appropriate professional bodies.

Commentary on second trimester abortion

The evolution of treatment regimens for second trimester abortion is very different from the early first trimester situation and is really an old obstetric problem of how to induce labour at a gestation when the uterus is normally not very responsive to oxytocic agents, whether this be after spontaneous fetal death or for abortion.

In the early first trimester, researchers in the 1980s were looking for a sufficiently effective technique to avoid surgery for abortion. These efforts were focused on the early weeks of pregnancy, when the gestation sac is small and the process of expulsion relatively brief, akin to that of miscarriage. From 9-13 weeks gestation the dominant method of abortion remains surgical, probably because the surgical procedure is still relatively simple and straightforward and the experience of medical abortion is more unpleasant, although it has been established that medical abortion can be safely undertaken at these gestations if it is the woman's preference. However the availability of

second trimester surgical abortion is generally limited as it is a more complex procedure than in the first trimester, requiring particular training and skills.

In the second trimester, medical methods involving prostaglandins, for instance extra-amniotic prostaglandins and later vaginal gemeprost, were already being used in the 1980s, so the early work involved adding pre treatment with mifepristone to existing regimens (see for example 532 and 570). Once mifepristone was routinely used prior to prostaglandins, further work was and continues to be done modifying the prostaglandin regimens with a view to developing optimal combinations.

In Australia, the alternative to second trimester abortion using mifepristone is currently usually abortion with prostaglandin alone. Women having second trimester medical abortions without mifepristone, most commonly after diagnosis of severe fetal abnormality, can expect to have a more protracted and therefore unpleasant experience of painful contractions than those who are prescribed mifepristone prior to prostaglandin.

When mifepristone becomes available it is used as pre treatment prior to prostaglandins, which would otherwise be used alone. This practice change was described by Dickinson et al²⁰, notably using a higher misoprostol dosage and frequency with mifepristone than previously without. Those clinicians and hospitals in Australia without access to mifepristone continue to use prostaglandin only regimens to induce second trimester abortion when indicated, although the recent evidence on which to base these regimens is now more slender than that incorporating pre-treatment with mifepristone.

The Cochrane review¹⁶ suggests that the question of optimal prostaglandin regimens in the second trimester remains unresolved, but expert bodies such as the RCOG have been able to make recommendations¹⁷. This is clearly an evolving clinical area; women will continue to need midtrimester abortions while it evolves; surgical options will be unavailable for many; clinicians will therefore use available evidence based medical regimens.

For these reasons, in the evaluator's opinion the expression of the second indication in the application is appropriate and the non recommendation of a specific prostaglandin regimen is defensible. Mifepristone in these circumstances could be conceptualised as priming for the induction of labour. For the same reasons, the evaluator thought that the currently registered gemeprost could appropriately be used after mifepristone, despite the fact that its PI does not mention mifepristone. Having said that, the nature of the published evidence and of existing clinical practice and experience is such that clinicians are more likely to prescribe misoprostol 'off-label'.

It can be expected that registration of mifepristone would result in the great majority of cases of use being in the early first trimester. While a minority would be in the second trimester, these cases are likely to be managed by specialist services with considerable experience in the use of prostaglandins, usually misoprostol, for second trimester abortion.

Balance

The balance of benefit and risk for mifepristone for early medical abortion must be seen in its context, the alternatives being less effective methods (all at this time 'unlabelled') or surgical abortion. In making this decision, women take into account the anticipated experience of the method for them, the efficacy of the method and the adverse events that are likely and possible. To do this they need good balanced information. For some it is important to avoid anaesthesia and surgery, preferring an experience that may seem to them more natural and leave them feeling more in control. Others prefer the planned timing and greater predictability of surgery and may prefer to be anaesthetized.

There is considerable evidence that up to 9 weeks of pregnancy (63 days gestation) many women needing an abortion prefer the medical option. Combination regimens of mifepristone with prostaglandin have the greatest efficacy and are preferable to regimens

of prostaglandin alone or methotrexate with prostaglandin. There is no alternative to mifepristone with comparable efficacy available in Australia, so that until mifepristone is available choice of method of abortion is restricted for most women.

For second trimester abortion the balance of benefit and risk for the use of mifepristone is usually weighed against alternative regimens of prostaglandins alone. Although there are not reliable data, surgical abortion in the second trimester is not widely available. Different regimens for second trimester abortions may not have different adverse event profiles but the main benefit of regimens including mifepristone is a shorter induction-abortion interval, that is, a shorter period of experiencing painful uterine contractions, exemplified by reduced prostaglandin requirements and a greater proportion of women aborting within 24 h. This is an important benefit at what is often a very difficult and distressing time for the patient.

In summary, from a patient perspective, the availability of mifepristone improves the available treatment options and choice of method has been shown to improve satisfaction with treatment.

Clinicians in Australia have been prescribing mifepristone under the authorised prescriber scheme and have demonstrated that there is substantial clinical demand for these options. Mifepristone has been used in the first trimester up to 63 days, that is, beyond the 49 days of the first indication of this application. It has also been used in the second trimester. For both indications, evidence based misoprostol regimens have been used but not those proposed in the application.

From a population health point of view, the introduction of medical abortion regimens does not appear to affect abortion rates but the proportion of abortions done medically increases over time, with a shift in service provision from the operating theatre to the outpatient clinic.

Conclusions

The overall benefit-risk balance of mifepristone for medical abortion up to 49 days gestation is positive, provided that it is prescribed as part of evidence based regimens, by adequately trained clinicians, to informed women who prefer this method, with written informed consent and access to 24 hour advice, emergency care and follow up until the procedure is complete.

In the second trimester the overall benefit-risk balance of mifepristone prior to prostaglandin regimens is positive, provided that it is prescribed as part of evidence based regimens and that abortion is conducted in a health care facility by suitably trained clinical staff with access to operating theatre services as needed.

Recommended Conditions for Registration

Mifepristone should be registered subject to the following conditions:

- It should only be administered for abortion after written informed consent is obtained.
- Women should be provided with written information about what to expect after first trimester medical abortion and how to obtain advice and emergency care on a 24 hour basis.
- Second trimester termination of pregnancy should only be undertaken by suitably trained staff in a health care facility with access to operating theatre facilities if needed.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of Ongoing Safety Concerns which are shown at Table 13.

OPR reviewer comment

Delayed diagnosis of an ectopic pregnancy may occur as a result of use of the medical method in very early pregnancy. As mentioned in the clinical evaluator's report there is no evidence that use of the medical method causes ectopic implantation of the conceptus. However, given the difficulty of diagnosing some ectopic pregnancies and the catastrophic consequences of missed or late diagnosis including death, the sponsor should include the Ongoing Safety Concern: 'Missed ectopic pregnancy' as an Important potential risk.

In the RMP, emphasis is placed on the safety concerns related to the use of mifepristone in early pregnancy. Amplified safety concerns with respect to infection, bleeding or uterine rupture and increased mortality are mentioned in tables of the RMP but the magnitude of the increased risk and the relative frequency of higher risk events have not been clearly explained.

Insufficient safety information is presented in the RMP for the use of mifepristone in the adolescent age group. The sponsor was requested to include 'Use in adolescents (<18 years of age)' as Important Missing Information.

Table 13. Ongoing Safety Concerns

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

Pharmacovigilance Plan

The sponsor has proposed routine pharmacovigilance activities to monitor all the specified Ongoing Safety Concerns, with special attention in Periodic Safety Update Reports (PSURs) for all the specified Important potential risks, Important missing information and the Pharmacological class effect. The sponsor did not provide a description of the routine pharmacovigilance system but instead advised that it was available on request.

The sponsor was requested to provide details of the routine pharmacovigilance activities relied upon in this section of the RMP. In addition the sponsor was asked to provide evidence that the proposed routine pharmacovigilance system is consistent with the

activities outlined in relevant TGA adopted EU guideline²⁴. No comment regarding the adequacy of these activities can be made at this time.

The sponsor should include 'Missed ectopic pregnancy' as an Important potential risk and 'Use in adolescents (< 18 years old). It was recommended that these Ongoing Safety Concerns be monitored by routine pharmacovigilance activities with special reference in the PSURs.

It was recommended the sponsor develop a Registry for the use of mifepristone and misoprostol to further determine the safety profile of this combination. In addition, registry data may provide additional clarification around the Important potential risks including Drug interactions, and Exacerbations of asthma which may not be severe but nevertheless more difficult to control. The registry mentioned by the sponsor is a prescriber registry, not a patient registry, and this is not considered to be a pharmacovigilance activity.

The summary tables of the RMP should be amended to incorporate the above recommendations.

Use beyond the first trimester of pregnancy should be given separate consideration in PSURs.

The sponsor indicates PSURs will be submitted routinely to the TGA as required. It was recommended that PSURs be submitted 6 monthly with the data lock date of no more than 60 days in order that the most contemporary information is presented.

Risk minimisation activities

The sponsor did not provide specific comment regarding the need for risk minimisation in the RMP but did indicate routine risk minimisation activities were considered to be sufficient.

OPR reviewer comment

It was recommended that the sponsor amend tables in the RMP to indicate that routine risk minimisation activities alone are insufficient to appropriately mitigate all the specified Ongoing Safety Concerns and to reflect the proposed use of additional risk minimisation activities outlined in 'Informed Consent, Compliance to the Method and Follow-up' and 'Training of Medical Practitioners' of the RMP.

Following marketing approval for Mifepristone Linepharma 200 mg and GyMiso® 200 µg tablets in Australia, the sponsor proposes to distribute these medicines to appropriately qualified medical practitioners for the purpose of following the approved protocols for the medical termination of first trimester pregnancy. Use of mifepristone as an adjunct to prostaglandin analogues for second trimester terminations is very likely to occur with admitted patients in a hospital setting, thus the M4 Med Ed Programme will focus on education for the use of the method for first trimester terminations. Medical education will be offered by the sponsor to appropriately qualified medical practitioners and the healthcare staff of their clinics to ensure that this information is delivered to women undergoing treatment.

