Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Misoprostol

Proprietary Product Name: GyMiso

Sponsor: MS Health

October 2012

TGA Health Safety Regulation

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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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Introduction to product submission

Submission details

Type of Submission	Extension of indications (New formulation, new indication)
Decision:	Approved
Date of Decision:	7 August 2012
Active ingredient(s):	Misoprostol
Product Name(s):	GyMiso
Sponsor's Name and Address:	MS Health[1]l, GPO Box 1635, Melbourne VIC
Dose form(s):	Tablet (uncoated, not scored)
Strength(s):	200 µg
Container(s):	Blister pack
Pack size(s):	4 x tablets
Approved Therapeutic use:	GyMiso® is indicated in females of childbearing age for the medical termination of a developing intrauterine pregnancy in sequential combination with a mifepristone 200 mg tablet, up to 49 days of gestation.
Route(s) of administration:	Oral (PO) or buccal
Dosage:	800 µg (4 tablets)
ARTG Number (s)	188015

Product background

Misoprostol is a prostaglandin E1 analogue. This AusPAR describes an application to register GyMiso, misoprostol 200 µg tablets, which is linked to a related application to register Mifepristone Linepharma 200 mg tablet. A single dose of 800 µg GyMisio is proposed to be used in combination with the 200 mg mifepristone tablets to achieve termination of pregnancy in women who are up to 49 days of gestation/days of amenorrhoea (DA). The 200 mg mifepristone dose is to be taken 36 to 48 h before the misoprostol dose.

Cytotec misoprostol 200 µg tablets are currently registered for use in Australia (ARTG R 63983) for the treatment of acute duodenal and gastric ulcers and for the prevention of stress induced upper gastrointestinal mucosal bleeding and lesions in post surgical patients in intensive care units. GyMiso is new formulation of misoprostol for a new indication. GyMiso is not proposed as a generic medicine with respect to Cytotec and no gastrointestinal indications are proposed for GyMiso.

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

The approved regimen for Cytotec® for gastrointestinal indications involves a total daily dose of 800 µg, taken in divided doses for periods of 14 days up to 12 months or even longer.

The sponsor proposed the following indication for GyMiso:

In adults and adolescents of childbearing age for the medical termination of a developing intrauterine pregnancy in sequential combination with Mifepristone Linepharma 200mg tablet, up to 49 days of gestation.

Cytotec® has been widely used off-label internationally and in Australia for many years for this and related gynaecological indications. Other prostaglandins are registered in Australia for obstetric and gynaecological indications as follows:

- Gemeprost (Cervagem®; vaginal pessary): For the softening and dilatation of the *cervix uteri* prior to transcervical, intrauterine operative procedures in the first trimester of pregnancy. Therapeutic termination of pregnancy in patients in the second trimester of gestation.
- Dinoprostone (Cervidil®; vaginal pessary): Cervical ripening in patients, at or near term, who have favourable induction features and in whom there is a medical or obstetrical indication for induction of labour.
- Dinoprostone (Prostin® E2; vaginal pessary): Induction of labour in term or near-term pregnant women who have favourable induction features; and who have singleton pregnancy with a vertex presentation.
- Dinoprost trometamol (Prostin® F2 alpha; injection ampoule) is indicated for the therapeutic termination of pregnancy during the first or second trimester. Prostin F2 alpha may be used for evacuation of the uterus in cases of foetal death in utero, missed abortion, as a non-surgical treatment for the evacuation of hydatidiform moles and as an alternative measure to complete therapeutic termination of pregnancy when intra-amniotic saline injections have failed.

Although the PI for Prostin F2 alpha lists first trimester termination of pregnancy as an indication, it must be administered intra or extra amniotically.

Regulatory Status

GyMiso® has been approved in France since 2003 for termination of early pregnancy in combination with mifepristone; it is also approved there for the management of early pregnancy failure (since 2003) and for preparation of the cervix for gynaecological procedures requiring entry into the internal cervical (since 2004).

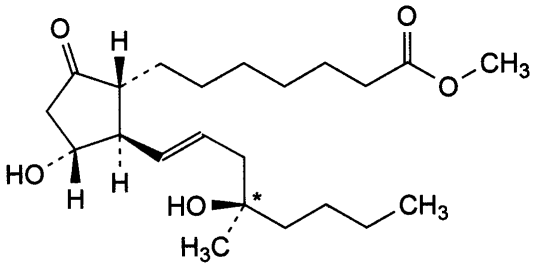
Product Information

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

II. Quality findings

Drug Substance

Misoprostol is a synthetic analogue of prostaglandin E1 with the structure depicted below:



its epimer at C* and their enantiomers

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

It has four chiral centres and is presented as a mixture of four stereoisomers in approximately equal proportions. The drug substance is a clear, colourless or yellowish oil that is practically insoluble in water. There are British Pharmacopeia (BP), European Pharmacopeia (Ph. Eur) and US Pharmacopeia (USP) monographs for misoprostol. For ease of manufacture (and increased stability) misoprostol is formulated (after full testing) as a misoprostol-hypromellose (HPMC) 1% dispersion by the drug substance manufacturer.

Drug Product

The proposed drug product is an immediate release uncoated tablet manufactured using conventional blending and direct compression techniques. It is a white, flat, round, tablet with 'ML' debossed on one side of the tablet and '200' on the other'. Excipients are conventional. The tablets are not scored.

The formulation proposed for registration was developed to be bioequivalent to overseas misoprostol tablets. It was approved for use in France in October 2003.

There are no official monographs for misoprostol tablets. The proposed impurities limit was deemed acceptable from a toxicological perspective given the product's administration as a single dose of four tablets (800 µg misoprostol). However, were *GyMiso* to be used off-label for indications with repeated administration (such as those for *Cytotec*), the impurity profile of *GyMiso* would not be considered acceptable based on the data currently available.

Other release and expiry limits are satisfactory, the tablets are adequately controlled.

A shelf life of 9 months when stored below 25°C with the additional storage condition 'store in the original package' is supported by the stability data provided.

Both oral and buccal administration of the *GyMiso* misoprostol 200 µg tablet are proposed.

A bioavailability study (Study No. JEI308, discussed below) has been provided to support oral administration of the proposed tablets. This is relevant in context of the clinical trials referred to in the submission.

Biopharmaceutic data demonstrating that bioavailability is the same for the oral and buccal routes of administration have not been provided; the applicant has instead chosen to demonstrate that efficacy is the same through these two routes of administration. This has been brought to the attention of the Clinical Delegate.

Biopharmaceutics

The submission included a bioavailability study (JEI308) that compared the proposed *GyMiso* misoprostol 200 µg tablet to an overseas reference product (sourced in France), *Cytotec* misoprostol 200 µg tablet, in healthy female subjects in the fasted state.

The *Cytotec* (Reference product) and *GyMiso* (Test product) misoprostol 200 µg tablet formulations were found to be bioequivalent with respect to peak plasma concentration (C_{max}), the area under the plasma concentration time curve from time zero to the last measurable time point (AUC_{0-t}) and area under the plasma concentration time curve from time zero to infinity ($AUC_{0-\infty}$). In both the *Cytotec* and *GyMiso* misoprostol tablet formulations, misoprostol acid was rapidly absorbed (time to peak plasma concentration (T_{max}= 15 minutes). The terminal elimination of misoprostol acid was rapid and concentrations were below the limit of quantification after just 4 h post dose in all but two subjects.

Clinical trial formulation(s)

The submission was literature based. The applicant has not provided quantitative data of the formulation of the reference products used in the biostudy or the clinical trials referred to in the submission, thus equivalence of the proposed product to the reference product(s) used in the clinical trials has not been conclusively established. Of the 68 publications referenced by the applicant, 20 specifically report use of *Cytotec* (these include product sourced from the USA, United Kingdom (UK), Australia, Denmark and France). *Cytotec* is considered likely to have been used in another 14 studies (based on the observation that no generic misoprostol product was available in the country in question at the time the particular study was conducted), the reference product used in the remaining 34 studies is unclear, although the applicant states that it is likely that *Cytotec*, or a therapeutically equivalent generic product, was used. This has been brought to the attention of the Clinical Delegate.

Food Effects

Under the heading, *Dosage and administration*, the proposed product information states *'There are no data available on the effect of food intake on the absorption of misoprostol. Misoprostol may be taken with or without food.'* However, the applicant has submitted an extract from the *Physicians' Desk Reference* for *Cytotec* misoprostol 100 and 200 µg tablets. This document states, that *'Maximum plasma concentrations of misoprostol acid are diminished when the dose is taken with food'*. Pharmacokinetic data contained therein suggest a statistical significance in C_{max} (fasting: 811 ± 317 pg/mL; high fat breakfast: 303 ± 176 pg/mL) and T_{max} (fasting 14 ± 8 min; high fat breakfast: 64 ± 79 min) after a high-fat meal. Differences in the reported AUC are not statistically significant (fasting: 417 ± 135 pg.h/mL; high fat breakfast: 373 ± 111 pg.h/mL).

The *Cytotec* PI recommends dosing with meals.

Pharmaceutical Subcommittee (PSC)

This application was considered at the 144th (2012/2) meeting of the PSC (Recommendation No. 2258 refers).

The subcommittee recommended that, subject to approval of the submission, only a composite pack (with Mifepristone Linepharma) be supplied. It also noted the risk of variable bioavailability with differences in timing of doses in relation to food (as noted above).

Conclusion

There are no objections to the registration of *GyMiso* misoprostol 200µg tablet blister pack with regard to chemistry, quality control and biopharmaceutic aspects.

III. Nonclinical findings

Introduction

The nonclinical submission was composed entirely of published literature. Few of the studies were directly relevant to the extension of indications. Literature regarding the pharmacology of misoprostol and mifepristone in combination was not provided; such nonclinical evidence to support efficacy for the proposed indication was instead found independently by the nonclinical evaluator. Much of the data considered general aspects of the toxicology of misoprostol and these were not specifically required given that a nonclinical assessment has already been made and that the proposed dose is equivalent and the duration of dosing is considerably shorter (1 day compared to up to 8 weeks) compared with that already approved. Many of the reports did not provide animal numbers or strains and provided so few experimental details that it was not possible to establish the adequacy of the studies for risk assessment (and none were Good Laboratory Practice (GLP) compliant).

Pharmacology

Primary pharmacology

Misoprostol is a synthetic prostaglandin E_1 methyl analogue[2]. Due to the fact that prostaglandins increase uterine contractile activity, misoprostol is potentially suitable to be used as an abortifacient[3, 4].

Misoprostol preferentially binds prostaglandin E_2 prostanoid (EP) receptor subtype 3, over other subtypes and preferentially binds the mouse EP_3 receptor over the rat EP_3 receptor.

Misoprostol induced contractile activity in isolated uterine tissue from Hartley guinea pigs. The 50% effective concentration (EC_{50}) varied depending on the stage of gestation, with the tissue becoming more sensitive later in gestation.

Secondary pharmacology

Misoprostol increases mucus secretion in the stomach and small intestine[3], inhibits gastric acid secretion and protects the gastric and duodenal mucosa from ulceration[5]. Misoprostol has been used extensively for the treatment of gastrointestinal (GI) ailments.

[2] Paumgarten F.J.R., Magalhães-de-Souza C.A., de-Carvalho R.R. and Chahoud I. (1995) Embryotoxic effects of misoprostol in the mouse. *Braz. J. Med. Biol. Res.* 28: 355–361.

[3] Campbell W.B. and Halushka P.V. (1995) Lipid-derived autacoids. Eicosanoids and platelet-activating factor. In Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th edition; eds J.G. Hardman, L.E. Limbird, P.B. Molinoff, R.W. Ruddon; McGraw-Hill, pp. 601–616.

[4] Graves C.R. (1995) Agents that cause contraction or relaxation of the uterus. In Goodman & Gilman's The pharmacological basis of therapeutics, 9th edition; eds JG Hardman, LE Limbird, PB Molinoff, RW Ruddon; McGraw-Hill, pp. 939–949.

[5] Bauer R.F. (1985) Misoprostol preclinical pharmacology. *Dig. Dis. Sci.* 30: 118S–125S.

Pharmacokinetics

The metabolism of misoprostol is well known. Misoprostol is rapidly converted by de-esterification to its free acid (SC-30695, which possesses significant pharmacological activity). Further metabolic conversion occurs over time via β-oxidation of the α-side chain, ω-oxidation of the β-side chain and reduction to the prostaglandin F analogues. The enzymes involved in the metabolism of misoprostol have not been identified, but they are likely to be the same enzymes involved in prostaglandin and fatty acid catabolism. The serum protein binding of the free acid metabolite of misoprostol is ~81–89%.

The main route of elimination of misoprostol's metabolites is via the urine and it is expected that most of misoprostol's metabolites will be eliminated in about 24 h. Misoprostol did not inhibit or induce cytochrome P450 (CYP450) enzyme levels/activity in rats.

Maximum plasma concentrations of misoprostol acid are diminished when the dose is taken with food and total availability of misoprostol acid is reduced by use of concomitant antacid[6].

Pharmacodynamic drug interactions

Administration on gestational days (GDs) 13–15 of 0.1 mg/kg/day PO misoprostol (around twice the proposed clinical dose in mg/m^2) in conjunction with mifepristone (≥0.025 mg/kg/day) increased the incidence of complete abortions in Hartley Guinea pigs relative to treatment with mifepristone alone. However, the incidence of complete abortions was around 50% at the highest tested dose of mifepristone (0.1 mg/kg/day; around 100 times lower than the proposed clinical dose on a mg/m^2 basis) plus misoprostol.

In rats, administration on GD8 of 0.3 mg/kg/day PO misoprostol (3.4 times the proposed clinical dose in mg/m^2) 2 h after 1 mg/kg mifepristone (0.05 times the proposed clinical dose in mg/m^2) caused 100% termination of pregnancy. These studies generally support the proposed indication.

Pharmacokinetic drug interactions

The potential for pharmacokinetic interactions between misoprostol and other drugs, particularly with mifepristone, was not examined *in vivo* in animals.

Mifepristone is mainly metabolized by CYP450 isozyme CYP3A4. Mifepristone irreversibly inhibits CYP3A4, with likely clinically significant inhibition *in vivo*. Mifepristone also inhibits CYP1A, 2B1 and 2D6, albeit to a lesser degree and reversibly. None of these enzymes are likely to be involved in misoprostol metabolism.