The M4 Med Ed plan has been drafted by the Marie Stopes International Medical Development Team to ensure, to the extent practical, that the Medical Method of termination is used in Australia responsibly and appropriately. The plan has been designed to limit the availability of these medicines to appropriately qualified and resourced medical practitioners and to ensure that medical practitioners, health care

24 3.1.2 Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)

professionals and patients have access to appropriate information regarding the safe and effective administration of Medical Method.

The elements of the M4 Med Ed Programme include:

- 1) Access and distribution: to ensure that only appropriately qualified health care professionals have access to Mifepristone Linepharma 200 mg and GyMiso® 200 µg tablets.
- 2) Education: provision of information regarding the appropriate use of the Medical Method including follow up to medical practitioners, other healthcare professionals and to patients.
- 3) Informed Consent: provision of pre printed Information Sheet and Patient Agreement to health care professionals to ensure that information for patients is available to assist the provision of informed consent by patients.
- 4) Product labelling and packaging and Consumer Medicine Information: inclusion of a 24 h toll free number staffed by registered nurses and website URL; to provide additional information to patients in an accessible and easy to understand format.
- 5) Monitoring: to test that the objectives of the educational programme are being met with healthcare professionals and patients. Periodic review of the pharmacovigilance database maintained by MSIA in Australia to ensure adverse event reporting is not unusual for particular centres relative to Australia as a whole.

MSIA plans to distribute mifepristone only to Australian medical practitioners that can provide evidence that they comply with criteria which is similar to the criteria used by the FDA for distribution of mifepristone in the USA. MSIA also intends to run a registry of qualified practitioners and to the extent reasonably practical, only distribute Mifepristone Linepharma 200 mg and GyMiso® 200 µg tablets directly to these practitioners that qualify and who have details entered into the registry. Both products for first trimester termination will be distributed to registered medical practitioners and or their nominated pharmacy.

It will be a requirement for all medical practitioners wanting access to Mifepristone Linepharma and GyMiso® to have completed the M4 Med Ed programme and to have passed the course evaluation. The programme may be offered remotely via learning modules on the Internet, or alternatively, may be provided directly to health care professionals as lectures by suitably qualified staff or agents of MSIA. The education modules included in Appendix 5 of the RMP are the versions of the education programme explaining the Marie Stopes Medical Process (MSMP) which is used in the UK and the modules discuss different medical methods for termination of pregnancy. These modules will be updated for use in Australia when the final Consumer Medicine Information (CMI) and PI of Mifepristone Linepharma 200 mg and GyMiso® 200 µg tablets are approved in Australia.

MSIA has developed an Information Sheet and Patient Agreement (ISPA) which outlines the medical method of termination procedure and some of the risks and side effects of treatment. This document can be used to provide written material to patients and can be used to gain written informed consent. The ISPA has been used extensively in Australia during the past 14 months and feedback has been sought on its effectiveness. It was provided to the TGA as part of MSIA's initial submission to provide mifepristone in Australia under the Authorised Prescriber scheme. It was evaluated by the Human Research Ethics Committee of the Queensland Clinical Trials Network and developed in accordance with the Vocabulary for CMI. It has been used within MSIA centres in Australia over the last 14 months in association with the use of mifepristone under the Authorised Prescriber scheme. MSIA routinely follows all patients and actively seeks feedback regarding the quality of the care provided by MSIA. The sponsor thus claims the ISPA has therefore been evaluated in clinical practice.

MSIA also intends to monitor the use of the Medical Method in Australia to evaluate the effectiveness of this programme. Monitoring may include:

- Periodic market research of medical practitioners and other healthcare professionals to determine the effectiveness of the education programme in meeting its objectives.
- Market research of consumers to validate the key messages in the website material and ISPA.
- In addition to routine pharmacovigilance, review of adverse event reporting on a centre by centre basis on the frequency and severity of adverse events relative to the country as a whole.
- Within MSIA centres continuous feedback on the services offered is sought from all patients, irrespective of the method used for termination of pregnancy.

The sponsor relies upon prescription only by registered prescribers in designated centres using secure distribution channels as a tool for risk minimisation for use in the early pregnancy indication. The sponsor did not provide any information regarding similar restriction of prescribing and distribution for use in second and third trimester pregnancy. The sponsor was requested to indicate if prescribers are required to be registered with the sponsor for access to mifepristone for the second and third trimester of pregnancy indications and if these prescribers are required to complete the same educational package or if additional or alternative materials are to be provided. If mifepristone is to only be available through secure distribution channels it is unclear how hospital pharmacies will access this for the later pregnancy indication. If mifepristone is to be available in hospital pharmacies, it is unclear how the sponsor can prevent prescribers not registered in their scheme from prescribing mifepristone for the early pregnancy indication.

The education package

The sponsor has advised that the M4 Med Ed plan has been drafted by the Marie Stopes International Medical Development Team. The sponsor should provide the background and qualifications of this team to demonstrate that appropriate clinical input has been factored into the M4 Med Ed programme. The IFSA has been described as having been evaluated in clinical practice. The outcomes of this evaluation and the tools for that evaluation have not been provided. Comment therefore cannot be made regarding the success of the program.

The sponsor was asked to elaborate in detail how the following criteria will be expected to be satisfied:

An eligible medical practitioner must:

- b) have the ability to assess the duration of pregnancy accurately;*
- c) have the ability to diagnose ectopic pregnancies*

The sponsor mentioned possible distribution to a nominated pharmacy. It was unclear if there will be bulk distribution to the medical practitioners at their clinics (or to their nominated pharmacy) who will then dispense the medicine, or whether the distribution will occur on a script by script basis. In the patient information p 27/57 'Common Misunderstanding 1', the sponsor states 'given the nature of a medication abortion, trained non-physician providers can be effective medication abortion providers. If other health professionals are to be prescribers the sponsor is requested to indicate how it will ensure these practitioners have sufficient skills for safe prescription of this medication. The sponsor is requested to indicate if the prescriber is using a nominated pharmacy for dispensing mifepristone whether the pharmacist will bear any responsibility for ensuring informed consent of the patient has been obtained before dispensing and that the script has been completed by a prescriber listed with the sponsor registry. If so, how will compliance

with this obligation be ensured. If not, how will the sponsor prevent scripts from prescribers who have not completed the education program from being filled.

The sponsor mentioned in 'Common misunderstanding 2' the clinician is reassured that 'while ultrasound is a useful tool both for gestational age dating and for identifying ectopic pregnancy, it is not essential'. The sponsor was asked to explain how clinicians may diagnose early ectopic pregnancy without the use of ultrasound, particularly as this is an essential criterion for the participation of a medical practitioner in the program. Furthermore, the patient provides consent for an ultrasound scan in the 'Medical Abortion – Mifepristone and Misoprostol Information Sheet'. If an ultrasound is unnecessary in the opinion of the sponsor, it should explain why the sample consent form includes consent for this investigation both pre and post procedure.

In the Draft Preparatory workbook, a urinary pregnancy test is recommended under a limited list of circumstances. The sponsor was requested to clarify the recommendations that will be made for pregnancy testing and which test type (urinary, serum qualitative or serum quantitative) will be recommended. The sponsor was requested to justify these recommendations in light of requirements such as the ability to diagnose ectopic pregnancy and the ability to determine if there are retained products of conception.

In the Draft Preparatory workbook the candidates are instructed that a separate pre-operative haemoglobin determination is not necessary as severe anaemia is easily detected on physical examination, and should be treated. The sponsor was asked to justify this statement as it applies to current Australian clinical practice.

It is stated in the Education package that Rhesus (Rh) testing is not essential however in the draft Product Information it is stated that 'In all instances, the use of mifepristone Linepharma 200 mg tablet requires rhesus determination and hence the prevention of rhesus allo-immunisation as well as other general measures usually taken during any termination of pregnancy.' The sponsor was asked to clarify this ambiguity.

The indication is for 'medical termination of a developing intrauterine pregnancyup to 49 days of amenorrhoea'. In the medical history to be noted on the sample client record card the clinician is to obtain the first day of the last period. This is one of multiple references throughout the education document to 9 weeks last menstrual period (LMP) gestational age. This is inconsistent with the indication in the application and must be amended.

Units of measure in the education package must be Standard International (SI) units; for example, a symptom of infection warranting evaluation by the physician is inappropriately discussed as sustained fever over 100.4 degrees.

The sponsor has provided an assurance that the education modules included in Appendix 5 of the RMP will be updated for use in Australia when the final CMI and PI of Mifepristone Linepharma 200 mg and GyMiso® 200 µg tablets are approved in Australia. The sponsor should also give an undertaking to submit these updated modules to the TGA for review before they are used and distributed in Australia. It is understood some of the points raised above may be corrected at that time. The sponsor was asked to clarify whether the update will only take place after approval of the change of indication for misoprostol. If so, the education strategy for the interim period should be provided.

The education material centres on the outpatient use of mifepristone for early first trimester abortion. Its use in later pregnancy abortion albeit likely in a hospital setting also merits an education strategy for health professional caring for patients in this setting. The sponsor is requested to outline their education plan for the inpatient setting.

Prescription outside the MSIA clinic framework

The sponsor's education package is focussed on the MSIA approach to medical abortion. The sponsor should provide an education strategy that is generalisable to all practitioners

who wish to use the product. The sponsor has applied for general registration of this product. The sponsor was requested to indicate whether clinicians who have successfully completed the training course but do not wish to or are unable to provide all services in accordance with the Marie Stopes framework be permitted to provide mifepristone and misoprostol to their patients.

The sponsor has not provided an education strategy for medical practitioners who practice outside the MSIA framework. The sponsor did not provide a strategy for assessing compliance with any guidelines provided in the education package for those practitioners in the general community. Specifically the sponsor did not address:

- How the sponsor will ensure health professionals will only be able to prescribe the product after completing the education program, for example, how they will prevent access through pharmacies holding stock for other prescribers who have completed the programme or via hospital pharmacies
- How the sponsor will ensure the health professional has the ability to assess the duration of pregnancy accurately and has the ability to diagnose ectopic pregnancies (given the educational material states that ultrasound is not essential)
- How compliance with the clinical principles outlined in the program will be ensured
- How the sponsor will ensure all patients provide written informed consent. The sponsor provides sample patient information and consent form already approved by the Queensland Human Research Ethics Committee, as an approved example but does not make clear whether prescribers in the general community will be required to obtain written consent from their clients and how compliance with this practice will be ensured.
- Where patients will be administered the medications (in a non- MSIA setting)
- How the sponsor will ensure adequate follow up of patients post administration of the product (to manage the important identified risks of bleeding, method failure and hypotension, and the Important potential risk of missed ectopic pregnancy).
- How the sponsor will collect adverse event data beyond spontaneous adverse event reporting outside the MSIA framework.
- Re-education requirements (whether there will be a programme to maintain currency on the prescriber registry)

The MSIA framework provides a 24 hour call centre for all its clients and the sponsor provides a free-call information service but the sponsor does not indicate if the prescribing practitioner will be expected to provide this level of care to all patients and how compliance with such a requirement would be ensured. In no place in the education package is the patient directed to their local emergency department for emergency care. A statement to this effect is recommended.