Misoprostol was not an inducer/inhibitor/substrate of CYP3A4. Therefore, it is not expected that concomitant administration of misoprostol and mifepristone will alter the pharmacokinetics of, or alter the exposure to either drug.

Maximum plasma concentrations of misoprostol acid are diminished when the dose is taken with food and total availability of misoprostol acid is reduced by use of concomitant antacid.

[6] Goldberg A.B., Greenberg M.B. and Darney P.D. (2001) Misoprostol and pregnancy. *N. Engl. J. Med.* 344: 38–47.

Toxicology

Acute toxicity

A review article on single dose toxicity was provided but it did not provide sufficient information regarding the experimental conditions (as recommended in the TGA adopted EU guideline for single dose toxicity[7]) to ascertain the adequacy of the studies.

Data were obtained in mice, rats and dogs. The most prominent adverse effects after single oral misoprostol administration were diarrhoea, emesis and decreased motor activity. Hypertrophy of mucous cells and deepening of the gastric pits were observed microscopically. These gastric effects have been observed and described previously under the nonclinical evaluation of the use of misoprostol for GI tract (GIT) ulcers. The lowest acute oral 50% lethal dose (LD_{50}) dose was observed in mice, at 27 mg/kg (81 mg/m^2), which is 153 times the recommended human single dose of 800 µg (0.016 mg/kg or 0.53 mg/m^2) for a 50 kg woman, on a mg/m^2 basis.

Repeat-dose toxicity

Published studies of up to 90 days duration in rats and 11 weeks in dogs were submitted. Only GIT tissues were examined microscopically. The studies were not GLP compliant and drug batches and strains of animals were not identified. It would have been advantageous to have used the mouse as the rodent species instead of the rat, as pharmacodynamic studies showed that mouse EP_3 receptors are ~16 times more sensitive to misoprostol than their rat counterparts and closer in sensitivity to human EP_3. The highest doses tested in the longest studies were >100 times (rats) and ~11 times (dogs) the human dose on a body surface area basis.

Body weight gain was not affected in rats receiving misoprostol at 300 µg/kg/day for 21 days but was decreased after treatment with ≥90 µg/kg/day for 90 days. The known effect of mucosal thickening of the stomach and duodenum was observed, with doses of ≥15 µg/kg/day for 21 days in rats. In dogs, stomach weight and gland length were increased with treatment at 300 µg/kg/day for 11 weeks, while body weight was unaffected.

Regarding the well known hyperplasia associated with the administration of exogenous prostaglandins, in a study in rats it was concluded that misoprostol increases cell survival and decreases cell shedding. However, in a study in dogs the authors concluded that the hyperplasia is caused by increased cell production and not decreased cell loss.

Genotoxicity

The potential genotoxicity of misoprostol was examined in the following tests described in the literature submitted by the sponsor: assays for mutagenicity in bacterial, yeast and mammalian (mouse lymphoma tk) cells; and for clastogenicity *in vitro* (Chinese hamster ovary cells) and *in vivo* (mouse bone marrow micronucleus test). All tests returned negative results for misoprostol, however it is not possible to ascertain from the details reported whether the studies were adequately conducted, as very few study details were provided. This relies on data previously evaluated by the TGA.

The genotoxicity statement in the Product Information document of ARTHROTEC® (a registered combination product including diclofenac sodium 50 mg and misoprostol 200 µg) states:

> "The mutagenic potential of misoprostol was tested in a battery of assays for gene mutations and chromosomal damage, all of which were negative".

[7] Single dose toxicity. 3BS1a. http://www.tga.gov.au/pdf/euguide/vol3bs1aen.pdf

Based on this information, there is no particular genotoxic concern and the overall assessment of genotoxic potential is considered adequate.

Carcinogenicity

The carcinogenic potential of misoprostol by the oral route was investigated in a published 2 year study in rats and a 21 month study in mice. Group size (>50/group) was appropriate and dual control groups were used. Three suitable dose levels were selected, with the highest dose levels causing survival to be reduced but not excessively so. There was no evidence of an effect of misoprostol on tumour occurrence or incidence in rats or mice receiving oral doses of up to 2.4 mg/kg/day for 2 years or 16 mg/kg/day for 21 months, respectively, which are 27–91 times the recommended human single dose of 800 µg (0.016 mg/kg for a 50 kg woman) on a mg/m^2 basis.

Reproductive toxicity

In two fertility studies performed in rats, male rats were treated from 70–71 days premating until mating and female rats were treated from 14–15 days before mating to gestationonal day (GD) 7 or until parturition; treated males were paired with treated females. The number of implantations was decreased at ≥1600 µg/kg/day. An increase in resorptions occurred at 1000 µg/kg/day in one study, but not at 1600 µg/kg/day in the other, and at 10000 µg/kg/day. Fetal and pup survival and development were not affected.

In two teratology studies performed in rats, there was no evidence of embryotoxicity, fetotoxicity or teratogenicity with dosing at ≤10 mg/kg/day on GDs 6–15 or ≤1600 µg/kg/day on GDs 7–17. In rabbits, administration at 100, 300 or 1000 µg/kg/day GDs 6 to 18 showed no evidence of fetotoxicity or teratogenicity, although there was an increased number of resorptions at 1000 µg/kg/day.

In a teratogenicity study, pregnant Han:NMRI mice were treated with single oral doses of 20 or 30 mg/kg of misoprostol on Day 10 of pregnancy. Maternal toxicity was evidenced by slight and reversible decrease in pregnancy weight gain at both doses. No embryofetal toxicity was observed at 20 mg/kg. However, the proportion of resorptions per implantation site was increased at 30 mg/kg. An increased incidence of cleft palate and skeletal abnormalities was also observed in surviving fetuses at this dose. Therefore, misoprostol was embryotoxic and teratogenic to mice at 30 mg/kg PO (170 times the proposed clinical dose on a mg/m^2 basis).

The dose at which teratogenicity was observed in mice (30 mg/kg PO, or 90 mg/m^2) was not evaluated in rats or rabbits. The lack of effects in rats could also be explained by the fact that misoprostol is 16 times more potent at binding to EP_3 receptors from mice than for rats.

Based on pharmacology parameters, mice are probably a better animal model for misoprostol-induced uterine contractile activity than rats.

In a rat pre/postnatal study using doses of 0.1, 1 and 10 mg/kg/day from GD 15 to day 20 postpartum, pup survival was unaffected, although a decrease in pup weight gain during lactation was observed at 10 mg/kg/day.

Pregnancy classification

No Pregnancy Category has been proposed, as appropriate for an agent indicated only for termination of pregnancy. However, if the indications of GYMISO® were to be extended beyond therapeutic abortion, Category X would be appropriate and consistent with other misoprostol products and indications.

Impurities

The proposed expiry limit for one impurity was deemed acceptable from a toxicological perspective for a single dose indication.

However, if the indications of GyMiso are extended to those of Cytotec®, or any indication that requires repeated administration of misoprostol, further toxicology qualification may be required. In the event that GyMiso was to be used off-label for indications with repeated administration (such as those for Cytotec®), the impurity profile of GyMiso would not be acceptable based on the data currently available.

Paediatric use

Misoprostol is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Nonclinical Summary and Conclusions

- The nonclinical was composed entirely of published literature. The search strategy was generally adequate, although literature regarding nonclinical efficacy in combination with mifepristone was not provided but were identified by the nonclinical evaluator. Many of the publications did not include animal numbers or strains and only limited experimental details were provided.
- Misoprostol is a synthetic prostaglandin E_1 methyl analogue. The mechanism of action of prostaglandins such as misoprostol is well known. Its abortifacient activity is based on the fact that prostaglandins increase uterine contractile activity. Misoprostol preferentially binds prostaglandin E_2 prostanoid subtype 3 receptors (EP_3) over other EP subtypes, with higher affinity of the mouse and human EP_3 receptor than the rat EP_3 receptor.
- Misoprostol induced contractile activity in isolated uterine tissue from Hartley guinea pigs, with increased potency seen later in gestation. Administration of 0.1 mg/kg/day misoprostol following mifepristone increased the incidence of complete abortions in Hartley Guinea pigs. In rats, administration of 0.3 mg/kg/day misoprostol (on GD 8) 2 h after 1 mg/kg mifepristone caused 100% termination of pregnancy.
- The predominant sign of toxicity following acute oral administration in animal studies has been shown to be diarrhoea, which occurred at threshold doses of 1.6 mg/kg in mice, 0.3 mg/kg in rats and rabbits and 0.03 mg/kg in dogs. Microscopic changes in the stomach were seen in single and repeat dose studies.
- Reproductive toxicity studies showed embryotoxicity (increased resorptions) at 1 mg/kg/day PO in rabbits, at 10 mg/kg/day in rats and at 30 mg/kg/day in mice. An increased incidence of skeletal abnormalities and cleft palate was observed at 30 mg/kg/day in mice.
- Primary pharmacology studies of misoprostol showed that misoprostol increases the incidence of complete abortions when administered in conjunction with mifepristone, in guinea pigs and rats, thus supporting the proposed indication.
- Embryofetal development studies suggest some teratogenic potential for the drug.
- The use of misoprostol under its new proposed indication involves the same dose (800 µg) but at a lower frequency (single dose) than that already approved for its use as a treatment of duodenal and gastric ulcers (daily for 4–8 weeks). No concerns regarding genotoxicity or carcinogenicity are raised by the nonclinical data, and the pattern of use with this product poses no increase in concern with regard to general toxicity.

- The proposed expiry limit for the impurity was considered acceptable for a single dose indication. However, in the event that GyMiso was to be used for indications with repeated administration (such as those for Cytotec®), the impurity profile of GyMiso would not be acceptable based on the data currently available.
- There are no nonclinical objections to the registration of GYMISO® for the proposed indication.
- Amendments to the draft Product Information were recommended.

IV. Clinical findings

Introduction

This submission was literature based and requested approval for a new gynaecological indication for misoprostol. It included one bioequivalence study. Literature references cited (as Studies 501-912) in this clinical evaluation are listed under *Appendix 1*. *Clinical References* at the end of this AusPAR.

The submission dated September 2011 (replacing an earlier version) noted the following clinical issues identified in presubmission planning:

- Whether tablets should be taken with or without food and the nature of the evidence for this.
- The need to demonstrate efficacy or equivalent bioavailability of buccal administration.

Clinical rationale

Termination of pregnancy in the first trimester has largely been undertaken surgically in Australia. Many women prefer medical regimens when available and in many parts of the world these now constitute the majority of procedures, especially in early pregnancy. Regimens combining the antiprogesterone mifepristone with prostaglandins have been shown to induce abortion safely and effectively, avoiding surgery for up to around 95% of women in early pregnancy. Since mifepristone was first registered in France over 20 years ago, much research has focused on prostaglandin regimens and misoprostol has become the prostaglandin of choice due to its efficacy and safety as well as storage and cost considerations. Although misoprostol is part of registered regimens for abortion in some countries, it is largely used off-label for gynaecological indications including in Australia. Mifepristone has been used with misoprostol in Australia since 2006 under authorised prescriber arrangements .

The sponsor notes that misoprostol has been used by gynaecologists over 10 years for its uterus contracting properties but that the current marketing authoridation holder of Cytotec® has not to date registered the off-label gynaecological and obstetrical indications. The purpose of the sponsor's application is to make GyMiso available as an approved medicine in the gynaecological setting in Australia.

Registration of misoprostol for gynaecological indications would support appropriate use of this medicine in preference to the off-label use of the registered alternative.

Formulation development

The application states that the formula for Cytotec® was available and the development of GyMiso was mainly a process of characterisation.

Some of the international literature reports which contribute to this application report the use of Cytotec® but in others the provenance of misoprostol is not specified. Several different sponsors are mentioned, including Pharmacia, Pfizer and Searle and it is not clear whether there is more than one site of manufacture.

The bioequivalence study included in the application tested GyMiso against the reference product Cytotec® (Pharmacia SAS), stated in the sponsor's submission to have been purchased in France and manufactured by Pharmacia UK.

In was also stated that the formulation of the batch of GyMiso used in the 2004 bioequivalence study is exactly the same as that of the current preparation, although there has been a change of site of manufacture. Comparative dissolution profiles have been undertaken.

Excipients

The registered formulation Cytotec® contains the following excipients: cellulose, hypromellose, sodium starch glycolate and castor oil. Quantities are not specified in the PI.

The proposed formulation GyMiso contains the same list of excipients.

Scope of the clinical submission

The clinical submission was literature based, presenting, summarising and commenting on published reports of the use of mifepristone with prostaglandins including misoprostol for pregnancy termination since the late 1980s. It includes a bioequivalence study of GyMiso and the reference product Cytotec®, which has been widely used in the presented literature.

The submission contained the following clinical information:

- A bioequivalence study of GyMiso and the reference product Cytotec®.
- A summary report of use by the sponsor of mifepristone with misoprostol under the Authorised Prescriber Scheme and the protocol used.
- Two periodic safety update reports (PSURs) with an addendum, a bridging safety report and 10 published references, mainly case reports, only one of which is included in the listed references.
- 125 published reports[501-625] relating to the development, efficacy and safety of medical abortion regimens with mifepristone and misoprostol. A revised listing of 23 references was identified as specifically relevant to the GyMiso application. These included 14 clinical trials[507, 509, 513, 515-523, 526, 528], 2 safety reports[514, 543] and 7 which the evaluator did not consider directly relevant because they dealt with mifepristone without prostaglandin[552], gemeprost regimens[510, 511], second trimester termination[512, 534], or exclusively with mifepristone/misoprostol interval, misoprostol route and/or gestation outside the indication under discussion[513, 508].
- 22 additional references "identified in support of information on misoprostol alone and on abortion methods in general". Eight of these report on pharmacokinetics and pharmacodynamics of misoprostol by different routes of administration and related matters[700, 701, 704, 901, 904-6, 919], 2 report on use of misoprostol in clinical trials concerning postpartum haemorrhage[702-3], 2 are clinical reviews[707, 709], 6 report on clinical outcomes of medical abortion regimens[705, 706, 708, 710, 908-9], 2 on safety[714-5] and 2 on follow up strategies[712-3].
- A copy of the relevant Royal College of Obstetricians and Gynaecologists (RCOG) Evidence-based Clinical Guideline dated 2004[911] (there is an updated version published after submission of the application[11]).

- "The Marie Stopes Medical Process – Mifepristone and Misoprostol": the protocol used by Marie Stopes for medical abortion with mifepristone and misoprostol[912].

The sponsor's Clinical Overview identified the reports 508 and 509 as pivotal. The evaluator did not agree with this choice but considered the assessment of the overall body of evidence to be more important than any one or two trials.

The sponsor's Clinical Efficacy and Clinical Safety summaries are taken from the linked mifepristone submission, on the basis that the two medicines are only to be used together.

Generally the submission was well organised and presented.

Paediatric data

The submission did not include paediatric data. Although the proposed indication includes adolescents, GyMiso will only be used in pregnancy, that is, after puberty is reached and so specific paediatric data are not required.

Good clinical practice

The Bioequivalence Study JEI308 was stated to be performed in accordance with good clinical practice, all applicable regulatory requirements and the Declaration of Helsinki (March 2003). The protocol was reviewed and approved by the local Institutional Review Board. No issues of ethical concern are raised by the study report, which appears to be consistent with the relevant TGA adopted EU guideline[8] (as annotated with TGA comments).

Pharmacokinetics

Table 1 shows the studies relating to each pharmacokinetic (PK) topic and the location of each study summary.

[8] CPMP/ICH/135/95. Note for Guidance on Good Clinical Practice. http://www.tga.gov.au/pdf/euguide/ich13595.pdf

Table 1. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK. Single dose	JEI308	
	Buccal route	Refs 901, 904	
	Oral route	Refs 905, 906	
	Vaginal route	Refs 905, 906	
	Sublingual route	Refs 904-6	
	Bioequivalence†. Single dose	JEI308	*
	Food effect	No primary studies; some discussion in the review article 704	

* Indicates the primary aim of the study. † Bioequivalence of different formulations.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

Pharmacokinetics in healthy subjects

Absorption

Sites and mechanisms of absorption

In addition to the bioequivalence study which reports on oral administration, several papers are presented which report pharmacokinetics after vaginal, sublingual and buccal administration of misoprostol, indicating effective absorption by these routes.

When administered orally misoprostol is rapidly absorbed and de-esterified to misoprostol acid, which is the active metabolite.

Bioavailability

From the bioequivalence study, mean peak concentration of GyMiso after a single dose of 400 μg administered orally in the fasting state is 1.10 ng/ml (standard deviation (SD) 0.42) at a mean of 15 minutes (0.246 h) after administration. This is consistent with several other sources cited in these references and the PI for Cytotec® which state that peak concentration occurs at about 30 minutes after oral administration.

Bioequivalence of clinical trial and market formulations

The only dose form used or referred to in any of the studies, including the published studies and the bioequivalence study (JEI308) is a 200 μg tablet.

The bioequivalence study was conducted with GyMiso and the reference product Cytotec®. It is stated that the Cytotec® for the study was purchased in France and manufactured by Pharmacia UK. It is not stated whether this is the source of Cytotec® marketed in Australia but the bioequivalence study was performed for the purpose of bridging with the published literature, much of which is European and American, rather than to establish comparability with Cytotec® marketed in Australia. Although Cytotec® has been used off-label in Australia for termination of pregnancy indications, this use makes little contribution to the literature under consideration. While some of the studies considered in the literature identify both Cytotec® and the sponsor from which it was obtained, others are less specific not mentioning the sponsor and sometimes referring only to 'misoprostol'.

The site of manufacture of GyMiso was moved from Taiwan to Spain between the conduct of the bioequivalence Study in 2004 and the submission of this application.

Dissolution studies are presented for batches of GyMiso manufactured in Taiwan and Spain as well as for a batch of Cytotec®.

Bioequivalence to relevant registered products

Nineteen healthy non pregnant normal weight volunteer women participated in a randomised, double blind, two-sequence, two-period crossover study conducted in a single centre in Taiwan, comparing the test product GyMiso with the reference product Cytotec® (Study JEI308).

A single dose of 2x200 µg tablets was given orally with water after 10 h fasting. No other route of administration was tested.

Results are summarised in Table 2.

Table 2: Bioequivalence parameters (study JEI308)

	Treatment A (Cytotec®)		**Treatment B (GyMiso®)**		**90% CI ratio of means (ANOVA log)**
	Mean (SD)	Median	Mean (SD)	Median	
AUC_{0-t} (h.ng/ml)	0.739 (0.234)	0.679	0.710 (0.247)	0.650	89.4-101
$AUC_{0-\infty}$ (h.ng/ml)	0.766 (0.241)	0.699	0.746 (0.259)	0.674	90.4-102
c_{max} (ng/ml)	1.19 (0.46)	1.14	1.10 (0.42)	1.07	83.4-105
T_{max} (h)	0.329 (0.201)	0.250	0.246 (0.129)	0.250	
$t_{1/2}$ (h)	0.522 (0.387)	0.483	0.581 (0.444)	0.476	

The 90% confidence intervals (CI) of the ratios of the means of C_{max} and AUC were within the predetermined acceptance range, allowing a conclusion that Cytotec® and GyMiso are bioequivalent.

Influence of food

No primary studies are presented addressing this question.

The Australian PI for Cytotec® states that for different gastrointestinal indications 800 μg per day should be taken in "four divided doses with meals…the last dose should be taken at bedtime" or "in divided doses with meals and at bedtime" or (in post-surgical intensive care unit (ICU) patients) "200 micrograms every four h". No explanation is provided for these recommendations.

A 1990 review article[704] reported that when misoprostol was administered after food, there was a substantial decrease in the rate of absorption as indicated by peak concentration but not the extent of absorption as represented by the area under the concentration curve. It hypothesised that administration after meals might reduce adverse effects to the extent that they resulted from high peak plasma levels.

The Bioequivalence Study JEI308 was conducted in the fasting state but the clinical studies usually do not specify whether misoprostol was administered while fasting or with or after food; it is likely that they include women who have taken oral misoprostol fasting, with food and after food.

If misoprostol taken with or after food is more slowly absorbed, as suggested by Collins[704], this probably does not matter, since it is known that vaginal administration results in more gradual absorption but may be equally or more clinically effective than oral administration.

The question of food effect is not resolved but the following statement from the proposed PI for GyMiso is reasonable: "There are no data available on the effect of food intake on the absorption of misoprostol. Misoprostol may be taken with or without food."[9]

Bioavailability during multiple-dosing

The review article[704] reported no accumulation nor pharmacokinetic changes with multiple dosing. Only a single dose is proposed in this application.

Other routes of administration

Oral, sublingual, buccal and vaginal routes of administration of misoprostol have been demonstrated to be effective in inducing early abortion in combination with mifepristone, depending on dose used and gestation. They may result in different adverse effect profiles for similar clinical efficacy outcomes.

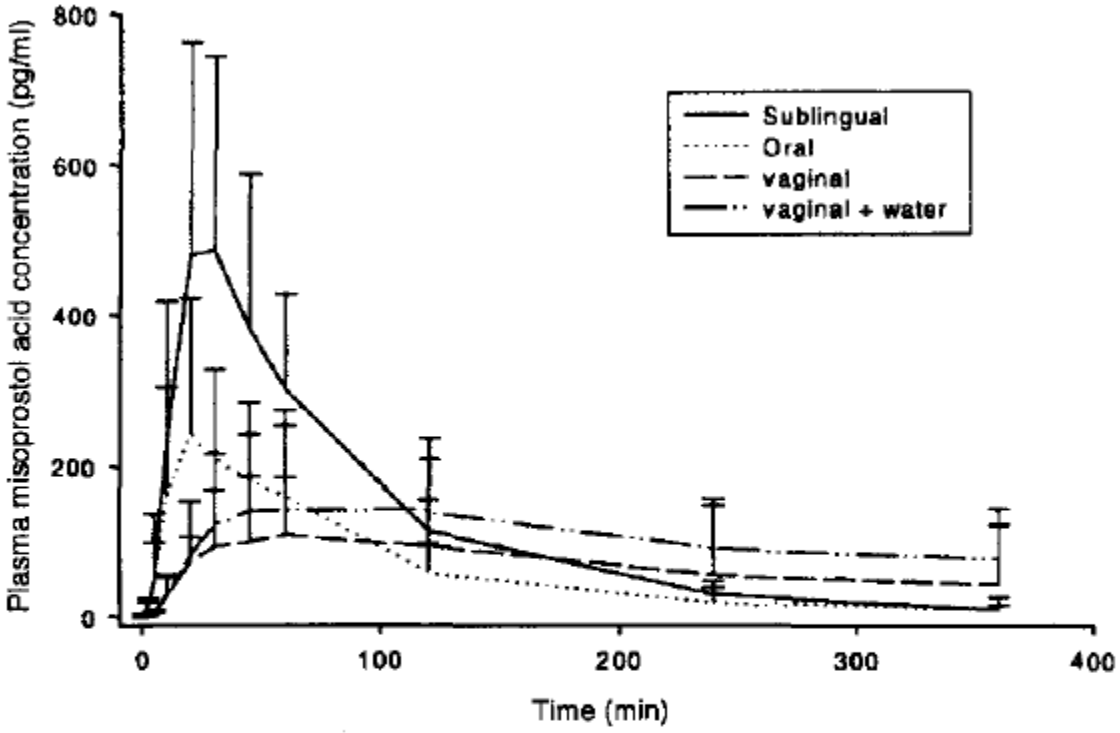
The application presents several pharmacokinetic studies of misoprostol, mainly examining different routes of administration. In Studies 901 and 905 Cytotec® sourced from Pfizer in USA was used but in studies 904 and 906, performed in USA and Hong Kong respectively, the brand and source of the misoprostol was not specified. Different sampling frequencies and assay methods were used, which limits comparisons between studies. Relative infrequency of sampling in the first 30-60 minutes is a limitation of Studies 901, 904 and 905.

Figure present the misoprostol concentration time curves for two of the studies and the overall findings are summarised in Table 3.

[9] Sponsor comment: The approved PI states: "Misoprostol should be taken 2 hours before or 2 hours after a meal",

Figure 2: Mean misoprostol concentrations by 4 routes (A)

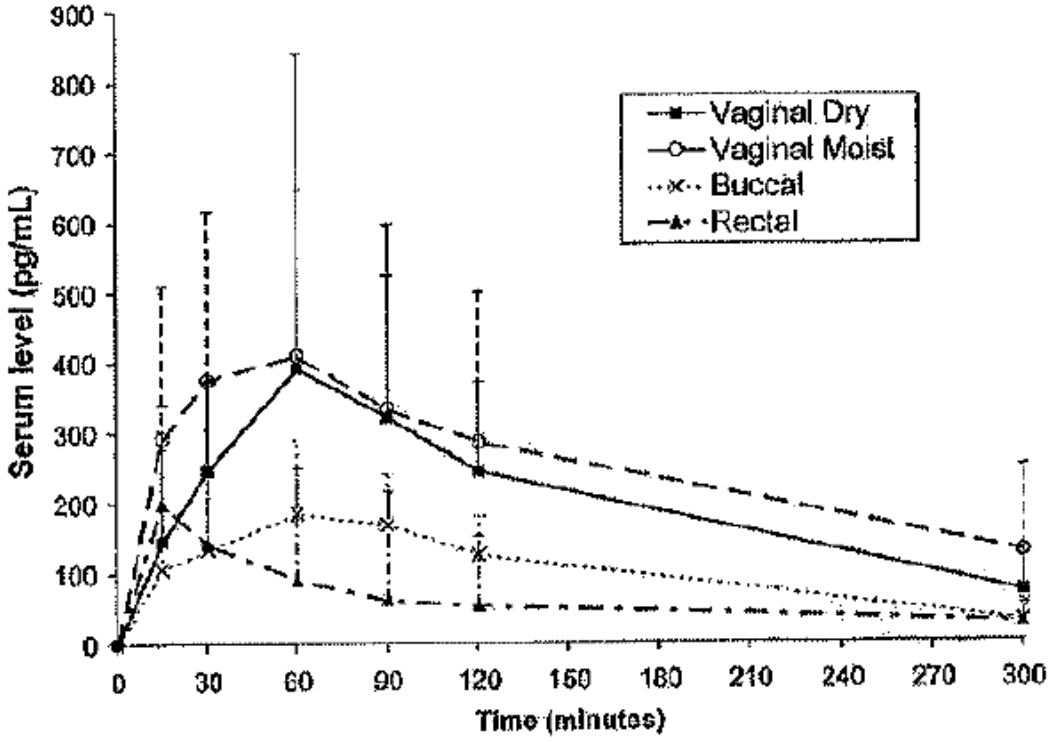
Error bars represent 1 SD. Reproduced from Tang et al[906].



Mean plasma concentration of misoprostol acid over time

Figure 3: Mean misoprostol concentrations by 4 routes (B)

Error bars represent 1 SD. Reproduced from Meckstroth et al[901].



Mean serum levels of misoprostol acid in pg/mL for epithelial routes of misoprostil administration over 5 h. Meckstroth. Misoprostol aborption and uerine response. *Obstet Gynecol* 2006.

Table 3: Summary of reported pharmacokinetic characteristics

Study Participants	Dose Assay	Route (number of women)	c_{max} pg/ml (SD) or [IQR]	t_{max} minutes (SD)	AUC_{0-t} pg*hr/ml (SD) or [IQR]	t hours	Number of PK samples 1-30 mins	31-60 mins	>60 mins
901 Pregnant Fasted	400µg GC/MS	Vaginal (10) Vaginal moist (10) Buccal (10)	445.9 (428.7) 427.1 (235.5) 264.8 (170.7)	91.5 (82.0) 51.0 (20.2) 84.0 (81.9)	[m]1025.0 (572.2) [n]1279.4 (877.3) [mn]519.6 (338.8)	5 5 5	2	1	8
904 Nonpregnant	800µg LC/MS	Crossover Buccal (10) Sublingual (10)	 [a]229 [140-1160] [a]1140 [817-2060]	 30 30	 [o]484 [350-2030] [o]1910 [1117-2680]	 ∞ ∞	2	2	2
905 Pregnant Fasted	400µg LC/MS	Sublingual (9) Vaginal (10)	[b]580 (178.1) [b]117 (42.1)	[h]30 (0) [h]102 (72)	[p]757.8 (200.5) [p]414.6 (128.2)	12 12	1	1	7
906 Pregnant Fasted	400µg GC/MS	Sublingual (10) Oral (10) Vaginal (10) Vaginal moist (10)	[cde]574.8 (250.7) [cfg]287.6 (144.3) [df]125.2 (53.8) [eg]162.8 (57.1)	[ij]26.0 (11.5) [kl]27.5 (14.8) [ik]72.0 (34.5) [jl]75.0 (31.6)	[qr]743.7 (291.2) [q]402.8 (151.6) [r]433.7 (182.6) 649.3 (333.8)	6 6 6 6	5	2	3
JEI308 Nonpregnant Fasted	400µg LC/MS	Crossover Oral GyMiso®(19) Oral Cytotec®(19)	 1100 (420) 1190 (460)	 14.8 (7.7) 19.7(12.1)	 746 (259) 766 (241)	 ∞ ∞	6	2	4

LC liquid chromatography
GC gas chromatography
MS mass spectrometry
c_{max} peak concentration
t_{max} time of peak concentration
AUC_{0-t} area under concentration curve
t time
SD standard deviation
IQR interquartile range
Matching superscript letters indicate values found to be significantly different from each other.