Potential for medication errors

Given the intended distribution to only registered prescribers the sponsor indicates there will be limited opportunity for members of the community to access large volumes of Mifepristone to enable an overdose to occur.

The sponsor provided information that it is unaware of any available evidence of off-label use in adults. The sponsor acknowledges there may be requests for use in adolescents. The sponsor states it expects informed consent will be obtained from the legal guardian of the patient in these circumstances.

OPR reviewer comment

The description of gestational age in terms of days of amenorrhoea may cause confusion for the prescriber and raises a potential source of error. LMP gestational age will reduce this risk as it is a commonly used term in clinical practice in Australia.

The single dose should be checked by the dispensing health professional before administration, thus there should be some mitigation against medication error. The medication is taken under the supervision of the health care professional. The medication regimen is outlined in the proposed patient information/consent form. Communication of the treatment plan comprises a component of the education package for prescribers. Medication error would come under the scope of incidents requiring documentation and reporting to Marie Slopes International Australia. The sponsor was requested to report all notified medication errors to the TGA.

The potential for off-label use exists with the current indication of 49 days gestational age. Previous use under the Authorised Prescriber scheme allowed use to 63 days gestational age. This raises the possibility of continued use in patients with first trimester pregnancies of 49 – 63 days LMP gestational age. The sponsor has not given consideration in the RMP or in the educational materials to consent for this procedure obtained from ‘independent minors’.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the submitted European Union Risk Management Plan (EU-RMP) is applicable without modification in Australia unless so qualified:

Additional safety concerns

It was suggested that the information contained in ‘Informed Consent, Compliance to the Method and Follow-up’ and ‘Training of Medical Practitioners’ of the RMP be noted as additional to ‘Risk minimisation plan’.

Given the difficulty of diagnosing some ectopic pregnancies and the catastrophic consequences of missed or late diagnosis including death, the sponsor should include the Ongoing Safety Concern: ‘Missed ectopic pregnancy’ as an important potential risk. This safety concern requires specific consideration in the risk minimisation plan and the pharmacovigilance plan with special reference in PSURs.

Gestational age should be consistently described in all documents, including educational materials, sample patient case records, PI and CMI. Gestational age in terms of duration should be consistent in all documents including the educational materials. It should be described in terms used in clinical practice in Australia. It is recommended to the Delegate that this be the date from the beginning of the last menstrual period.

Insufficient detail is provided defining the specific safety concerns when mifepristone is used in termination of pregnancy beyond 49 days. The sponsor was requested to better define the risks of use in this group and to provide an English language translation of the main reference for this indication.

Insufficient safety information is presented in the RMP for the use of mifepristone in the adolescent age group. The sponsor was requested to include ‘Use in adolescents (<18 years of age)’ as Important missing information. This safety concern requires specific consideration in the risk minimisation plan and the pharmacovigilance plan with special reference in PSURs.

Pharmacovigilance Plan

The sponsor indicated that PSURs will be submitted routinely to the TGA as required. It was recommended that PSURs are submitted 6 monthly with the data lock date of no more than 60 days in order that the most contemporary information will be presented.

Use beyond the first trimester of pregnancy including off-label use should be given separate consideration in PSURs.

The registry mentioned by the sponsor (see Risk Minimisation section of this evaluation) is a prescriber registry, not a patient registry, and this is not considered to be a pharmacovigilance activity. It was recommended the sponsor put in place a mandatory registry of patients prescribed mifepristone.²⁵

It was recommended the sponsor develop a Registry for the use of mifepristone and misoprostol to further determine the safety profile of this combination. In addition, registry data may provide additional clarification around the Important potential risks including Drug interactions and Exacerbations of asthma which may not be severe but nevertheless more difficult to control.

Risk Minimisation

The sponsor should amend RMP tables to indicate that routine risk minimisation activities alone are insufficient to appropriately mitigate all the specified Ongoing Safety Concerns and to reflect the proposed use of additional risk minimisation activities outlined in 'Informed Consent, Compliance to the Method and Follow-up' and 'Training of Medical Practitioners' of the RMP.

The sponsor relies upon prescription only by registered prescribers in designated centres using secure distribution channels as a tool for risk minimisation for use in the early pregnancy indication. The sponsor did not provide any information regarding similar restriction of prescribing and distribution for use in second and third trimester pregnancy. The sponsor was requested to indicate if prescribers are required to be registered with the sponsor for access to mifepristone for the second and third trimester of pregnancy indications, and if these prescribers are required to complete the same educational package or if additional or alternative materials are to be provided. As mifepristone is to only be available through secure distribution channels please indicate how hospital pharmacies will access this for the later pregnancy indication. If mifepristone is to be available in hospital pharmacies, how will the sponsor prevent prescribers not registered in their scheme from prescribing mifepristone for the early pregnancy indication?

The sponsor has not given consideration in the RMP or in the educational materials to consent for this procedure obtained from 'independent minors'.

Education programme

Units of measure in the education package must be SI units for example, "symptom of infection warranting evaluation by the physician is sustained fever over 100.4 degrees".

The education material centres on the outpatient use of mifepristone for early first trimester abortion. Its use in later pregnancy abortion albeit likely in a hospital setting also merits an education strategy for health professional caring for patients in this setting. The sponsor was requested to outline their education plan for the inpatient setting.

If the product is approved for registration the sponsor should provide all updated Australian specific educational materials including patient consent forms for approval by the TGA post registration but before supply.

²⁵Sponsor comment: This point was resolved as discussed in the section *Specific Conditions Applying to these Therapeutic Goods* on page 89 of this AusPAR.

VI. Overall conclusion and risk/benefit assessment

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

The current application was largely literature based: no original efficacy and safety studies have been conducted to support the proposed indication but one bioequivalence study against each of a French mifepristone and a US sourced mifepristone tablet were included. Individual patient data were available only for the bioequivalence studies.

Quality

The quality evaluator notes that mifepristone is a steroid derivative with multiple chiral centres but which is presented as a single enantiomer. It is practically insoluble in water and at intestinal pH but is soluble at acid pH (below pH 3). The sponsor thus micronises mifepristone in the proposed tablets. No unusual excipients are present.

Mifepristone per se conforms to the US Pharmacopoeia. A shelf life of three years has been approved for the blister pack that contains a single tablet.

Two bioequivalence studies (Studies CAL2015-002 and CAL2015-001) compared Mifepristone Linepharma (test) doses of 1 X 200 mg tablet to Mifegyne tablets (reference) product (sourced in France) or to Mifeprex, Danco Laboratories tablets (reference) product (sourced in the USA). Both studies were of similar design.

Study No. CAL2015-001 compared Mifepristone Linepharma (test) doses of 1 X 200 mg tablet to Mifeprex, Danco Laboratories tablets (reference) product (sourced in the USA). These studies were of conventional single dose, open label, randomised, two treatment, two period, two sequence, two-way crossover studies design, conducted in healthy, fasted women of normal weight (aged between 18 to 39 years). Fifty-six women were randomised in each study. Forty eight women completed the study (this aligned with the expectation of a 15% drop-out rate). There was a 28 day washout period between doses. Not all enrolled volunteers finished the studies (four dropped out due to adverse events, four other women due to emesis, and of note vomiting occurred in 14.3% of subjects) and not all of the data in Study 01 were used.

The other study, Study No CAL2015-002) compared Mifepristone Linepharma (test) doses of 1 X 200 mg tablet to Mifegyne tablets (reference) product (sourced in France). Fifty-six women were enrolled and fifty of these completed the study. The dropouts were due to adverse events (n=5) or emesis (n=1).

The formulations in Study 01 met the criteria for bioequivalence. The formulations in Study 02 met the criteria for bioequivalence in terms of extent of absorption but not C_{max} (90% CI for ratio of C_{max} was 103.33 - 126.66%).

More detail on these studies is provided in the clinical evaluation report.

The evaluator suggested; "Given the pH dependent solubility of mifepristone, it seems possible that bioavailability might be lower in achlorhydric subjects."

Registration of Mifepristone Linepharma was recommended with respect to chemistry, quality control and bioavailability aspects.

Comments:

- At the 141st Meeting of the PSC (26 September 2011), the Subcommittee recommended that, subject to approval, the product should be presented as a composite pack with mifepristone and that the composite pack include appropriate and clear warnings and clear instructions for use. The proposed labels will need to be revised in this event. This is a reasonable risk management activity but it shall need to await registration of the two active components.

- The PSC also noted the risk of variable bioavailability with differences in timing of doses in relation to food.
- As mentioned, no study on the effect of food was submitted. This is unfortunate because the Delegate regarded it as plausible that food will affect the rate and extent of absorption by reason of raising gastric pH and by facilitating bioavailability in the event of a high fat meal. Moreover, the suggested dose of mifepristone has fallen over the past two decades, possibly increasing the risk of therapeutic failure if the extent of absorption is reduced. At the least, Mifepristone Linepharma should not be taken within 2 h of a meal the Delegate suggested.²⁶
- Mifepristone Linepharma was shown to be of acceptable quality and to be bioequivalent to a product that is likely to have been used for the purpose in the USA and to be absorbed to a similar extent as the one that is sold in France. However, it is inexplicable that there are slight differences in the bioavailability parameters as reported by the quality and clinical evaluators, given that they are both quoting the applicant's data.

Nonclinical

The data that were submitted was comprised entirely of published literature; overall the published literature was adequate. See the note on GLP in the nonclinical report.

With regard to pharmacodynamics, misoprostol preferentially binds to glucocorticoid receptors, "displaying nanomolar potency in receptor binding and cell-based functional assays *in vitro*". Efficacy in producing abortions was shown in five non human species (including cynomolgus monkeys). Synergistic effects with an older prostaglandin E₂ analogue, sulprostone were shown in guinea pigs.

Pharmacokinetic data were similar across several species, including humans.

Mifepristone is rapidly absorbed and is bound (97-99%) to plasma proteins, chiefly α 1 acid glycoprotein. This protein binding is saturable in humans at clinical doses. Mifepristone was found to act as a irreversible inhibitor of CYP3A4 in experiments with recombinant human enzyme. This suggests some potential for significant drug interactions. Excretion was via the faecal route, as metabolites. The principal metabolites of mifepristone, monodemethylated, didemethylated and hydroxylated derivatives, retain significant anti-progesterone and anti-glucocorticoid activity but reduced antiprogestosterone activity.

Mifepristone does not share metabolic pathways with misoprostol.

No potential was shown for genotoxicity or mutagenicity in the studies that were undertaken; carcinogenicity studies have not been done.

Mifepristone showed low acute toxicity by oral dosing in mice, rats and dogs.

Repeat dose toxicity to 6 months in rats and cynomolgus monkeys showed effects on reproductive tissues, pituitary and adrenals. A study in female rats suggested that the effects on the reproductive tissues were reversible. Also noted were effects on thyroid, the liver and the kidney. However, only the high dose groups exceeded clinical exposure levels (see table of the estimated exposure ratios in these studies under Nonclinical Findings above).

Some teratogenic potential was shown in several species; this is considered plausible and possibly related to the effective withdrawal of progesterone, for example, to the uterus.

²⁶ Sponsor comment: The approved PI states: "It is recommended that Mifepristone Linepharma should not be taken within 2 hours of a meal."

Some changes to the product information document, the consumer medicines information document and the safety specification of the Risk Management Plan were suggested.

Registration was not opposed on nonclinical grounds.

Comments:

Carcinogenicity studies are not required for this single use agent. Mifepristone's effects on reproductive tissues, pituitary and adrenals might have been consistent with the respective receptor antagonistic effects or enhancement of the action of oestrogen.

Clinical

The evaluation report has addressed the indication in first trimester abortion as originally proposed, "In sequential combination with a prostaglandin analogue up to 49 days of amenorrhoea (DA)."

The evaluator discusses the context of use of drug-induced abortion: "For a woman the choice between surgical and medical abortion involves balancing the pros and cons of surgery and anaesthesia against those of a treatment with a slightly lower efficacy, involving more pain and bleeding, which allows some women to feel more in control but is perceived as more unpleasant by others. There is good evidence that satisfaction with treatment is greater when women are able to have their preferred method." [Reference 572 is presumably the basis for this.]

Pharmacodynamics

The applicant has relied on a review article to support the statements in the proposed PI. The evaluator summarises this in the clinical evaluation. When administered during pregnancy mifepristone increases decidual prostaglandin release, sensitises the myometrium to the contraction inducing activity of prostaglandins and induces cervical ripening.

Supportive clinical studies are mentioned in the report; it is observed that doses of mifepristone of up to 800 mg given alone are insufficiently efficacious to produce an abortion 49 days of gestation.

Comments:

The minimal effective dose to produce an abortion 49 days of gestation is not known but available data support the use of 200 mg in preference to previously used higher doses. See clinical evaluation above for the evidence to support the dose to be used with misoprostol and the dosing interval of 24-48 h between mifepristone and misoprostol to produce an abortion 49 days of gestation.

Bioequivalence

As stated by the evaluator, "The demonstration of bioequivalence is a necessary foundation on which to base the use of published literature associated with the reference medicinal products, which comprises a major part of the application."

The two bioequivalence studies included evidence of independent ethics approval and compliance with Indian and international guidelines for medical research, including the International Conference on Harmonization E6 'Guideline for Good Clinical Practice' (GCP) and the Declaration of Helsinki (Tokyo 2004). The studies were conducted in accord with TGA adopted EU guideline and the FDA guidance on the conduct of bioequivalence studies.

Study CAL052015-002

Both “per protocol” (PP, n=49) and “modified per protocol” (n=48) results were presented, the latter excluding one statistical outlier who had a very low C_{max} for the reference product (Mifegyne®). As mentioned by the quality evaluator, the former analysis is the valid one, so formal bioequivalence was not shown for C_{max} .

That is, the test and reference products are bioequivalent in terms of extent of absorption but not by C_{max} . The T_{max} values were reported to be quite similar (both had a mean value of 0.75 h).

Comment:

The clinical evaluator said, “The case for exclusion of a single value and presentation of a modified PP population analysis could be argued despite this being outside the guideline cited; if this were accepted, bioequivalence would be demonstrated according to the protocol and guidelines.” Post hoc data manipulation is not in accord with the adopted guidelines, neither is resort to secondary analyses of metabolites. However, the evaluator has also observed that the extent of absorption of mifepristone is acceptably similar. The elimination half-life in this and the next study was approximately 35 h.

Study CAL052015-001

The $AUC_{0-\infty}$ value was based on 47 participants after excluding one value in accordance with the pre defined approach to residual values; population parameters for C_{max} and AUC_{0-t} were presented for the 48 participants.

As reported, bioequivalence was established within acceptance limits.

No study was conducted to study the *effect of food* on the rate and extent of absorption of mifepristone after oral dosing. Studies in certain populations (elderly, children) are not relevant. The evaluator finds that there is a lack of specific information about the safety and efficacy of mifepristone in the presence of co morbidities and so makes some inferences about the effect of renal impairment (minor effects are expected) and hepatic impairment (impaired hepatic function is likely to have a bearing on its elimination), so the PI should recommend caution in renal failure and hepatic impairment.

The evaluator discusses some potential metabolic interactions involving CYP 3A4.

Overall, the evaluator found that the bioequivalence studies are adequate to bridge clinical efficacy and safety data that were generated using the Mifegyne® and Mifeprex® brands.

Phase III Studies

None of the studies has been identified in the application as pivotal.

The evaluator has summarised the available data in tabulations according to the two proposed indications.

Indication (1): mifepristone for medical abortion up to 49 days gestation

No study was identified as pivotal by the evaluator.

See Tables 7-10 in the clinical report for information on the dose finding of mifepristone, for studies pertaining to the interval between mifepristone and misoprostol and for a presentation of studies that contributed information on prostaglandin regimens and the interval to their administration.

However, two studies were considered to be pivotal in terms of the proposed dose, route and indication for the accompanying application to register misoprostol for use in this indication.

In that application, the studies are known as Studies 509 and 528. Study 509 does not appear to have been referred to in this application. [Please refer to the section in the AusPAR for GyMiso *Request for ACPM's Advice* for a summary of these two studies. Study

528 is particularly relevant to this application because it used the regimens proposed for registration in Australia. This study appears in passing in Table 9 in the clinical evaluation report of this AusPAR.]

The evaluator considers that a dose of mifepristone 200 mg appears to be adequate for this indication; it is not clear whether 100 mg is the minimal effective dose. "...virtually all studies published from 2001 onwards report on 200 mg doses of mifepristone." A qualitative appraisal of the studies submitted suggested that at least 24 h after dosing with mifepristone is needed before a prostaglandin can be administered; this should be more than 24 h for oral misoprostol. "When populations ≤ 49 DA were examined, all regimens with an interval between mifepristone and misoprostol >24 h and a dose of misoprostol ≥ 600 μ g (including 800 μ g in divided doses 2 h apart) had complete abortion rates of at least 93%."

Comment:

It is noted from Table 9 that buccally or sublingual misoprostol appears to be more likely to be successful than the same dose (800 μ g) given orally, based on indirect comparisons. The vaginal route of administration has not been sought for misoprostol for this indication. The weight of evidence supports the applicant's choice of a single dose of mifepristone 200 mg for this indication.

Indication (2): mifepristone for medical abortion in the second trimester

See Table 11 for a description of doses and accompanying prostaglandin regimens. It is notable that mifepristone 600 mg does not seem to be more efficacious than a dose of 200 mg; the follow-on dose of prostaglandin is relevant, however. References 532, 537 and 529 reported studies which used mifepristone 200 mg with gemeprost to follow. Dilapan is a device, a hygroscopic cervical dilator made of a hydrogel.

There is limited information on the optimal interval between the administration of mifepristone and the use of a prostaglandin, "In the absence of other evidence, it is appropriate to recommend the 36-48 h interval."

The evaluator discusses the potential role of misoprostol [which has not been sought]:

"Cochrane review: main results and authors' conclusions.

When used alone, misoprostol was an effective inductive agent, though it appeared to be more effective in combination with mifepristone. ... No randomised trials comparing doses of misoprostol were identified; however low doses of misoprostol appear to be associated with fewer side-effects while moderate doses appear to be more efficient in completing abortion...

Medical abortion in the second trimester using the combination of mifepristone and misoprostol appeared to have the highest efficacy and shortest abortion time interval²⁷."

"2004 RCOG guideline

For mid-trimester abortion (13–24 weeks of gestation) medical abortion with mifepristone followed by prostaglandin is an appropriate method and has been shown to be safe and effective...

27 However, the Delegate quoted from the discussion section of the same Cochrane review:

"The optimal dose of vaginally administered misoprostol is difficult to ascertain since there are no randomised studies comparing various dosing schemes for vaginal administration. Four randomised clinical trials showed that the induction to abortion interval with 3-hourly vaginal administration of prostaglandins was significantly shorter than 6-hourly administration without significant increase in side-effects (Comparisons 15 and 16).

There is insufficient data to make any gestational, age-specific recommendations on the dosage and regimen for abortion. Since the uterus becomes more sensitive to prostaglandins with increasing gestational age, reducing the dosage or frequency of administration should be considered at later gestational ages (Ho 2007). The age range considered in this review includes 12 through 28 weeks of gestation. Overall, from the design of the included studies, there is no indication for confounding by gestational age."