The peak concentrations reported for oral misoprostol in the Bioequivalence Study JEI308 are higher than all but the values reported for sublingual administration in Study 904, noting particularly the differences in sampling frequency in the first half hour. Although not conclusive, the findings suggest that peak concentrations are later with the buccal and vaginal routes than after oral or sublingual administration. The relative values further suggest the decreasing order of peak concentrations to be sublingual>oral>vaginal>buccal and for area under concentration curve sublingual>oral, vaginal (similar)>buccal.

It is reasonable to conclude that peak concentration and area under concentration curve values are of a similar order for each of the routes examined.

Buccal route

This application proposes the buccal route as an alternative to oral administration of misoprostol. The bioequivalence study did not examine this route and none of the presented references directly compares the pharmacokinetics of buccal and oral routes, probably because the progression of research interest over time was from oral to vaginal to sublingual and buccal routes, so that both oral and buccal routes have been compared with vaginal administration but not with each other.

Meckstroth et al[901] compared buccal and vaginal administration and did not find significant differences in values for C_{max} or T_{max}, although AUC values were significantly lower for buccal administration. Pharmacodynamic effects were comparable.

Schaff et al[904] compared buccal and sublingual routes of administration and found significantly lower C_{max} and AUC with the buccal than with the sublingual route.

Some reports note that misoprostol may be incompletely dissolved after 20-30 minutes in the buccal space. Schaff et al[904] removed remnants, Meckstroth et al[901] asked the participant to move them within the buccal space to encourage further dissolution, while some clinical reports advocate swallowing any remnant after 30 minutes.

Sublingual route

Three studies compared sublingual with other routes of administration[904-6]. Sublingual administration was found to result in significantly higher peak concentrations and AUC values than oral, buccal and vaginal routes. T_{max} was significantly earlier after sublingual than after vaginal but not buccal or oral administration.

Vaginal route

There has been considerable interest in the vaginal route of administration of misoprostol and many studies demonstrate its clinical efficacy. The submitted studies show comparable patterns of bioavailability to those reported for the other routes, with later and lower peak concentrations than those following oral or sublingual administration, lower AUC than that following sublingual administration but higher than that following buccal.

Some reports note that dissolution of tablets in the vagina may be incomplete, with remnants found if a vaginal examination is later undertaken, for example when misoprostol is given prior to surgical abortion.

Distribution

Plasma protein binding

The review article[704] reported serum protein binding at 85%, the Australian PI for Cytotec® at 80-90% and the proposed PI for GyMiso 81-89%, based on a 1985 review article submitted by the sponsor.

Metabolism

Sites of metabolism and mechanisms / enzyme systems involved

Misoprostol is rapidly de-esterified in plasma to misoprostol acid, the active metabolite, the concentrations of which were monitored in all reported pharmacokinetic studies[704]. No unchanged misoprostol is detected in urine[704].

Metabolites identified in humans

Active metabolites

Misoprostol acid is the active metabolite of misoprostol.

Other metabolites

The Collins review[704] reports that misoprostol acid is further metabolised to several other metabolites.

Excretion

Routes and mechanisms of excretion

The Collins review article[704] reported 80% of a radioactive dose being recovered from urine and faeces within 24 h. The Australian PI for Cytotec® states that 73% of the radioactivity of an oral dose of radiolabelled misoprostol is excreted in the urine with an additional 15% excreted in the faeces; about 56% of total radioactivity being eliminated in urine within 8 h.

Intra- and inter-individual variability of pharmacokinetics

Where quoted, the coefficients of variation for the pharmacokinetic parameters in the literature studies were of the order of 30-50%.

Pharmacokinetics in the target population

The pharmacokinetic studies were undertaken in healthy nonpregnant volunteer women of reproductive age (Study 904 and the bioequivalence study) and in pregnant women up to 13 weeks gestation prior to surgical abortion (Sstudies 901, 905 and 906). These findings are expected to be similar to those in the target population of women up to 7 weeks gestation requesting medical abortion.

Pharmacokinetics in other special populations

Age

No specific studies were performed in adolescents, although they are included in the indication. It is unlikely that misoprostol would behave differently in postpubertal young women than in adults.

Evaluator's overall conclusions on pharmacokinetics

The Bioequivalence Study JEI308 shows that GyMiso is rapidly absorbed when administered orally and provides adequate evidence that GyMiso is bioequivalent to Cytotec® to allow bridging with the international literature on misoprostol. The application presents literature studies which demonstrate adequate absorption of misoprostol when administered by other routes, including buccal, vaginal and sublingual, with some differences between routes in the resultant pharmacokinetic parameters.

There is not enough information to make a recommendation about food intake and oral administration of misoprostol; it is probably not important to overall efficacy but a contribution to variation of response cannot be ruled out. [10]

The following factors may contribute to variation in response to misoprostol:

- Individual variation in misoprostol pharmacokinetics.
- The period for which misoprostol concentration is above an undefined threshold level may be more important to clinical efficacy than rapidity of absorption and/or peak concentration.
- Lower peak concentrations may be associated with better adverse effect profiles.
- Dissolution profiles at very low pH would suggest relatively reduced absorption may occur from the stomach.
- Variations in food intake prior to oral dosing may contribute to some of the variation in response.
- Several published papers suggest enhanced liver metabolism due to first pass effect as a reason for lower oral efficacy.
- There may be some local effects of vaginally administered misoprostol.
- Individual responsiveness may vary and uterine responsiveness is known to vary with gestation.

In the evaluator's opinion there was sufficient pharmacokinetic information available to base judgments about dose and route of administration on the very substantial body of published clinical studies. While there are clearly some pharmacokinetic differences between the various routes of administration, which are likely to contribute to the observed differences in efficacy and adverse effect profiles, it is reasonable on

[10] Sponsor comment: The approved PI states: "Misoprostol should be taken 2 hours before or 2 hours after a meal".

pharmacokinetic grounds to consider oral, sublingual, buccal and vaginal routes of administration of misoprostol for gynaecological indications.

Pharmacodynamics

Studies providing pharmacodynamic data

There are no submitted specific pharmacodynamic studies. A summary of the reference report 901 is presented as Table 4.

Table 4: Uterine tone and activity timepoints

All times expressed in minutes as mean (standard deviation). Activity measures not shown.

Route of administration of misoprostol	Time to onset of increased tone	Time to first uterine contraction	Time to sustained uterine activity	Time to peak uterine activity	Number with sustained uterine activity
Vaginal	27.2 (16.8)	81.8 (69.7)	105.6 (60.8)	231.0 (67.9)	8/10
Vaginal moist	17.4 (7.0)	98.2 (55.9)	127.8 (45.5)	273.3 (31.6)	9/10
Buccal	41.2 (35.8)	67.1 (49.1)	90.0 (60.7)	264.0 (23.7)	8/10
Rectal	102.5 (127.5)	79.2 (71.2)	118.8 (75.5)	166.7 (83.7)	4/9

Uterine activity after both vaginal routes and buccal administration were very similar, despite some significant differences in pharmacokinetic parameters. Significantly fewer women had sustained uterine activity after rectal administration of misoprostol.

The sponsor's Clinical Overview provided a brief summary, stating that "misoprostol increases the uterine contractility as early as 8 minutes after oral intake, with a maximal effect 25 minutes after intake." This statement is not specifically referenced and differs slightly from the values presented in the literature reports provided and discussed.

The 1990 review by Collins[704] outlines the development of misoprostol for gastrointestinal indications and the research report by Meckstroth et al[901] and summary report by Gemzell-Danielson[910] provide some data on the effects of misoprostol on the uterus.

The published clinical literature provides abundant confirmation that misoprostol induces uterine contractions and expulsion of early pregnancy and can induce labour later in pregnancy. The desired clinical effect is a direct result of the pharmacodynamic effects.

Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

Mechanism of action

Misoprostol is a prostaglandin E1 analogue. There is little further comment in the application about its mechanism of action.

Pharmacodynamic effects

Primary pharmacodynamic effects

Misoprostol, when administered by the oral, vaginal, buccal or sublingual route causes an increase in uterine tone and the induction of uterine contractions[901, 910], which have been measured in the reported studies in pregnant women given misoprostol prior to surgical abortion. A substantial clinical literature confirms that misoprostol is effective in inducing uterine contractions and abortion, particularly following administration of mifepristone.

One of the studies summarised in reference 910 recorded substantially greater increases in uterine contractility when a prostaglandin was administered 48 h after mifepristone than when the same dose was used without this pretreatment. The other studies examined misoprostol alone.

Secondary pharmacodynamic effects

The gastrointestinal effects of misoprostol are secondary for the proposed indication but primary for the approved indications for Cytotec®. The review article[704] presented noted that misoprostol reduces gastric secretion and protects gastric mucosa against the effects of nonsteroidal anti-inflammatory drugs by increasing mucosal blood flow, mucus production and bicarbonate secretion. These effects may contribute to the adverse effects which are observed when misoprostol is used for gynaecological indications.

Time course of pharmacodynamic effects

The participants in the pharmacodynamic studies were women at 8-12 weeks gestation who were given misoprostol while fasted, a few h prior to surgical abortion. The dosage groups comprised about 10 women each.

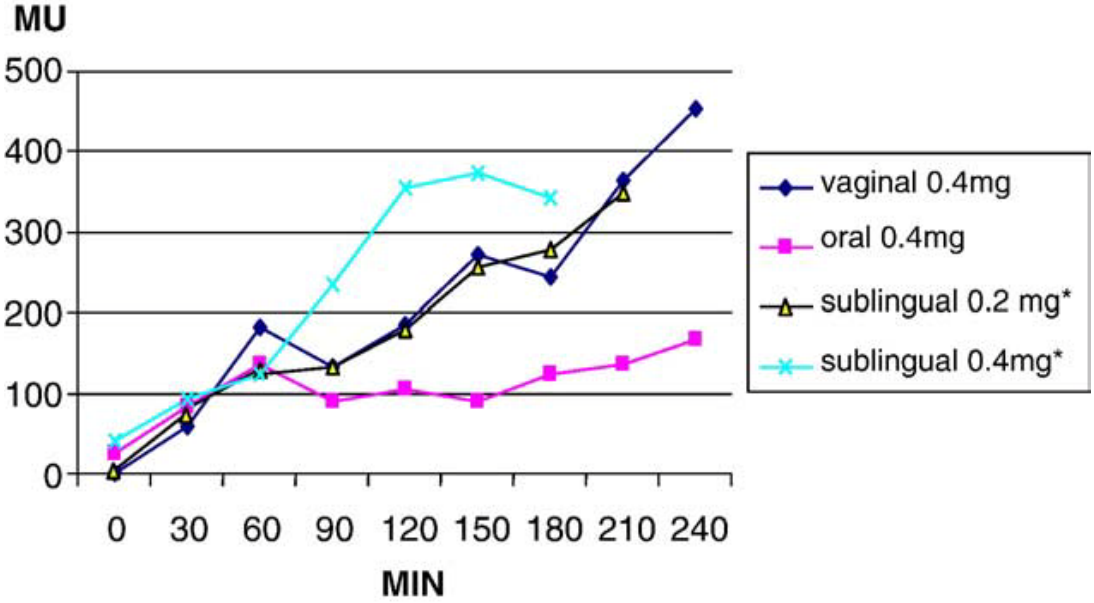
The studies reported in references 901 and 910 found the first increase in uterine tone to occur at means of around 8 minutes for oral, 10-12 minutes for sublingual, 17-27 minutes for vaginal and 41 minutes for buccal administration of 400 μg misoprostol.

Most women developed sustained uterine contractions; in Study 901 after a mean of 90-105 minutes (SD 45-60 minutes) and in Study 910 after 2 h. Uterine activity had peaked by the end of the study, 5 h after the misoprostol dose.

Gemzell-Danielsson et al[910] reported on two similar studies, both of which found a significantly earlier rise in uterine tonus after oral administration of misoprostol than after vaginal but significantly lower uterine activity at 2 h and overall in the oral groups, with a less consistent response. Figure 4 shows mean uterine activity in graphical form, demonstrating the lower activity after oral than vaginal or sublingual administration.

Figure 4: Mean uterine activity 4 doses/routes (A)

MU=Montevideo Units. Reproduced from Gemzell-Danielsson[910] in which it was modified from a previous publication by the same group.