For mid-trimester medical abortion, a dose of 200 mg of mifepristone is adequate... Mifepristone 200 mg orally, followed 36–48 h later by misoprostol 800 micrograms vaginally, then misoprostol 400 micrograms orally, 3-hourly, to a maximum of four oral doses...

The following regimen is licensed within manufacturer's summary of product characteristics and is also appropriate for mid-trimester medical abortion:

Mifepristone 600 mg orally, followed 36–48 h later by gemeprost 1 mg vaginally every 3 h to a maximum of five pessaries.

This regimen is unlicensed."

Of Australian reports^{19,20} "The two reports of second trimester termination of pregnancy both used 200 mg mifepristone orally followed by an initial dose of 800 µg misoprostol vaginally after 24-48 h or 0-72 h and further doses of 400 µg orally 3 hourly. Rates of surgical intervention were high at 33% and 25%." Use of misoprostol in Australia has been via the vaginal route of administration.

The evaluator concluded, "Second trimester prostaglandin regimens were not systematically examined in the application and no regimen is recommended." "In the second trimester the addition of 200 mg mifepristone prior to prostaglandin regimens reduces the induction-abortion interval and the total dose of prostaglandin required."

Comment:

The evaluator concluded, in regard to second trimester abortion, "The evidence and recommendations for a 200 mg dose of mifepristone and a 36-48 hour interval between mifepristone and misoprostol are appropriate for both early and second trimester termination of pregnancy." Mifepristone followed by gemeprost is the likely feasible combination for use in Australia because only gemeprost will have this indication; Marie Stopes has not sought the indication for GyMiso. Gemeprost has the indication, "Therapeutic termination of pregnancy in patients in the second trimester of gestation." The preference for misoprostol over gemeprost may be understood in terms of logistical grounds (refrigeration is not needed), easier dosing schedule and lower cost. None of these is a relevant consideration, however.

The final quotation from the 2004 RCOG guideline is somewhat enigmatic because the "Summary of Product Characteristics" (UK) is a corresponding European document to the Australian PI.

The approved dosing regimen of gemeprost is, "Therapeutic Termination (Second Trimester of Pregnancy). One pessary to be inserted into the posterior vagina fornix at three hourly intervals to a maximum of five administrations. If termination is not well established after five pessaries, a second course of treatment may be started 24 h after the initial commencement of treatment." The evaluator mentions this in the report.

Prostin F2 alpha is a less likely therapeutic alternative and it has not been used with mifepristone. Neither gemeprost nor Prostin F2 alpha's PIs will refer to mifepristone, however, mifepristone's PI will have to refer to a prostaglandin analogue that is registered for use in midtrimester abortion.

Safety

As introductory remarks, the evaluator commented that the adverse event picture results from the procedure and the use of two different medicinal products as well as the fact that nausea, vomiting, dizziness and breast tenderness are common in normal pregnancy. Many of the common adverse events are highly subjective and both perceptions and reporting and ascertainment of adverse events vary between studies. Overall, there are greater risks associated with childbirth at term. The safety data includes a mix of published clinical trial data and postmarketing data.

Besides the many millions of doses of mifepristone that have been given in countries where it has been marketed, the evaluator notes that, "Over 25,000 mifepristone recipients are listed in the first trimester Tables 7-9 and 2,200 in the second trimester Table 11. The application safety review presents tables reported to represent 190,000 women exposed to mifepristone, mainly in 200 mg doses." In addition there have been numerous reviews based on post marketing data.

Bleeding is very common and is intrinsic to the process, "Up to 30-50% of women will have some spotting or bleeding after mifepristone and before prostaglandin, with up to about 3% of women in the first trimester aborting during this phase; most of those who have not already bled will have some bleeding within a few hours of prostaglandin administration. Most studies report a median duration of bleeding of around 12 days, with a range up to 60 days, some of which may be spotting. Some studies have reported that it is usual for 2-3 days of bleeding to be considered heavier than normal menses." In one review, perhaps at most 2.6% of women required curettage. Less than 1% required transfusion; the frequency is higher in mid trimester abortion but still <1%.

Serious adverse events include Infection, "In the table of adverse events endometritis is listed as common (1-10%), salpingitis and infection as uncommon (0.1-1%) and toxic shock syndrome as very rare (<0.1%)." See clinical evaluation for a discussion of international experience of serious infections. The link between vaginally administered misoprostol and Clostridial infections has been suggested but not established.

Therapeutic failure has been reported as up to 7% of cases when misoprostol is used with a prostaglandin analogue up to 49 days of amenorrhoea (DA). [For 49 days of gestation, the failure rate would be no less and is likely to be slightly greater]. Failure rates are slightly higher in second trimester abortion but referral for surgery is more likely than repeat dosing of prostaglandins.

In terms of managing risk, the evaluator opines, "While women should certainly be encouraged to keep in touch with the treatment facility, they need good information about what to expect, how to get advice day or night and to be provided with information that will assist their usual health professional to provide ongoing care as necessary. The complications which may arise unexpectedly can usually be managed by any facility which can provide care for early pregnancy and miscarriage."

Comments: Issues about the quality of the safety data include sensitivity and bias. However, the studies on first trimester termination of pregnancy include a published report of at least one Phase III registration study for the proposed regimen. Moreover, the events described in Table 12 are likely to be qualitatively accurate and to represent very common and common adverse events. The former include Gastrointestinal adverse effects. The latter include severe haemorrhage, spotting, endometritis, breast tenderness and fainting.

Conclusions and Recommendations of Clinical Evaluator

Some changes to the text of the product information document have been recommended.

The benefits of mifepristone relate to its efficacy, "In the first 49 days of pregnancy a 200 mg dose of mifepristone followed 36-48 h later by a suitable misoprostol regimen results in at least 93% complete abortions without a need for surgical intervention, thus avoiding surgery and analgesia for those women who prefer this method. It can be acceptable for prostaglandin to be self-administered and the abortion to take place at home if this is the woman's preference and there is adequate support and access to emergency care if needed.

In the second trimester, treatment with 200 mg mifepristone 36-48 h prior to an evidence based course of prostaglandins decreases the induction-abortion interval, reducing

prostaglandin dosage required and increasing the proportion of women who will abort inside 24 h.”

The risks are as discussed for adverse events.

In regard to using misoprostol in the second trimester, the evaluator comments, “In the opinion of the evaluator, for these reasons prostaglandin regimens should not be fixed and clinicians should be encouraged to use current evidence based regimens, as recommended and updated by appropriate professional bodies.”

Other Data

Marie Stopes’ Data:

Between September 2009 and August 2011 there had been 13,345 first trimester abortions and four known cases of infection. One of these was a fatal case. A separate series in South Australia¹⁹ reported six infections in 6,670 *surgical* and medical first trimester abortions.

TGA Data

Some information has been provided by the Experimental Products section of the TGA. These tabulated figures relate to the number of women prescribed mifepristone (all brands) as detailed in the table that immediately follows. As at 26 June 2012, 178 medical practitioners have a current authorisation under subsection 19(5) of the Therapeutic Goods Act 1989 to prescribe mifepristone for the termination of pregnancy. The prescribers are able to choose the supplier of mifepristone but the misoprostol that was chosen is almost certainly Cytotec.

Since its approval under the Authorised Provider scheme, a total of 832 reports of **adverse events** has been provided to the TGA as shown below (reports received to 25 June 2012), corresponding to use in 22,500 women. The data are related to both mifepristone and misoprostol, including the vaginal route.

Table 14. Adverse events provided to the TGA since approval under the Authorised Provider scheme

Adverse event	No.
Ongoing pregnancy following treatment requiring D&E or D&C	132
Significant postpartum haemorrhage - requiring transfusion	23
Retained products of conception requiring D&C or D&E	599
Cervical tear noted following initial dilatation	5
Uterine perforation or rupture	2
Nausea and vomiting	14
Infection/Suspected infection/Endometritis	29
Postpartum haemorrhage – not requiring transfusion	28
Abdominal Pain	6
Fainting, dizziness, vomiting	2
Dehiscence of caesarean section scar	2
Death - sepsis	1

Note: The detail contained in these AE reports varies greatly. The rate of reporting is probably not a true reflection of the number of events occurring. Authorised Prescribers in South Australia (SA) and those endorsed by the Queensland Clinical Trials Network Inc. Human Research Ethics Committees (QCTN HRECs) appear to have the best reporting systems in place.

Therapeutic failure and retained products are the commonest adverse events but the events more clearly and plausibly related to misoprostol include nausea and vomiting; faintness, dizziness and vomiting; and possibly uterine perforation and rupture.

Table 15. Total number of patients for whom RU486 has been prescribed

Reporting period (6 monthly)	No. patients supplied							
	NSW	Vic	Qld	SA	WA	Tas	NT	ACT
2006								
1 Jan to 30 June 2006	0	0	0	0	0	0	0	0
1 July to 31 Dec 2006	0		7	0	0	0	0	0
2007								
1 Jan to 30 June 2007	0	0	3	0	0	0	0	0
1 July to 31 Dec 2007	0	0	4	0	0	0	0	0
2008								
1 Jan to 30 June 2008	0	23	0	0	71	0	0	0
1 July to 31 Dec 2008	22	32	7	0	72	0	0	0
2009								
1 Jan to 30 June 2009	0	42	4	130	77	0	0	0
1 July to 31 Dec 2009	1154	412	323	187	356	0	0	0
2010								
1 Jan to 30 June 2010	1467	798	520	478	409	0	0	0
1 July to 31 Dec 2010	1669	989	847	449	659	0	0	0
2011								
1 Jan to 30 June 2011	1805	1189	931	589	952	0	0	0
1 July to 31 Dec 2011	1831	1467	1190	640	695	0	0	0

NSW=New South Wales; Vic=Victoria; Qld=Queensland; WA=Western Australia; Tas=Tasmania;
NT=Northern Territory; ACT=Australian Capital Territory.

Risk management plan

At the time of the Overview by the Delegate, the RMP was not yet fully satisfactory. Aspects of concern included:

- Risks/potential risks such as continuing pregnancy, missed diagnosis of ectopic pregnancy, use of misoprostol in adolescent females for which there are no data in regard to safety and efficacy; and,
- Adequacy of instruments to mitigate risk such as adequacy of professional training and accreditation; adequacy of the evaluation of the informed consent (Information Sheet and Patient Agreement form); and,
- Need for a patient registry to assess safety in use outside of the current tightly controlled environment with Marie Stopes.