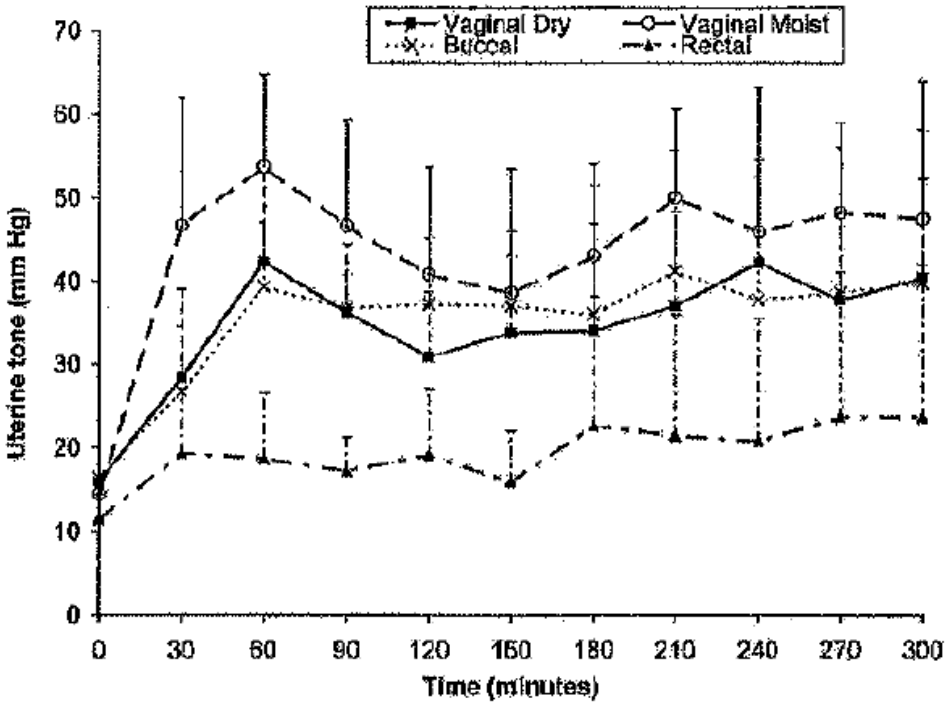


Study 901 found similar uterine activity with vaginal and buccal administration of misoprostol, despite significantly lower area under plasma concentration curve values in the latter, although the patterns of absorption were similar.

Figure 5 and Figure 6 present uterine tone and activity for 4 different routes of administration of misprostol, showing that buccal and vaginal administration produce similar pharmacodynamic responses, despite the different pharmacokinetic patterns noted.

Figure 5: Mean uterine tone 4 routes

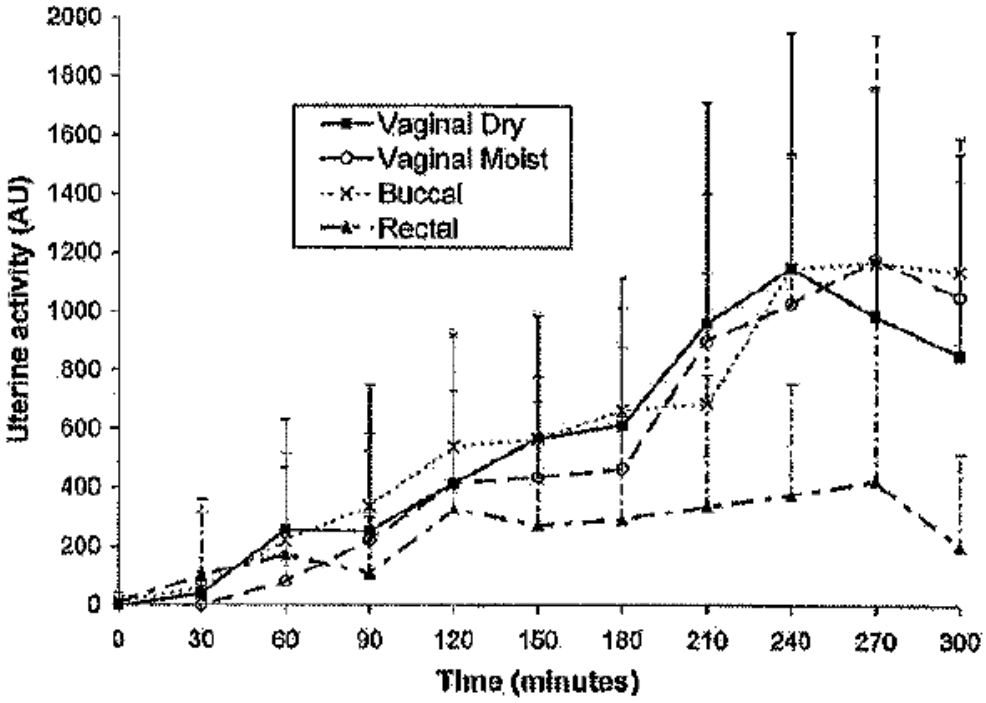
Error bars represent 1 SD. Reproduced from Meckstroth et al[901].



Mean uterine tone in mm of Hg for four epithelial routes of misoprostol adminsitraiton over 5 h.

Figure 6: Mean uterine activity 4 routes (B)

Error bars represent 1 SD, AU=Alexandria Unit. Reproduced from Meckstroth et al[901].



Mean uterine tone in Alexandria Units (AU) for four epithelial routes of misoprostol adminsitraiton over 5 h. Alxandria Units estimate area under the pressure-time curve for uterine contractions.

Evaluator's overall conclusions on pharmacodynamics

The studies reported provide clear evidence of the induction of increased uterine tone and uterine contractions by misoprostol when administered by the oral, vaginal, buccal and sublingual routes. The response appears to be earlier after oral and sublingual than after vaginal or buccal misoprostol but overall greater after vaginal, buccal or sublingual than oral misoprostol.

These findings are consistent with abundant clinical evidence of the efficacy of misoprostol at inducing abortion. They contribute to understanding of the observed clinical differences between varying routes of administration of misoprostol.

Efficacy

Dosage Selection for the Pivotal Studies

Dosage selection for the pivotal studies is based on the evolving body of clinical work; the dose used in early studies may have been influenced by the available formulation of misoprostol as a 200 μg tablet. Misoprostol has been used with mifepristone in regimens to induce abortion since the early 1990s and has been the main prostaglandin used, largely replacing gemeprost, since around 2000. Studies as early as 1993[601] reported high efficacy rates with mifepristone followed by 400 μg misoprostol orally and subsequent studies have largely used doses of 400-800 μg via several routes.

Clinical Efficacy

The main efficacy question for this application is whether misoprostol used with mifepristone produces adequate complete abortion rates for the gestations under consideration. As there is no registered regimen for medical abortion in Australia, this does not require comparative trials so much as consideration of whether demonstrated success and failure rates in populations treated with mifepristone and misoprostol are acceptable in clinical use. It would appear that efficacy rates of 90-95% are clinically acceptable, allowing 90-95% of women who choose medical methods of abortion to avoid surgery. Many of the presented references contribute to the considerable body of evidence concerning women's preferences and satisfaction with treatment but these aspects were not evaluated.

The evaluation of the companion application for registration of Mifepristone Linepharma covered the evolution of medical abortion regimens, which is not repeated here. When abortion is indicated, it is now well established that medical abortion is a safe and effective alternative to surgical methods and is preferred by many women[11(ch4.5)]. Further, methods now recommended by the RCOG include mifepristone and misoprostol[11(ch7.2)].

This evaluation assumes that optimal regimens for early medical abortion include 200 mg mifepristone prior to prostaglandin, as discussed in the Mifepristone LinePharma clinical evaluation (see Mifepristone LinePharma AusPAR). Given the previously established equivalence of 200 mg and 600 mg doses, studies using either or both doses of mifepristone were considered relevant by the evaluator.

[11] Royal College of Obstetricians and Gynaecologists (RCOG). The Care of Women Requesting Induced Abortion. Evidence-based Clinical Guideline Number 7, November 2011 http://www.rcog.org.uk/womens-health/clinical-guidance/care-women-requesting-induced-abortion Updated version of reference 911: accessed January 2012.

It is noted that the agreed literature search strategy for the Mifepristone Linepharma application was focused on regimens using mifepristone with oral misoprostol and excluded studies limited to other routes of administration, although some studies which used more than one route were included. The current application proposes buccal administration as an alternative to the oral route and several relevant references have been added to this application. The evaluation focuses on these two routes; some commentary on other routes is included but these have not been systematically examined by the sponsor or in this evaluation. This evaluation also focuses on studies which allow examination of efficacy rates in the gestation range ≤49 days, noting that some of these studies separate analyses for ≤42 and 43-49 days.

There is a considerable volume of accumulated clinical evidence regarding mifepristone and misoprostol for medical abortion, dating from prior to registration of mifepristone in several countries and reported in the subsequent decade in USA and two decades in France and UK. It is the cumulative content of this body of evidence as well as individual studies on some aspects which contribute to the current state of knowledge.

The current question is not whether there is a treatment effect but what are optimal regimens for medical abortion at different gestations, based on efficacy and adverse event profiles. The evaluator has therefore used summary tables addressing different aspects of treatment regimens rather than large numbers of summaries of individual studies.

Although the companion application sought registration of mifepristone both prior to 49 days gestation and after the first trimester, the current application seeks registration of misoprostol only for the first indication.

The application uses the expression days of amenorrhoea (DA), which is also used in describing many of the studies. Duration of amenorrhoea is not always an accurate predictor of gestational age, which can be accurately assessed by ultrasound examination when there is doubt clinically. The evaluator therefore used the expression 'days gestation' (DG) in the evaluation where gestation is the important parameter and/or has been confirmed.

Pivotal efficacy studies

The application identifies two World Health Organization (WHO) Task Force studies[508-9] as pivotal. While they were indeed pivotal to the development of medical abortion regimens, one of them[508] included only women from 57-63 days gestation and used mifepristone with gemeprost not misoprostol. It is not considered pivotal to this application. The other study[509] is reasonably included as pivotal, for its scale and the presentation of regimens and outcomes of medical abortion with mifepristone and oral misoprostol rather than the comparison of two different mifepristone doses which was its main objective. The clinical overview also refers to "the other four pivotal trials" but these could not be identified.

The evaluator included Study 528 as pivotal because it compares the two routes of administration of misoprostol proposed in the application.

Study 509

Study design, objectives, locations and dates

This was a multicentre double blind randomised controlled trial comparing the abortifacient efficacy and side effects of two single doses of mifepristone (200 versus 600 mg) followed 48 h later by an oral dose of 400 μg of misoprostol in women with an early pregnancy. It was conducted in seventeen centres in thirteen countries and reported in 2000.

Comment: For the purposes of this application the comparison between the two doses of mifepristone, which was the main purpose of the study, is not directly relevant.

Inclusion and exclusion criteria

Pregnant women requesting legal termination of pregnancy at ≤35 days delay in menses (that is equivalent to ≤63 days amenorrhoea) were included. Other inclusion and exclusion criteria related to confirmation of pregnancy and gestation and reasonable exclusions on the basis of other health or medical conditions.

Study treatments

There were two treatment arms. Participant women received a single oral dose of either 200 mg or 600 mg of mifepristone, followed 48 h later (Day 3) by a single oral dose of 400 μg misoprostol. They were observed for 3 h and returned for follow up evaluation on Days 15 and 43.

Efficacy variables and outcomes

The main efficacy variables were:

- completeness of abortion
- need for emergency or elective curettage prior to first menstruation
- failure of attempted abortion.

The primary efficacy outcome was complete abortion as determined at the first follow up visit. It could be confirmed by passage of the products of conception, a negative pregnancy test or an empty uterus on ultrasound examination (only performed if necessary) and no emergency or elective curettage during the period up to first menstruation.

Classification of outcomes was as follows:

- complete abortion
- incomplete abortion: curettage needed
- missed abortion: nonviable pregnancy on ultrasonography
- failed attempted abortion: continuing pregnancy despite treatment
- unclassified failure: clinical diagnosis of missed or failed attempted abortion when ultrasonography unavailable.

Randomisation and blinding methods

A computer generated random number sequence was developed in Geneva and stratified randomisation conducted at each centre, using a fixed block size of four and four gestational age strata (≤14, 15-21, 22-28 and 29-35 days menstrual delay).

Blinding was achieved by using identical appearing pill bottles which were labelled with study number, centre name and sequentially allocated participant number and which contained three tablets, either three 200 mg mifepristone tablets or one mifepristone tablet and two identical appearing placebo tablets. Participants and investigators remained blinded to treatment allocation but analysts in Geneva were not.

Analysis populations

The main analysis was by intention-to-treat, pooling those lost to follow up with undetermined failures in a single category. A secondary analysis excluded women with unknown outcomes, those who had not taken misoprostol and those with protocol violations.

Sample size

Sample size calculations were based on a hypothesis that the complete abortion rate would be 96% for the higher and 92% for the lower dose of mifepristone. For a power of 90% and one-sided alpha of 0.05, 601 participants were needed in each group; 1589 were enrolled "to increase the power further and to allow for losses to follow up".

Statistical methods

Outcomes between groups or categories of delay of menses were compared by using relative risks or odds ratios and 95% CI, using Taylor series to calculate CI for crude relative risks. Adjustment for centres was also undertaken.

Participant flow

A total of 1589 recruited participants were randomised: 792 women had 200 mg mifepristone and 797 had 600 mg; all were included in the main analysis.

For the secondary analysis the following were excluded (numbers for lower and higher dose groups respectively):

- 8 and 9 participants with protocol violations (see next section)
- 3 and 5 who took mifepristone but not misoprostol
- 17 and 24 who were lost to follow up, including 3 in each group who had an elective surgical abortion before misoprostol or when abortion had not occurred 3 h after misoprostol.

This left a total of 1530 participants in the secondary analysis; 766 in the lower dose and 764 in the higher dose group.

Major protocol violations/deviations

Eight in the lower dose and 9 in the higher dose group were later found to have protocol violations; 14 of these were outside the gestational limits of the study or missing gestational information, one was breastfeeding and two were taking excluded medicines. It was reasonable to exclude these from the secondary analysis and this is unlikely to have affected the study conclusions.

Baseline data

Demographic data were compared between the two treatment arms and were, as stated, similar in all important respects. They also reflect the likely patient group in which these regimens may be used. The breakdown by gestational age was similar in the two groups.

Results for the primary efficacy outcome

Results are summarised in Table 5, with complete abortion occurring in 89.3% of the lower mifepristone dose group and 88.1% of the higher mifepristone dose group. Continuing pregnancies (failed attempted abortion) occurred in 2.8% and 1.9%, with total failure rates of 10.7% and 11.9% respectively.

Comment: The complete abortion rates would be about 91% in both groups if women with unknown outcomes were excluded from the denominator as was done in most of the presented studies.

Table 5a: Study 509: outcomes of treatment by mifepristone dose

Values given as number (%) [95%CI]. Reproduced from reference 509.