It is evident that there has been some lack of agreement about the proposed indication (use in adolescents) and about a registry. However, the RMP evaluator was quite clear about this:

“It is recommended the sponsor develop a Registry for the use of mifepristone and misoprostol to further determine the safety profile of this combination. In addition, registry data may provide additional clarification around the Important potential risks including Drug interactions, and Exacerbations of asthma which may not be severe but nevertheless more difficult to control. The registry mentioned by the sponsor (see Risk Minimisation section) is a prescriber registry, not a patient registry and this is not considered to be a pharmacovigilance activity”.

Risk-benefit analysis

Delegate considerations

Method failure will occur in a significant minority of women. When this occurs, ectopic pregnancies will be over represented in these women. Added to method failure are risks that are not drug related but abortion related, such as infection, haemorrhage and retained products, there is a need for adequate risk minimisation. Therefore, the risk minimisation measures that include prescriber training, patient information and follow-up and a patient registry (at least for a few years) are supported. Clearly, mifepristone should never be used in circumstances where there is no ready resort to surgical intervention. The committee's comments are requested.

If registration proceeds, the implementation of an RMP satisfactory to the TGA will imposed as a condition of registration.

The use of a composite pack to support safe use in the first trimester indication was suggested by the Pharmaceutical Subcommittee. The Delegate supported this suggestion but it will have to be implemented after registration occurs.

Because Marie Stopes did not see fit to register GyMiso for the second trimester indication, misoprostol cannot be explicitly advocated as the prostaglandin to be used. The only reasonable choice would appear to be gemeprost, the indications of which are broad enough not to exclude use with mifepristone. Marie Stopes was alerted to this at presubmission meetings. The Delegate therefore amended the proposed indication accordingly. Prescribers may elect to use misoprostol as an unapproved use, as they have done hitherto, until Marie Stopes applies for the indication. This will be the advice given to third party correspondents.

Questions Addressed to the Advisory Committee on Prescription Medicines (ACPM)

Without wishing to limit or constrain the Committee's discussion or general advice, the following specific questions were asked.

1. There appears to be no reasonable basis for suggesting the routine use of antibiotics to prevent sepsis. Does the Committee agree? It is proposed that every effort be made instead to follow-up the women that receive mifepristone and misoprostol. Does the Committee have a view about this?
2. Is the committee satisfied that dose finding for both indications is adequate?
3. For the second trimester indication, is there sufficient evidence to support the use of mifepristone followed by gemeprost?
4. Is the proposal by the clinical evaluator to delete the precautionary statement on depression of glucocorticoid activity reasonable?

Proposed Actions

The application by Marie Stopes International Australia to register Mifepristone Linepharma uncoated, unscored tablets containing mifepristone 200 mg, supplied in single tablet blister packs should be approved.

The registered indication should be:

"Mifepristone Linepharma 200 mg tablet is indicated in women and adolescent girls of childbearing age for:

1. Medical termination of a developing intra-uterine pregnancy. In sequential combination with a prostaglandin analogue up to 49 days of gestation.
2. Preparation for the action of registered prostaglandin analogues that are indicated for the termination of pregnancy for medical reasons beyond the first trimester."

The product information and risk management plan should be modified to the satisfaction of the TGA.

The application was submitted for ACPM's advice.

Response from Sponsor

The sponsor has comments on the Request for ACPM's Advice (dated 4 July 2012) for the application to register Mifepristone Linepharma 200 mg tablet in Australia.

The comments relate mainly to aspects of the Risk Management Plan (RMP) discussed by the Delegate in the Overview. In the first paragraph, the Delegate states that "the current version is evidently not yet fully satisfactory", and lists several aspects. These points and those of the RMP Evaluator in "Summary of Recommendations" are addressed below, where the sponsor indicates agreement with the comments from TGA, and/or undertakings in respect of the comments.

1. RMP Issue: Evaluation of Informed Consent

The Delegate noted that an adequate evaluation of the informed consent (Information Sheet and Patient Agreement Form) should be confirmed, as risk mitigation.

The sponsor committed to undertake some testing of the material, for its ease of comprehension, prior to its publication and use.

2. RMP Issue: Use in Adolescents

The Delegate noted that it is evident that there has been some lack of agreement about the proposed indication (use in adolescents).

The sponsor was in agreement that the proposed indication is for use in females of childbearing age.

The RMP evaluator raised a question as to why information on the lack of data on use in adolescents was omitted from the safety specification in the RMP as “Important Missing Information”.

The sponsor added this information to a revised RMP submitted to the TGA. The acceptability of these revisions can be reviewed in detail with the RMP evaluator when the sponsor agrees the final RMP satisfactory to TGA.

3. RMP Issue: Missed Ectopic Pregnancy

The RMP evaluator recommended that “missed ectopic pregnancy” be included as an Important potential risk.

The sponsor agreed for this to be included in the final RMP satisfactory to TGA.

4. RMP Issue: Submission of PSURs

The RMP evaluator recommended PSURs be submitted six monthly with a data lock of no more than 60 days. It was also recommended that use of mifepristone beyond first trimester (including off-label use) should be given separate consideration in the PSURs.

The sponsor agreed to these recommendations for inclusion in the final RMP satisfactory to the TGA.

5. RMP Issue: Use of Additional Risk Minimisation Activities

The RMP evaluator recommended revision to the tables (Summary of planned minimisation actions) regarding use of additional risk minimisation activities.

The sponsor agreed for this to be included in the final RMP satisfactory to TGA.

6. RMP Issue: Educational Programme

The RMP evaluator recommended that the Educational Programme should emphasise that the proposed indication (that is, up to 49 days of gestation) for registration differs from that used under the Authorised Prescriber scheme (up to 63 days of gestation).

The sponsor agreed and would like to highlight that this distinction has been made in the Education Manual.

The RMP evaluator recommended that prescriber education be offered to all prescribers including RANZCOG qualified prescribers.

The sponsor committed to offer the educational programme to all prescribers.

The RMP evaluator requested clarification on the mechanism of supply and the safeguards to ensure prescriber training.

The sponsor noted that supply of Mifepristone Linepharma and GyMiso will be to hospital and retail pharmacies in a manner similar to other Prescription Medicines in Australia. Medical Practitioners will be able to prescribe Mifepristone Linepharma and GyMiso as for other Prescription Medicines in Australia. The sponsor will strongly recommend that all doctors participate in training before prescribing mifepristone and misoprostol. Medical practitioners who are fellows of RANZCOG or hold the Diploma of the RANZCOG (DRANZCOG) will be offered training even though they will have specialized in obstetrics and gynaecology. The sponsor noted that it is not possible to compel a medical practitioner to undertake such training, nor to comply with training. In practice, compliance with educational training will most likely be the cumulative result of the prospective offering from the sponsor, the prescriber's duty of care and the requirements of medical liability insurance. Further, it is the intention of the sponsor to apply to the Pharmaceutical Benefits Scheme (PBS) for listing of Mifepristone Linepharma and GyMiso and it may be possible to negotiate conditions on

supply via the Authority Prescription mechanism to include evidence of completion of adequate training.

The RMP evaluator requested clarification on how participants in the Educational Programme will be assessed and an undertaking for the educational materials to be reviewed by TGA prior to use in Australia.

The sponsor has prepared a comprehensive participant assessment tool for the Education Programme, which includes pre assessment, post assessment and case studies, and this tool will shortly be reviewed by a medical expert in the field. The sponsor was seeking accreditation for this program from RANZCOG, and would submit the application for accreditation such that participants will be able to obtain Continuing Professional Development points for completing the course. The Medical Education Programme will be delivered online and made freely available to all medical practitioners. Further information relating to this and education materials will be included in the RMP documents provided to TGA for review.

The RMP evaluator suggested an educational strategy should be considered for later pregnancy termination.

The sponsor notes this topic is covered in the Education Manual Section 9.1, which has previously been shared with the TGA. Use of mifepristone for termination of pregnancy beyond the first trimester is highly specialized and part of a multimodal treatment protocol where mifepristone is used as adjuvant therapy to medical or surgical procedures. These procedures are likely to be performed under the supervision of a specialist obstetrician and gynaecologist, who will be a member of the RANZCOG, and as such, will have advanced training. It should be noted that these clinicians are highly likely to be using mifepristone under the Authorised Prescriber programme in Australia for this indication at present, and will be very familiar with the use of the drug. Termination in second trimester is a minor indication with approximately 700 procedures performed each year in Australia (MBS code 16525). Irrespective, the sponsor undertook to offer training to all medical practitioners.

The RMP evaluator requested that the sponsor provide sufficient detail of a strategy for assessing compliance with any guidelines provided in the education package for those practitioners in the general community (that is, prescribers operation outside of a MSIA clinic).

The sponsor noted that MSIA is a clinic network and provides approximately 30% of the abortions in Australia each year. MSIA has requested to change sponsorship from MSIA to a separate legal entity called MS Health, a pharmaceutical marketing and distribution company, for supply in commercial phase. Importantly, irrespective of the identity of their employer, all medical practitioners who wish to prescribe mifepristone will be subject to the same opportunities for training, medical information and aftercare. Since a medical abortion involves a sequence of events over a number of days and where a patient is not under the continuous supervision of a healthcare professional, the sponsor provided the following elements to ensure that medical practitioners as well as patients have access to information and aftercare that are designed to improve compliance with guidelines. The elements of this programme are shown in Table 16.

Table 16. Programme Details

<i>Element provided by Sponsor (to be MS Health)</i>	<i>Available to</i>	<i>Assessment of compliance</i>
<i>Education Programme – on line</i>	<i>Any medical practitioner or other health care professional in Australia</i>	<i>Review of the education assessment records.</i>
<i>Prescriber Registry</i>	<i>Record of all medical practitioners that successfully complete training.</i>	
<i>Information Sheet and Consent Form – available in print and on line</i>	<i>Any healthcare professional in Australia</i>	
<i>Product Information and Consumer Medicine Information</i>	<i>PI: Any health care professional in Australia CMI: in product packs, available on Sponsor website and via pharmacy dispensing software</i>	
<i>24 hour nurse after care</i>	<i>1300 telephone number is printed on product packaging, PI, CMI, Information Sheet and Consent Form and Sponsor website.</i>	<i>All calls are answered by qualified nurses who are trained in the use of the medical method of abortion. All calls are recorded in a retrievable database and monitored. All calls are referred to the Medical Affairs and Pharmacovigilance team for review. (Note 30% of MSLA clients treated with mifepristone under the Authorised Prescriber programme utilize this service at present).</i>
<i>Follow up text message with key symptoms of concern and Aftercare number</i>	<i>Any medical practitioner in Australia can register a patient for this follow up service.</i>	<i>Monthly review of requests for this service. Weekly review of message receipt failures. Any failures followed up.</i>
<i>Medical Affairs and Pharmacovigilance telephone support</i>	<i>Facility for medical enquiries and reporting of spontaneous adverse events</i>	<i>Monthly review of enquiries and responses and adverse events. Six monthly review and PSUR preparation.</i>

7. RMP Issue: Patient Registry

There are a number of references to a Patient Registry in the Delegate's Report for Mifepristone Linepharma and GyMiso®.

The sponsor considers that Patient Registries can be a very useful form of post marketing surveillance, particularly when the efficacy or safety of a product is in question. However, the type of registry proposed would require registration and follow-up of every patient. There are a number of important factors to be weighed in the context of a Patient Registry in Australia, as described below, and the sponsor respectfully requested that these and an alternative approach as discussed with TGA be considered in addressing the requirements for pharmacovigilance in this case.

The following are important considerations in the context of a Patient Registry:

- Use of mifepristone and misoprostol in termination of early pregnancy is not a new treatment. Mifepristone was first registered in France and China in 1988 and it is registered in over 52 countries of the world, including the EU, USA and New Zealand. As noted by the Delegate (GyMiso® Overview), over 1.5 million women have been treated in the US alone, according to postmarketing data reported by the FDA. The medical method is therefore supported by both published clinical trials as well as reporting of pre-market and post-market experience.*
- From a pragmatic perspective, abortion is a sensitive issue and patients demand privacy. A mandated registry for mifepristone users will be a detraction and will interfere with*

the use of the method. Gaining informed consent will also be problematic, since it must be a fully transparent process and registry participation will be listed. The alternative option of surgical abortion will not involve data collection (outside of South Australia) and would present as a more attractive treatment option for both patients and clinicians, with a lower administrative burden for the latter. Follow-up for the medical method will be very difficult and loss to follow-up will result in an imperfect database.

- *With respect to follow up, in the MSIA Authorised Prescriber Programme (APP) experience, one third of patients opt not to return to the clinic for follow up and of this number, only half of these patients can be reached by telephone. Patients do make choices regarding their medical care, and despite the best efforts of the health care providers, will not participate in follow up. This is acknowledged in the RCOG Clinical Guideline Number 7, Guideline 8.6 which states that “many women fail to attend for follow-up.....every effort should be made to ensure that women leave the abortion facility with effective contraception and with information about where to go for further advice or treatment of symptoms...”*
- *The government of South Australia operates an abortion registry and excellent data are published annually on all abortion methods to inform the medical community. This service includes medical abortion with mifepristone and misoprostol. The South Australian experience with over 1,300 patients was published by Mulligan and Messenger in 2011¹⁹. The sponsor notes that this registry is an alternative information source, gathered as it is on a State wide level by a governmental body rather than a pharmaceutical entity.*

The sponsor understands that the TGA’s objective for a Patient Registry is to collect data on the adverse event profile of the medical method in Australia. The sponsor has had preliminary discussions with a clinical statistician and understands that to detect an adverse event of incidence of 1% and 0.1%, then approximate sample sizes of 1,500 and 15,000 patients are required, with 95% confidence intervals of 0.5% and 0.05%, respectively. The sponsor proposes that a significant database already exists from the use of mifepristone for termination of first trimester pregnancy under the APP in the MSIA network. The MSIA experience, gained from its suburban clinic network, now covers treatment of over 20,000 women under the APP since 2009. Of particular importance, a report on the first 13,345 cases treated by MSIA has been submitted for publication and provides a summary of the efficacy and safety of the treatment regimen, including data such as failure rate (3.48%) and complication rate (3.89%). The sponsor considers that this clinical experience meets the objective of a Patient Registry. Moreover, an update to this first report from the MSIA clinic network can be prepared involving 20,000 patients, and will provide data from a sample size that will detect an adverse event rate of 0.1%. If this data set is not deemed sufficient, then the sponsor could continue to collect data for a defined period to be agreed with the TGA. This activity is proposed as a pharmacovigilance tool, and if so agreed, the sponsor considers that this undertaking will effectively provide the same clinically relevant data as envisaged in a postmarketing Patient Registry.

Advisory Committee Considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered this product to have an overall positive benefit-risk profile for the following indication;

For use in women of childbearing age for:

1. *Medical termination of a developing intra-uterine pregnancy. In sequential combination with a prostaglandin analogue up to 49 days of gestation.*
2. *Preparation for the action of prostaglandin analogues during the termination of pregnancy for medical reasons beyond the first trimester.*

The ACPM agreed with the delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- a statement in the *Dosage and Administration* and *Precautions* sections to ensure awareness by consumers and prescribers of the safety risks for patients with concomitant corticosteroid treatment.
- a statement in the appropriate sections of the *Precautions* section of the CMI to ensure the accurate reflection of teratogenic risk should the treatment fail, noting that this risk rating applies to sequential use of misoprostol.

The ACPM advised that the conditions of registration should include the following:

- full implementation of the Risk Management Plan including robust prescriber education and consumer information,
- a mandatory two week follow up of all patients

The ACPM did not support the inclusion of a patient registry as an appropriate strategy; but recommended that the sponsor be required to conduct and submit further Phase IV studies to support the required pharmacovigilance of this product

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

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Mifepristone Linepharma oral tablet containing the new chemical entity mifepristone 200 mg, indicated for:

Mifepristone Linepharma 200 mg tablet is indicated in females of childbearing age for:

- 1. Medical termination of a developing intra-uterine pregnancy. In sequential combination with a prostaglandin analogue up to 49 days of gestation.*
- 2. Preparation for the action of registered prostaglandin analogues that are indicated for the termination of pregnancy for medical reasons beyond the first trimester."*

Specific Conditions Applying to these Therapeutic Goods:

- 1) The implementation in Australia of the Mifepristone Linepharma (mifepristone) Risk Management Plan (RMP), version: 28 August 2012, included with this submission and any subsequent revisions, as agreed with the TGA and its Office of Product Review.
- 2) The Product Information include a black box warning at the top of the document as specified below:

It is important that all patients receiving this medication 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. See ***Special Warnings and precautions for use*** section.

- 3) The Consumer Medicine Information (CMI) must include a black box warning at the top of the document as specified below:

It is important that all patients receiving this medication 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.

- 3) The CMI document must be included in every box of the Product.
4) The RMP to be amended to include these measures in the Risk Minimisation section and supplied to the TGA.

Appendix 1. Clinical References

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Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

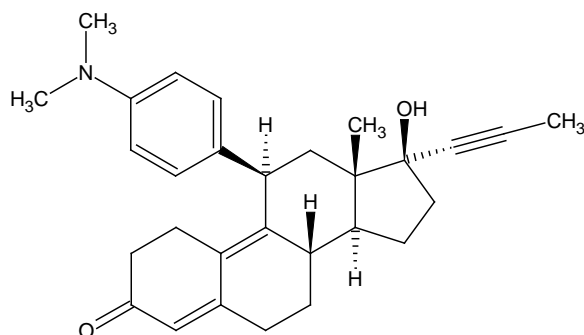
Therapeutic Goods Administration

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

www.tga.gov.au

Reference/Publication #

It is important that all patients receiving this medication 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. See ***Special warnings and precautions for use*** section.



PRODUCT INFORMATION – Mifepristone Linepharma 200 mg Tablet

Pharmacology

Pharmacodynamic properties

Pharmacotherapeutic group: Other Sex Hormone and Modulator of the Reproductive function/ Antiprogesterone. 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 (antiprogesterone, antiglucocorticoid and antiandrogenic) activity.

Pharmacokinetic properties

Absorption

PRODUCT INFORMATION – Mifepristone Linepharma 200 mg Tablet

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%.

Distribution

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.

Metabolism and excretion

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.

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

Clinical trials

PRODUCT INFORMATION – Mifepristone Linepharma 200 mg Tablet

In clinical trials the results vary slightly according to the prostaglandin analogue used and the time of application. Overall, for pregnancies up to 49 days of amenorrhoea (DA), the efficacy rate for a regimen combining 200 mifepristone followed 36 – 48 hours later by 400 µg oral misoprostol, a prostaglandin E1 analogue, ranges between 89.2 and 91.5%. Using oral misoprostol, 600 µg once or 800 µg (either as a single administration or as two administrations 2 hours apart) yields efficacy rates in the range of 93-98%.

Evidence based guidelines and reviews may be consulted for alternative prostaglandin regimens and regimens to be used after 49 days gestation. The suggested regimens are not optimal for use after 49 days. Failures are due to either incomplete abortion or to persisting pregnancy: in practical terms, whatever their nature, failure necessitates a surgical procedure (vacuum aspiration or dilatation and curettage).

For termination of pregnancy-beyond first trimester, pretreatment with 200 mg mifepristone facilitates the procedure: the induction to abortion interval is reduced, as well as the need for prostaglandin analogues (gemeprost or misoprostol). Several studies report prostaglandin regimens used in the gestation range of 12-24 weeks associated with median induction-abortion intervals in the range of 5-8 hours and over 90% of women aborting within 24 hours. Surgical evacuation was needed in 10-12%, with some studies reporting as high as 20-30%.

Indications

Mifepristone Linepharma 200 mg tablet is indicated in females of childbearing age for:

1- Medical termination of a developing intra-uterine pregnancy. In sequential combination with a prostaglandin analogue up to 49 days of gestation.