Ref.	Pregnancy age (DA)	Study features	Success rate	Other endpoints
509	< 64	Randomized, 2 parallel groups (200 and 600 mg MF) followed by 400 mcg oral misoprostol	200 mg (n= 792): 89.3% (95% CI: 86.9-91.3) 600 mg (n= 797): 88.1% (95% CI: 85.6-90.2) Decline in efficacy rate with pregnancy age identical in both groups.	Median time to expulsion, expulsion within 3hrs after misoprostol identical in both groups

Table 5b: Outcomes of treatment by treatment group. Values are given as n (%) (96% CI).

Outcome	Dose of mifepristone	
	200 mg (*n* = 792)	600 mg (*n* = 797)
Complete abortion	707 (89·3) [86·9–91·3]	702 (88·1) [85·6–90·2]
Incomplete abortion	27 (3·4) [2·3–4·9]	37 (4·6) [3·3–6·3]
Missed abortion	19 (2·4) [1·5–3·7]	12 (1·5) [0·8–2·6]
Failed attempted abortion	22 (2·8) [1·8–4·2]	15 (1·9) [1·1–3·1]
Unclassified failure	0 (0·0) [0·0–0·5]	7 (0·9) [0·4–1·8]
Undetermined	17 (2·1) [1·3–3·4]	24 (3·0) [1·9–4·4]
TOTAL	792 (100·0)	797 (100·0)

The overall efficacy of the regimens for the whole group was 89% with 95% CI of 87-90%. The authors concluded that although there were fewer side effects, the regimens including misoprostol were less effective than those they had previously investigated using gemeprost as the prostaglandin (94% efficacy with 95% CI 91-96%) and considered a different prostaglandin; higher dose of misoprostol or different route of misoprostol administration might be needed.

Results for other efficacy outcomes

Table 6 shows the overall results by group and stratified by gestation. There was a statistically significant decrease in efficacy of both regimens with increase in gestational age; from 92.2% in the earliest group to 80.3% in the latest (χ^2 for trend 16.4, $p<0.01$). This was also reflected in continuing pregnancy rates (failed attempted abortion), which were 1.4% in the ≤14 days delay group, 1.2% in the 15-21 days delay group, 2.7% in the 22-28 days delay group and 9.0% in the 29-35 days delay group (χ^2 for trend 16.6, $p<0.01$).

The study authors concluded that efficacy was too low to justify the use of these regimens after 21 days menstrual delay, that is 49 days of amenorrhoea.

Table 6: Study 509: failure rate by mifepristone dose and gestational group

Crude relative risks (RR) and adjusted odds ratios (OR) of failure to achieve complete abortion by treatment group and menstrual delay. Reproduced from reference 509.

Variable	No. of women	Failure rate (%)	RR (95% CI)	OR (95% CI)*
Mifepristone dose (mg)				
600	797	11·9	1·0 (Referent)	1·0 (Referent)
200	792	10·7	0·9 (0·7–1·2)	0·9 (0·6–1·2)
Menstrual delay (days)†				
≤ 14	488	7·8	1·0 (Referent)	1·0 (Referent)
15–21	508	10·8	1·4 (0·9–2·1)	1·4 (0·8–2·2)
22–28	452	13·3	1·7 (1·2–2·5)	2·2 (1·3–3·6)
≥ 29	137	19·7	2·5 (1·6–4·0)	2·3 (1·1–4·5)

*Adjusted for effect of centres.
†Total no. of women with information on delay = 1585.

The median time of expulsion was 51 h after mifepristone, with 47.9% of low dose and 49.4% of high dose mifepristone patients expelling products of conception within 3 h of misoprostol administration.

Study 528

Study design, objectives, locations and dates

This was a multicentre open label randomised controlled trial to estimate the effectiveness of 800 μg oral and buccal misoprostol 24-36 h after mifepristone 200 mg for medical abortion at 57-63 days since the last menstrual period (LMP) and to compare the effectiveness of the two regimens in all included women (including earlier gestations). It was conducted in seven centres in the USA between September 2006 and May 2007.

Inclusion and exclusion criteria

Adult women (≥ 18 years old) seeking medical abortion up to 63 days amenorrhoea were included. Other inclusion and exclusion criteria related to medical contraindications and logistic considerations and were reasonable.

Study treatments

There were two treatment arms. Participant women received a single oral dose of 200 mg of mifepristone, followed 24-36 h later by 800 μg misoprostol, taken at home either orally or buccally according to random assignment. Women assigned to buccal administration were instructed to hold two 200 μg pills in each cheek pouch for 30 minutes and then to swallow any remnants. They were asked to keep a diary and return for follow up 7-14 days after taking mifepristone, when a clinical assessment, usually including vaginal ultrasound examination, was undertaken. If there was a continuing pregnancy, suction curettage was recommended. If there was a non viable pregnancy (sac or other products of conception), women were offered suction curettage, expectant management or a further dose of misoprostol. For the latter two options, a further review was planned 7 days later, when suction curettage was recommended if there was a persistent non viable pregnancy. Suction curettage was also performed if medically necessary (for example for excessive bleeding) or at the woman's request.

Efficacy variables and outcomes

The primary outcome variable was successful medical abortion, defined as a complete abortion without surgical intervention at any point regardless of the number of doses of misoprostol taken.

The secondary outcome variable was the effect of a second dose of misoprostol.

Randomisation and blinding methods

Assignment was computer generated with randomisation sequence using random blocks of eight and stratified by study centre. Opaque envelopes were prepared by staff not involved in the study and assigned to participants in numerical sequence.

The study was not blinded, allocation being revealed to clinicians and participants upon opening the envelopes.

Analysis populations

Intention-to-treat and per-protocol analyses were undertaken. These were not significantly different so only the per-protocol analysis was presented.

Sample size

Sample size calculations were based on the anticipated proportion of women at 57-63DA (15-20%) and estimated efficacy of 93% with 95%CI of ± 5%. 105 women in each arm in that gestational band would require enrolment of around 1,200 women; 425 women in each arm would be able to detect a 5% difference between the arms at the anticipated 95% efficacy with 80% power at the 95% confidence level. Enrolment was discontinued after 966 women when 265 women in the 57-63DA band had been randomised, ensuring at least 210 analysable cases.

Statistical methods

The SPSS program[12] was used for data analysis. Outcomes were compared between groups using χ^2 or Fisher exact test and for the effect of gestational age χ^2 for trend was used.

Participant flow

Nine hundred and sixty-six recruited participants were randomised: 484 women to buccal and 482 to oral administration.

Two withdrew from each arm before mifepristone and one from the buccal arm before misoprostol. Forty-seven women in the buccal and 45 in the oral administration groups were lost to follow up, leaving 434 and 435 respectively. Four hundred and twenty-one and 426 respectively were included in the per protocol analysis after excluding 13 and 9 respectively for protocol deviations.

Some 9.5% of participants were lost to follow up after administration of misoprostol.

Comment: This is a common problem in studies of medical abortion (see discussion below) and it is reasonable to conduct analysis based on those with known outcomes, while acknowledging that there is some room for error here.

Major protocol violations/deviations

Apart from one ectopic pregnancy in the buccal group, the protocol violations all related to dosage, timing and/or route of administration of misoprostol. The numbers are small and it was reported that the findings of the per protocol analysis were not significantly different from the intention to treat analysis.

Comment: While a case can be made for excluding patients who were known not to have followed the protocol, given that the misoprostol was self administered at home it is quite likely that there were other protocol violations which may have not been recognised. An

[12] SPSS is a computer program used for survey authoring and deployment, data mining, text analytics, statistical analysis, and collaboration and deployment (batch and automated scoring services).

intention to treat analysis may have been more appropriate but is unlikely to have affected the study conclusions.

Baseline data

Demographic data were compared between the two treatment arms and were similar except that there was a difference in age (25.8 years for oral compared with 26.7 years for buccal administration, significant at p=0.02) of doubtful importance.

Results for the primary efficacy outcome

Treatment outcomes are summarised in Table 7; failure rates and continuing pregnancy rates for the various gestational groups are depicted in Figure 7.

Overall the efficacy of buccal misoprostol was greater than that of oral administration (96.2% compared with 91.3%, p=0.003), with almost identical results for the intention to treat analysis. Among women with pregnancies of 57-63DA, efficacy was higher after buccal than oral administration (94.8% compared with 85.1%, p=0.015). The frequency of ongoing pregnancy was significantly higher in that gestational band for women who had oral misoprostol (7.9% compared with 1.7%, p=0.029). There were no significant differences between the routes of administration in the other gestational bands. There was no significant difference in the success of buccal administration with gestational age, although there was some decline with advancing gestational age. There was however a significant decline in success rates after oral administration, from 96.1% ≤49DA to 85.1% at 57-63DA (p<0.001).

Table 7: Study 528: treatment outcomes

Reproduced from reference 528.

Gestational Age (d)	Oral	Buccal	RR (95% CI)
Success*	91.3* (389/426) (88.2–93.8)	96.2* (405/421) (93.9–97.8)	0.95 (0.92–0.98)
42 or less	97.8 (90/92) (92.4–99.7)	98.7 (75/76) (92.9–100.0)	0.99 (0.93–1.03)
43–49	94.7 (107/113) (88.8–98.0)	96.4 (132/137) (91.7–98.8)	0.93 (0.86–1.00)
50–56	88.8† (95/107) (81.2–94.1)	95.7† (89/93) (89.4–98.8)	0.69 (0.56–1.04)
57–63	85.1* (97/114) (77.2–91.1)	94.8* (109/115) (89.0–98.1)	0.90 (0.82–0.98)
Failure	8.7* (37/426) (6.2–11.8)	3.8* (16/421) (2.2–6.1)	2.29 (1.29–4.04)
Ongoing pregnancy	3.5* (15/426) (2.0–5.7)	1.0* (4/421) (0.3–2.4)	3.71 (1.24–11.07)
42 or less	2.2 (2/92) (0.3–7.6)	1.3 (1/76) (0.0–7.1)	1.65 (0.15–17.87)
43–49	0.9 (1/113) (0.0–4.8)	0.7 (1/137) (0.0–4.0)	1.21 (0.08–19.17)
50–56	2.8 (3/107) (0.6–8.0)	0.0 (0/93) (0.0–3.2)	–
57–63	7.9* (9/114) (3.7–14.5)	1.7* (2/115) (0.2–6.1)	4.54 (1.0–20.55)
Medically necessary	2.6 (11/426) (1.3–4.6)	1.9 (8/421) (0.8–3.7)	1.36 (0.55–3.34)
Persistent sac	2.3 (10/426) (1.1–4.3)	1.0 (4/421) (0.3–2.4)	2.47 (0.78–7.82)
Patient request	0.2 (1/426) (0.0–1.3)	0.0 (0/421) (0.0–0.7)	–

RR, relative risk; CI, confidence interval.
Data are %, (n/N), or (95% confidence interval), unless otherwise specified.
* $P<.048$, comparing oral and buccal groups.
† $P<.10$, comparing oral and buccal groups.

Figure 7: Study 528: failure rates and ongoing pregnancy rates with gestation

Reproduced from reference 528.

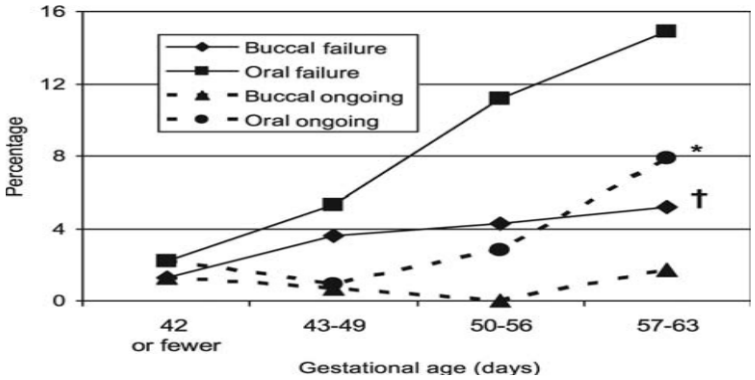


Fig. 2. Illustration of how failure rates and, more specifically, ongoing pregnancy rates increased with gestational age, particularly in the group of women that took oral misoprostol. * Difference between ongoing pregnancy rates by regimen is statistically significant at 57–63 days since the LMP (P=.029). † Difference between failure rates by regimen is statistically significant at 57–63 days since the LMP (P=.015).

Winikoff. Misoprostol by Mouth in Medical Abortion. Obstet Gynecol 2008.

Illustration of how failure rates and more specifically, ongoing pregnancy rates increased with gestational age, particularly in the group of women that took oral misoprostol. *Difference between ongoing pregancy rates by regimen is statistically significant at 57-63 days since the LMP (P=.029). †Difference between failure rates by regimen is statistically significant at 57-63 days since LMP (P=.015). *Winkoff*. Misoprostol by Mouth in medical Abortion. *Obstet Gynecol* 2008.

Results for other efficacy outcomes

Fourteen women treated with buccal misoprostol and 12 with oral misoprostol had a second dose of misoprostol at the follow up visit, of whom 92.9% and 50.0% respectively (p=0.026) achieved a successful outcome, improving the success rate for buccal by 3.1% and for oral misoprostol by 1.5%.

Other efficacy studies

No further individual studies are summarised, as the evaluator felt the larger body of evidence is best digested as summary tables. All of the studies included in the efficacy tables are prospective clinical trials except for Study 908, which reports a large retrospective clinical series. Most of the included trials are randomised, although not all arms have been included in the tables, for instance if prostaglandins other than ɔstol were used. Study 539 is a prospective cohort study.

The tables include fourteen clinical trials from the sponsor's listing taken from the 501-625 group, omitting those outside gestation limits, not using misoprostol or using only routes not under consideration in the current application. Among the additional studies provided with the current application, six reported clinical outcomes: four of these[705-6, 708, 710] reported on medical abortion in a range of clinical environments internationally, using 400 μg doses of misoprostol after mifepristone. Efficacy rates ranged from 84-98.6% and the studies were not informative about the efficacy of regimens under consideration in this application. Study 909 reported on a large randomised WHO study examining two doses of misoprostol given sublingually or vaginally and although of interest was not directly relevant to the current efficacy considerations. Study 908 was included. It was a retrospective audit reporting 1349 women up to 59DG who had mifepristone followed by 800 μg buccal misoprostol and 278 women up to 54DG who had mifepristone followed by 800 μg oral misoprostol. There was a substantial proportion above the reported numbers

of unknown outcome due to loss to follow up. The study is identified in the tables as an audit.

Efficacy endpoints

Primary endpoint: "complete abortion"

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. This definition includes as treatment failures continuing pregnancies, missed or incomplete abortions and curettage performed for any reason including bleeding or unwillingness to wait for abortion to occur. 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. Expectant and medical management (usually using misoprostol) are now accepted approaches to early miscarriage, including when an intact sac is present[13].

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."

[13] RCOG The management of early pregnancy loss 2006. http://www.rcog.org.uk/files/rcog-corp/uploaded-files/GT25ManagementofEarlyPregnancyLoss2006.pdf Accessed December 2011.

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."

The RCOG comments[11(ch5.2)]:

"Rates of surgical evacuation following either medical or surgical abortion vary according to experience, diagnostic criteria and intervention thresholds, and these will vary between centres."

In many 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, 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.

Secondary endpoint: continuing pregnancy

Where reported, the evaluator has included in the tables numbers and rates of continuing live pregnancies, that is failed attempted abortion. In most studies this diagnosis was confirmed by ultrasound examination and refers to an intrauterine sac with a fetal heart detected. Although the time after misoprostol at which the examination was undertaken varied between studies it is likely to be more consistently recognised and defined than the other categories of failed medical abortion, particularly surgical intervention, which has such variable indications, and incomplete abortion, rates of which vary considerably according to when and how it is assessed.

Further, it is especially important not to miss a continuing pregnancy, as this might result in a woman realising much later that she is unexpectedly still pregnant. The other categories of failed procedure are likely to resolve spontaneously with time or to result in symptoms which will lead a woman to seek medical attention. The potential symptoms and risks are similar to those experienced by women at various stages of miscarriage and should be managed similarly.

Choice of prostaglandin

For the last 10 years or so, almost all studies of medical abortion report misoprostol as the prostaglandin used. Gemeprost had been previously established to be safe and effective but misoprostol is preferred by clinicians and researchers because it is stable at room temperature and can be given by several different routes; it is also more cost effective. Studies using mifepristone (200 mg or 600mg) with gemeprost but with no misoprostol arm, achieved complete abortion rates of around 94% to 56DA[506], around 92% to 56DA[511],

95% to 63DA[604] and 94.8% to 63DA[571]. Two studies directly compared misoprostol with gemeprost after mifepristone to 63DA; neither found significant differences between complete abortion rates. In study 515 there were 96.7% (95% CI 94.9-98.5%) complete abortions after 0.5 mg gemeprost vaginally and 94.6% (95% CI 92.3-96.9%) after 600 μg misoprostol orally. In Study 513 there were 96.2% complete abortions after 0.5 mg gemeprost vaginally and 98.7% after 800 μg misoprostol vaginally

Misoprostol is thus established as a suitable alternative to gemeprost for early medical abortion and now recommended by the Guideline Development Group of the RCOG[11(ch7.2)].

Interval between mifepristone and misoprostol

The conventional interval is 36-48 h based on the understanding that this time is needed for the antiprogesterone effects to enhance prostaglandin response (see also Mifepristone Linepharma AusPAR). One study found a significantly lower complete abortion rate with a 6-8 h than a 48 h interval between mifepristone and oral misoprostol (50% versus 91%)[502]. A pilot study examined mifepristone with immediate misoprostol given buccally and reported a complete abortion rate of 72.5% (95%CI 56.1-85.4) in the ≤49 DA group[579], which is not clinically acceptable. Other studies have reported acceptable complete abortion rates with oral or buccal misoprostol given at least 24 h after mifepristone[520, 526, 528] (Table 8).

There are not sufficient data to make a recommendation about intervals lower than 24-48 h between mifepristone and oral or buccal misoprostol. Some studies suggest acceptable complete abortion rates of at least 95% may be achieved with shorter mifepristone/misoprostol intervals when misoprostol is administered vaginally[584, 563, 594, 557]; these are not considered further here.

Studies using oral or buccal misoprostol up to 49DA

Table 8 summarises the efficacy outcomes of studies which used oral or buccal misoprostol up to 49DA or presented outcomes for this gestational band, grouped according to the dose used. The evaluator included studies with at least 100 participants in the group under consideration and studies using 200 mg and/or 600 mg doses of mifepristone, identifying in the tables those who used the 600 mg dose in some or all participants. The group of studies is similar to those in tables in the sponsor's Clinical Overview but the evaluator has omitted the gemeprost entries and the gestations beyond 49 DA, included more detail about the studies and separated the dosage groups. The evaluator included two studies which reported buccal use of misoprostol and some additional studies in the 400 μg (518, 520 and 539) and 800 μg categories (522, 908). Continuing pregnancy rates are included where known for this gestational band. Study 908 was a retrospective audit, all of the rest being prospective and mainly randomised controlled trials. Reference 601 reported two prospective studies undertaken in France in 1991-2 in the rather early days of medical abortion; it is likely that they included a higher proportion of earlier gestation pregnancies than the later studies.

For some studies subanalyses were reported separately for gestational bands of ≤ 42 days and 43-49 days, while others grouped these as ≤ 49 days. The table indicates with a ♭ those which include all gestations up to 49 days, the unmarked populations referring only to 43-49 days. Those which include only the upper band (43-49DA) might be expected to have slightly lower efficacy rates than those including earlier gestations (see also below).

Table 8: Efficacy of different oral and buccal doses of misoprostol after mifepristone

Report	Misoprostol dose µg BU=buccal all others oral	Interval after mifepristone (hours)	Number analyzed this regimen all gestations	Number 43-49DA þ includes ≤42DA	Complete abortions	Continuing pregnancies
601	400^	48	488	488 þ	96.9%	0.8%
601	400^±200@4 hours	48	385	385 þ	98.7%	0.3%
509	400*	48	1585	508	89.2%	1.2%
518	400^	36-48	219	143 þ	89%	0.7%
520	400±rpt @24 hours	24-48	319	120	93.0%	0
521	400	48	354	354 þ	91.5%	3.6%
539	400^	48	859	827 þ	92%	1%
507	600*	48	220	119 þ	97.5%	0
520	600±rpt @24 hours	24-48	319	124	92.5%	
515	600	48	386	113	95.6%	<1%
517	600	48	149	149 þ	94.6%	2.0%
523	600	48	440	163	89.6%	
518	400+400^±rpt@4-8days	36-48	268	176 þ	93% 96% after rpt	0.6%
519	400+400±rpt@3-7days	24	548	348 þ	90% 95% after rpt	1.1%
522	800+400 12hrly	36-48	723	236 þ	93.6%	
528	800±rpt@7-14days	24-36	426	113	94.7%	0.9%
908	800±rpt@24hours (audit)	24	278	127	95.3%	0.8%
528	800BU±rpt@7-14days	24-36	421	137	96.4%	0.7%
908	800BU±rpt@24hours (audit)	24-48	1349	467	98.1%	

*includes 200 and 600mg mifepristone doses
^600mg mifepristone

The "400+400" group had an initial dose of 400 µg misoprostol followed by a repeat dose 2 h later based on the idea that this might improve efficacy by sustaining serum levels for longer, more like those observed with vaginal administration[519]. In Studies 518, 519, 520, 528 and one of the 601 studies, a repeat dose of misoprostol could be given at the interval indicated if abortion had not occurred. In Study 522, 400 µg misoprostol was taken orally twice daily for a further 7 days. In Studies 518 and 519 the repeat dose was given vaginally and complete abortion rates reached 96% and 95% respectively by 2 weeks.

The studies within each dosage group are not directly comparable; they have several different approaches to follow up including repeat doses of misoprostol. They do give an idea of the extent and consistency of the studies and their findings despite variations in clinical practice as described later in this evaluation. In summary, reported efficacy rates are:

- 89-98.7% for the studies using 400 µg oral misoprostol
- 89.6-97.5% for 600 µg orally
- 90 and 93% for "400+400 µg" orally
- 95-96% for "400+400 µg" orally (repeat dose allowed)
- 93.6-95.3% for 800 µg orally (repeat dose allowed)
- 96.4-98.1% for 800 µg buccal misoprostol (repeat dose allowed).

It is unclear how frequently a repeat dose was prescribed in these studies and it is also unknown to what extent the repeat dose and to what extent delaying outcome assessment and timing of surgical intervention may have affected reported complete abortion rates.

For these populations up to 49DA, two studies using 400 µg and one using 600 µg doses reported continuing pregnancy rates over 1%, with one using a divided dose of 800µg reporting a rate of 1.1%.

These results suggest that acceptable efficacy rates can be achieved with all the regimens presented. They appear be more consistent with 800 µg doses given orally or buccally when a repeat dose is an option; the wide variation in other groups may reflect variations in practice.

Studies comparing routes of administration of misoprostol

Table 9 summarises randomised controlled trials which compared different dosages and regimens of misoprostol up to 49DA. This table presents some of the material in the sponsor's Clinical Overview but the evaluator again omitted the gemeprost data, included more detail about the studies, restricted the entries to reports up to 49DA and for clarity included less information about different types of failure.

All of the included studies also examined later gestations, for which there were different outcomes and conclusions; these are considered further below. Most of these studies found no significant difference between efficacy rates in the gestational range up to 49DA. The exceptions were Studies 518 and 519 which found significantly higher efficacy rates with 800 µg misoprostol given vaginally than with 400 µg orally once or twice; in Study 518 following 600 mg and Study 519 after 200 mg mifepristone. The other studies found no significant difference between efficacy rates for 800 µg vaginally and orally[522] (with follow up oral doses), 800 µg orally and buccally[528] or between 800 µg vaginally and 600 µg or 400 µg orally when a repeat dose was permitted[520].

Table 9: Comparisons between dosages and routes of administration of misoprostol after mifepristone

Report	Misoprostol dose µg PO=oral, PV=vaginal, BU=buccal	Interval after mifepristone (hours)	Number analyzed this regimen (all gestations)	Number 43-49DA ♭ includes ≤42DA	Complete abortions §,¶ p<0.01	Continuing pregnancies
518	400 PO^	36-48	219	143 ♭	89%§	0.7%
518	400 PO+400 PO^	36-48	268	176 ♭	93%§	0.6%
518	800 PV^	36-48	522	349 ♭	97%§	0.6%
519	400 PO+400 PO±800 PV@3-7days	24-36	548	348 ♭	90%¶	1.1%
519	800 PV±800 PV@3-7days	24-36	596	383 ♭	97%¶	0
520	400 PO±rpt @24hours	24-48	319	120	93.0%	0
520	600 PO±rpt @24hours	24-48	319	124	92.5%	<1%
520	800 PV ±rpt @24hours	24-48	318	128	92.1%	0
522	800 PO+400 PO 12hrly	36-48	723	236 ♭	93.6%	<2%
522	800 PV +400 PO 12hrly	36-48	727	240 ♭	94.6%	<1%
522	800 PV	36-48	723	223 ♭	95.1%	<1%
528	800 PO±rpt@7-14days	24-36	426	205	94.7%	0.9%
528	800 BU±rpt@7-14days	24-36	421	213	96.4%	0.7%

*includes 200 and 600mg mifepristone doses
^600mg mifepristone

^ 600 mg mifepristone

These results suggest that when 800 µg doses of misoprostol are used, oral, buccal and vaginal routes of administration result in comparable efficacy up to 49 days gestation.

Although the vaginal route was not considered in the application and therefore not reviewed in detail in the evaluation, the evaluator noted that studies included in the current submission reported consistently high complete abortion rates for gestations up to 56 or 63 days when vaginal misoprostol was used after mifepristone with rates from 93-98.7% in 11 studies.

Gestational considerations

Although the application relates only to gestations up to 49 days, there is a considerable volume of information regarding later gestations, which may have a bearing on the choice of regimen prior to 49 days. Table 10 summarises studies which examined outcome differences by gestational band, including making comparisons between different regimens within various gestational ranges. For clarity the evaluator did not included details of the regimens such as follow up doses, as the purpose of the table is to highlight within study differences.

The horizontal highlighting indicates studies which demonstrated a decrease in efficacy with increasing gestation and includes the relevant cells; in only some cases were the ongoing pregnancies compared and/or found to be significantly different. Significant decreases in efficacy were found with increasing gestation in 7 of the 12 oral misoprostol regimens, including doses of 400, 600 and 800 μg. The 5 studies without significant gestational decreases in efficacy were also distributed across these dosages. Neither of 2 buccal regimens and only one of 6 vaginal regimens was associated with significant gestational decreases in efficacy but for several of these there was at least a small absolute decline with increasing gestation.

Studies 518-528 in the lower part of the table were randomised controlled trials which compared different routes of misoprostol administration. Efficacy rates for the different regimens within each gestational band are shown in the "complete abortion" column for that band, in the right of the cell with matching superscript letters for significantly different rates. When a study found no significant difference in efficacy rates between the regimens for a given gestational band, the efficacy rates are shown at the left of the cell without a superscript letter.

Each of the studies which compared regimens in the 57-63 day range found significant efficacy differences, with buccal[528] and vaginal[518, 519, 522] misoprostol more effective than oral administration.

Differences were less consistent in the 50-56 day range, with Studies 518 and 519 reporting vaginal as more effective than oral misoprostol. Studies 520 and 522 found no significant differences between vaginal and oral routes and Study 528 found no significant difference between oral and buccal administration at this gestation. Most studies found comparable complete abortion rates up to 49 days gestation, as discussed above.