2- Preparation for the action of registered prostaglandin analogues that are indicated for the termination of pregnancy for medical reasons beyond the first trimester.

Contraindications

This product should not be prescribed in the following situations:

- *In all indications:*
 - known hypersensitivity to the active substance or to any of the excipients;
 - chronic adrenal failure;
 - severe disease (e.g. asthma uncontrolled by treatment) necessitating exogenous steroid administration;
 - known or suspected hypocoagulation diseases, treatment with anticoagulants

PRODUCT INFORMATION – Mifepristone Linepharma 200 mg Tablet

- *In medical termination of a developing intra-uterine pregnancy:*
 - uncertainty about pregnancy age;
 - suspected ectopic pregnancy;
 - contraindication to the prostaglandin analogue selected
- *Preparation for the action of prostaglandin analogues during terminations for medical reasons:*
 - contraindication to the prostaglandin analogue selected.

Precautions

Mifepristone Linepharma (or misoprostol) should not be administered if an intrauterine contraceptive device is present: it should be removed first.

- *In all indications:*

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.

- *In medical termination of a developing intra-uterine pregnancy:*

Rare serious cardiovascular accidents have been reported following intramuscular administration of prostaglandins including misoprostol. For this reason women with risk factors for cardiovascular disease or established cardiovascular disease should be treated with caution.

- *In preparation for the action of prostaglandin analogues during terminations for medical reasons beyond the first trimester:*

The precautions related to the prostaglandin analogue used should be followed where relevant.

Special warnings and precautions for use

- *Warnings:*

In the absence of specific studies, Mifepristone Linepharma is not recommended in patients with:

- Anaemia
- Renal failure,
- Hepatic impairment or failure

PRODUCT INFORMATION – Mifepristone Linepharma 200 mg Tablet

- Malnutrition

- *Medical termination of a developing intra-uterine pregnancy:*

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

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

- The necessity to combine treatment with a prostaglandin analogue
- The need for follow-up within 14 to 21 days after intake of Mifepristone Linepharma in order to confirm 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 counseled 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 prostaglandin 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, which occurs in up to around 7% of the cases prior to 49 days gestation makes follow-up mandatory in order to check that the expulsion is completed. Up to 49 days about 1% will have continuing pregnancies, the rest needing curettage for other reasons.

- Bleeding

The patient must be informed of the occurrence of prolonged vaginal bleeding (an average of 10 to 16 days after Mifepristone Linepharma 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 0.1-0.2% of cases up to 49 days gestation and around 0.5% in the second trimester, 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 she should contact and where to go, in the event of any problems emerging, particularly in the case of very heavy vaginal bleeding.

PRODUCT INFORMATION – Mifepristone Linepharma 200 mg Tablet

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 or prolonged 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. No causal relationship between these events and the use of mifepristone and misoprostol has been established. Doctors evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event. In particular, a fever, 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. 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, haemoconcentration, and generally feeling tired or unwell. Most of these deaths occurred in

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women who used vaginally administered misoprostol however 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%.

In all instances, the use of Mifepristone Linepharma 200 mg tablet requires rhesus determination and hence the prevention of rhesus allo-immunisation as well as other general measures usually taken during any termination of pregnancy.

Effects on fertility

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.

During clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses. To avoid the potential exposure of a subsequent pregnancy to mifepristone, it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after Mifepristone Linepharma administration.

Use in pregnancy

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.

In humans, the few reported cases of malformations do not allow a causality assessment for mifepristone alone or associated with the prostaglandin analogue. Therefore, data are too limited to determine whether the molecule is a human teratogen.

Consequently:

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- 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 mandatory (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, the available data are too limited to justify a systematic termination of an exposed pregnancy. In that event, careful ultrasonographic monitoring of the pregnancy should be carried out.

Use in lactation

Mifepristone is a lipophilic compound and may theoretically be excreted in the mother's breast milk. However, limited data is available. Consequently, Mifepristone Linepharma use should be avoided during breast-feeding.

Paediatric use

Limited data are available for use of Mifepristone Linepharma in women under 18 years.

There is no relevant use of Mifepristone Linepharma in the prepubertal paediatric population in the indications.

Use in the elderly

There is no relevant use of Mifepristone Linepharma in the elderly population in the indications.

Genotoxicity

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.

Carcinogenicity

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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.

Interactions with other medicines

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 anesthesia.

Adverse effects

The adverse events reported with mifepristone, classified according to frequency and system organ class, are summarized as shown in Table 1.

Table 1: Adverse Events for the Combined Use of Mifepristone and a Prostaglandin Analogue		
MedDRA	Adverse events (frequency)	
System Organ Class	Very common (≥ 1/10)	Common (> 1/100 to < 1/10)
Gastro-intestinal disorders	Nausea Vomiting Diarrhoea Dizziness Gastric discomfort Abdominal pain	
Nervous system disorders	Headache	
Reproductive system and	Vaginal bleeding Uterine spasm	Prolonged post-abortion bleeding Spotting

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Table 1: Adverse Events for the Combined Use of Mifepristone and a Prostaglandin Analogue		
MedDRA	Adverse events (frequency)	
System Organ Class	Very common ($\geq 1/10$)	Common ($> 1/100$ to $< 1/10$)
breast disorders		Severe haemorrhage Endometritis Breast tenderness Heavy bleeding
General disorders and administration site conditions	Fatigue Chill / fever	Fainting

Adverse Events reported with mifepristone, classified as “Uncommon” ($\geq 1/1000$ to $< 1/100$) are summarized as shown below:

- Reproductive System and Breast disorders: Haemorrhagic shock, Salpinitis.
- Infections and Infestations: Infection
- Vascular Disorders: Hot flush
- Skin and Subcutaneous Tissue Disorder: Skin Rash/ Pruritus

Adverse Events reported with mifepristone, classified as “Rare” ($\geq 1/10000$ to $< 1/1000$) and “Very Rare” ($< 1/10000^*$) are summarized as shown below:

- Gastro Intestinal Disorders: Gastec Bleeding
- Nervous System Disorders: Epilepsy, Neurogenic Tinnitus
- Reproductive System and Breast Disorders: Bilateral adnexal mass, Intrauterine adhesion, Ovarian cyst rupture, Breast abscess, Haematosalpynx, Uterine rupture
- General disorders and administration site conditions: Anaphylaxis, Periorbital edema
- Infections and infestations: Toxic Shock Syndrome
- Vascular Disorders: Superficial Thrombo-phlebitis, Hypotension
- Cardiac Disorders: Myocardial infarction, Induced Adam-Stokes Syndrome
- Respiratory, Thoracic and Mediastinal Disorders: Bronchospasm, Induced bronchial asthma
- Skin and Subcutaneous tissue disorders: Urticarial reaction, Toxic Epidermal necrolysis

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- Pregnancy Puerperium and perinatal conditions: Hydatiform mole, Ectopic pregnancy, Amniotic band syndrome, Gestational trophoblastic tumor, Uteroplacental apoplexy
- Hepatobiliary disorders: Abnormal liver function tests, Hepatic failure, Hepatorenal failure
- Blood and lymphatic system disorders: Thrombotic thrombocytopenic purpura, Thrombocytopenia, Induced systemic lupus erythematosus
- Renal and urinary disorders: Renal Failure
- Neoplasms Benign, Malignant and Unspecified: Elevated alpha-feto protein, Elevated carcinoembryonic antigen
- Musculoskeletal and Connective Tissue Disorders: Limb spasm
- Eye Disorders: Ophthalmoplegia
- Psychiatric Disorders: Mania

* Including occasional case reports

- Bleeding is an almost constant part of the procedure, whatever the prostaglandin analogue use, 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 that is observed in approximately 3 to 12% of the cases, depending on the pregnancy age and the prostaglandin analogue used, and needs specific treatment. It can necessitate a blood transfusion in 0.1-0.2% of cases up to 49 days gestation and around 0.5% in the second trimester. It can be prolonged for several days after prostaglandin analogue administration and sometimes leads to a decrease in hemoglobin 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.
- Infectious complications, including *Clostridium sordellii* toxic shock appear rare but can lead to fatal outcome. 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. 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, haemoconcentration, and generally feeling tired or unwell. Most of these deaths occurred in women who used vaginally administered misoprostol. No causal relationship between mifepristone and misoprostol use and an increased risk of infection or death has been established.

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The issue of the outcome of persisting pregnancy in the case of failure of the medical method remains incompletely solved: although up to date there does not seem to be clear-cut fetal malformations attributable to mifepristone or to prostaglandin analogues, such possibility cannot be definitively ruled out and women should be adequately counseled 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 mifepristone does not appear able to terminate an ectopic pregnancy.

Dosage and administration

1. *Medical termination of developing intra-uterine pregnancy, in sequential combination with a prostaglandin analogue up to 49 days gestation*

The method of administration is as follows:

200 mg of mifepristone (1 tablet containing 200 mg) orally, followed 36 to 48 hours later by the administration of a prostaglandin analogue.

Acceptable prostaglandin regimens include misoprostol (200 µg tablet) orally, either as 800 µg (4 tablets) in a single intake, or if preferred, as 400 µg (2 tablets), to be repeated after 2 hours. Evidence based guidelines and reviews may be consulted for alternative prostaglandin regimens and regimens to be used after 49 days of gestation.

2. *Preparation for the action of prostaglandin analogues during the termination of pregnancy for medical reasons beyond the first trimester.*

The method of administration is as follows:

200 mg of mifepristone (1 tablet containing 200 mg) orally, followed 36 to 48 hours later by the scheduled prostaglandin analogue administration, which will be repeated as often as indicated.

No studies have been conducted on the effect of food intake on the absorption of mifepristone. It is recommended that Mifepristone Linepharma should not be taken within 2 hours of a meal.

Overdosage

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.

Presentation and storage conditions

PVC/PVDC/Aluminum blister of 1 tablet

Pack size of 1 tablet

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Store below 30°C.

Keep in the original carton in order to protect from light

Keep out of reach of children

Name and address of the sponsor

MS Health

Suite 129, 135 Cardigan Street

Carlton VIC 3053

Australia

Licensed from Linepharma (France)

Poison schedule of the medicine

Schedule 4

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

29 August 2012

Date of most recent amendment

18 September 2012

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