Table 10: Within study comparisons by gestational group

Report	Misoprostol dose µg Route PO=oral, BU=buccal, PV=vaginal	Significance of trend to decreased efficacy with increasing gestation	≤42days			43-49days			50-56days			57-63days		
			n	complete abortion	cont preg	n	complete abortion	cont preg	n	complete abortion	cont preg	n	complete abortion	cont preg
507	600 PO*	p<0.02		→		119 ♭	97.5%	0	69	91.3%	0	32	84.4%	3.1%
509	400 PO*	p<0.01 χ^2trend	488	92.2%	1.4%	508	89.2%	1.2%	452	86.7%	2.7%	137	80.3%	9%
513	800 PV	not significant		→		233 ♭	99.6%	0	167	98.2%	0	57	96.5%	1.7%
515	600 PO	not significant	41	97.6%		113	95.6%	<1%	140	95.1%	3.4%♯	92	91.3%	←
539	400 PO^	p<0.001		→		827 ♭	92%	1%	678	83%	4%	510	77%	9%
908 (audit)	800 BU	not significant	491	>98.7%		467	98.1%		342	98.3%		46	95.7%	
908 (audit)	800 PO	p<0.04	121	>98.8%		127	95.3%	0.8%	28	92.9%	3.6%	0		
518	400 PO^	not quoted		→		143 ♭	89%[a]	0.7%	42	81%[b]	0	34	65%[c]	2.9%
518	400+400 PO^			→		176 ♭	93%[a]	0.6%	65	89%[b]	0	27	90%	3.7%
518	800 PV^			→		349 ♭	97%[a]	0.6%	113	97%[b]	0	60	90%[c]	0
519	400+400 PO			→		348 ♭	90%[d]	1.1%	135	89%[e]	0.7%	65	88%[f]	1.5%
519	800 PV			→		383 ♭	97%[d]	0	146	97%[e]	0	67	97%[f]	0
520	400 PO	not significant	135	97.1%		120	93.0%		47	92.2%		0		
520	600 PO	p<0.01 χ^2trend	121	97.6%		124	92.5%		51	86.4%		0		
520	800 PV	p=0.01 χ^2trend	112	99.1%		128	92.1%		59	90.8%		0		
522	800 PO +BD	not significant		→		236 ♭	93.6%		240	93.3%		264	90.2%[g]	2.3%
522	800 PV +BD	not significant		→		240 ♭	94.6%		246	93.1%		254	96.5%[gh]	0
522	800 PV	not significant		→		223 ♭	95.1%		242	93.4%		268	92.2%[h]	0
528	800 PO	p<0.001	92	97.8%	2.2%	113	94.7%	0.9%	107	88.8%	0.8%	114	85.1%[i]	7.9%[j]
528	800 BU	not significant	76	98.7%	1.3%	137	96.4%	0.7%	93	95.7%	0	115	94.8%[i]	1.7%[j]

*includes 200 and 600mg mifepristone doses
^600mg mifepristone
→ ≤42days included with 43-49
♭ includes≤42days
← 57-63days included with 50-56
♯ includes 57-63days
cont preg=continuing pregnancy
Highlighting indicates significant trend to decreased efficacy with increasing gestation
Superscript letter indicates significant difference between groups marked with the same letter (within study)

It is reasonable to conclude that there is a tendency for complete abortion rates after mifepristone and misoprostol to decrease with increasing gestation up to 63 days and that this is both statistically and clinically significant following oral administration of misoprostol. A variety of routes of administration can result in acceptable complete abortion rates up to 49 days gestation but beyond 49 days it is increasingly likely that buccal or vaginal administration will result in significantly higher efficacy rates than oral misoprostol. Continuing pregnancy rates appear to increase with gestation also, the numbers generally being too small for detailed analysis, although there was a substantial and significant difference between oral and buccal groups in the 57-63DA band for Study 528.

Table 1 summarises outcomes for whole study populations for those studies which included women up to 63DA and in the lower section 56DA, separated into vertical columns by route of administration. This is similar to the material in the sponsor's Clinical Overview, but the evaluator organized it differently, included participant numbers, included less information about different types of failure and omitted the single study comparing sublingual and vaginal administration. The evaluator added the study reported in reference 526 comparing buccal with vaginal administration, which was not included in the other tables because it did not provide subanalyses for gestation ≤ 49DA.

Of all the studies of oral misoprostol conducted up to 63DA, only two (515 and 507) achieved complete abortion rates of at least 93% and these were 93.6 and 94.6%. The studies limited to 56DA (516 and 520) achieved rates of 86-95% with concerning rates of continuing pregnancy. For the vaginal and buccal routes of administration, the lowest rate was 93%, with complete abortion rates up to 98.7% reported. The rates of continuing pregnancy tended to be higher when the later gestational age groups were included but these data do not allow comparative conclusions on this aspect.

This analysis confirms the findings of the analyses by gestational subgroup that oral administration of misoprostol is less effective than vaginal or buccal administration when patients beyond 56DA and possibly 49DA are treated.

In the evaluator's opinion, while oral administration of misoprostol can result in acceptable efficacy up to 49DA, vaginal and buccal routes are preferable on efficacy grounds.

Table 11: Efficacy for study populations up to 63 days gestation

Report	Oral				Vaginal (800µg)			Buccal(800µg)		
	n	Dose µg	complete abortion	cont preg	n	complete abortion	cont preg	n	complete abortion	cont preg
Up to 63 days										
509	792	400	89.3%	2.8%						
509	797	400	88.1%	1.9%						
519	548	400+400	90%	1.1%	596	97%	0			
518	220	400	84%	0.9%						
518	269	400+400	92%	0.7%	522	96%	0.4%			
522	740	800	92.3%	1.2%	741	94.7%	3.0%			
522					738	93.5%	4.2%			
528	426	800	91.3%	3.5%				421	96.2%	1.0%
515	386	600	94.6%	2.3%						
513					457	98.7%	0.2%			
507	220	600	93.6%	0.5%						
523	450	600	87.7%	1.1%						
Up to 56 days										
520	319	400	94.7%	0						
520	319	600	93.4%	0.3%						
520	318	800	94.3%	0						
516	145	400	86%	7%						
516	148	400+400	92%	1%						
526					213	93%	1.9%	216	95%	0.9%

cont preg=continuing pregnancy

Other studies

The sponsor's experience

Marie Stopes International Australia (MSIA) reports treating 12,830 women with mifepristone and misoprostol for medical abortion from September 2009 to June 2011; 14.9% were beyond 49DA (up to 63DA) and efficacy (complete abortion without surgery) was reported as 96.7%, with 0.6% continuing pregnancies. For 1,913 women beyond 49DA the efficacy rate was 92.8% with 0.9% continuing pregnancies. No information is provided on follow up rates.

The protocol described is 200mg mifepristone orally followed 24-48 h later by 800 µg misoprostol administered buccally by the woman at home. She may return to the centre for a further dose of misoprostol if no bleeding has occurred within 24 h of the misoprostol dose; otherwise a follow up visit is scheduled 2 weeks later.

Analyses performed across trials (pooled analyses and meta-analyses)

The application presented some tabulations but not pooled analyses or meta-analyses. The evaluator has also relied on tabulations of relevant studies, as the heterogeneity of clinical practice in this area both around details of regimens and definition and assessment of efficacy endpoints makes pooling of limited value. Some material from published meta-analyses and guidelines is presented below.

Cochrane review: Medical methods for first trimester abortion

This review[14] included 58 trials and undertook 13 comparisons; many relevant to this application were limited to one or two trials, with meta-analyses where possible often involving only 2-4 trials because of heterogeneity. The main results and authors' conclusions were reproduced in the mifepristone evaluation (Mifepristone Linepharma AusPAR). The comparisons did not include systematic examination according to gestation and apply to a broader gestational range than the proposed indication for GyMiso. Excerpts relevant to misoprostol regimens to be used following mifepristone are reproduced below.

"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."

"Vaginal misoprostol is more effective than oral administration, and has less side effects than sublingual or buccal."

2011 RCOG Guideline[11]

An updated version of the 2004 Evidence-Based Guideline[911] included in the application was published in late 2011. Buccal, sublingual and initial oral dosage were not considered in the 2004 version but the evolving evidence has led to their inclusion. The relevant recommendation from the new edition is reproduced below.

"RECOMMENDATION 7.19

The following regimens are recommended for early medical abortion:

- At ≤ 63 days of gestation, mifepristone 200 mg orally followed 24-48 h later by misoprostol 800 micrograms given by the vaginal, buccal or sublingual route.
- At ≤ 49 days of gestation, 200 mg oral mifepristone followed 24-48 h later by 400 micrograms of oral misoprostol."

This RCOG guideline also notes that misoprostol is included in one of the licensed uses for mifepristone for abortion care in Great Britain, this being 600mg mifepristone followed 36-48 h later by 400 μg oral misoprostol up to 49 days amenorrhoea.

Evaluator's conclusions on clinical efficacy for GyMiso®:

> *Use in adults and adolescents of childbearing age for the medical termination of a developing intrauterine pregnancy in sequential combination with Mifepristone Linepharma 200mg tablet, up to 49 days of amenorrhoea (DA)*

An extensive published literature supports the appropriateness of misoprostol used in sequential combination with mifepristone 200 mg for this indication. The reports presented in the application and summarised in the clinical overview include several large

[14]Kulier R, Kapp N, Gülmezoglu AM, Hofmeyr GJ, Cheng L, Campana A. Medical methods for first trimester abortion. Cochrane Database of Systematic Reviews 2011, Issue 11. Art. No.: CD002855. DOI: 10.1002/14651858.CD002855.pub4.

and well conducted prospective studies and clinical trials examining a range of dosage regimens.

The companion application for registration of Mifepristone Linepharma established that regimens involving 200 mg mifepristone followed by prostaglandin are optimal for the induction of early medical abortion.

Studies considered in both applications confirm that misoprostol can achieve comparable outcomes to the main alternative prostaglandin, gemeprost. The advantages of misoprostol in ease of storage, cost and alternative routes of administration have resulted in it largely replacing gemeprost in clinical use for abortion, as reflected in the literature presented in the applications.

Studies have been published on many different misoprostol regimens and research continues in this area; understanding of optimal regimens at different gestations is likely to continue to evolve.

The studies presented support an interval of 24-48 h between mifepristone and misoprostol given orally or buccally to achieve complete abortion rates over 90%, as rates of 50-70% have resulted from shorter intervals. Some studies suggest that complete abortion rates above 90% may be achievable with shorter intervals when misoprostol is administered vaginally.

Efficacy rates above 90% have been reported with doses of 400 μg, 600 μg, 400 μg repeated after 2 h and 800 μg misoprostol given orally following mifepristone. Variations may be due in part to variations in regimens, for instance whether repeat doses of misoprostol are given and different practices in terms of timing and methods of follow up such as routine ultrasound. Higher efficacy rates appear to be more consistently achieved with 800 μg doses than lower doses but 600 μg doses may also result in acceptable rates. In 800 μg (single or divided dose) regimens which include a repeat dose of misoprostol if abortion has not occurred after a variable time interval (1-14 days), complete abortion rates of at least 93% are reported.

Up to 49DA oral misoprostol has acceptable outcomes as described above. The application did not systematically examine vaginal and sublingual routes of administration of misoprostol. It did include reports of pharmacokinetic, pharmacodynamic and clinical studies using the buccal route, which in the evaluator's opinion provide sufficient evidence to support its clinical use. Study 528 showed no siginificant difference in efficacy of oral and buccal routes up to 49DA; Studies 526 and 908 were also informative.

This indication has an upper limit of 49DA. The data presented in the application confirm a tendency for complete abortion rates after mifepristone and misoprostol to decrease with increasing gestation up to 63 days and that this is more pronounced following oral administration of misoprostol. While a variety of routes of administration can result in acceptable complete abortion rates up to 49 days gestation, beyond 49DG it is increasingly likely that buccal or vaginal administration will result in significantly superior efficacy rates.

In the evaluator's opinion, 800 μg misoprostol administered orally 36-48 h after 200 mg mifepristone is an acceptably effective regimen for medical abortion up to 49 days gestation, particularly with provision for a repeat dose if needed. The evaluator further considerered buccal administration of 800 μg to be an equally effective alternative, with the advantage that its efficacy does not decrease to the same extent with increasing gestation.

The sponsor's Clinical Overview presented the evolution of prostaglandin regimens after mifepristone for early medical abortion, the sequential steps summarised as follows:

- It was recognised that oral misoprostol and gemeprost could achieve equivalent results.
- The realisation that this did not hold after 49DA prompted exploration of other routes of administration of misoprostol.
- Vaginal administration of misoprostol was found to match gemeprost outcomes to 63DA.
- Reports of toxic shock deaths after vaginal misoprostol triggered a search for further alternative routes, with the sublingual and buccal routes now being examined.

The evaluator's only significant disagreement with the conclusions of the sponsor's Clinical Overview is that the statement that buccal misoprostol "seems to limit the risk of toxic shock syndrome which could result from vaginal administration" is not substantiated.[15] Despite the very reasonable concerns that have been widely discussed in the literature, a causal link has not been established between route of administration and fatal infections and indeed a fatality after buccal administration of misoprostol has now been reported.

Safety

The application relies largely on the safety analyses undertaken for the companion application for registration of Mifepristone Linepharma, which is reasonable given that it considered the safety aspects of mifepristone given with prostaglandins including misoprostol and that it is proposed that GyMiso® be used only in conjunction with mifepristone. The evaluator therefore adapted the mifepristone safety evaluation to exclude the sections and comments relevant only to mifepristone or to other prostaglandins and those relevant to second trimester abortion. The evaluator added sections summarising and commenting upon additional material provided in the current application or found in the literature.

It is often difficult to determine whether particular symptoms, side effects or adverse events are due to mifepristone, misoprostol or the process of abortion itself. The following should be noted:

- 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.
- Some events may vary in frequency with gestation at which abortion occurs.
- Analysis is further complicated by the fact that some commonly reported adverse events such as nausea, vomiting, dizziness and breast tenderness are common in normal pregnancy.
- For many of the common adverse events perceptions, reporting and ascertainment methods vary greatly.

For the 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".

[15] Sponsor comment: Based on the evaluator's opinion this observation was removed from the RMP by the sponsor.

Because this is a literature based application there are no individual patient data (except for the bioequivalence study) so the available material consists of that which the authors of each study either specifically examined or considered sufficiently important or relevant to publish; it is likely to cover the more serious adverse events and safety outcomes and the commoner adverse events.

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

Studies providing evaluable safety data

Pivotal efficacy studies

Study 509 collected data on the secondary outcomes of side effects, namely nausea, vomiting, diarrhoea, lower abdominal pain after mifepristone and before misoprostol, after misoprostol and at any time during treatment as well as the need for blood transfusion. Hourly assessments of vital signs and side effects were undertaken during a 3 h observation period after administration of misoprostol. The means of assessment were not reported but the data appear to be almost complete for the specified symptoms.

In Study 528, women were asked to keep a diary for up to 15 days after mifepristone administration to record misoprostol administration, pain, bleeding, adverse effects and medications taken.

Other studies

Most of the clinical reports included in the submission commented on safety and adverse events, which were variably ascertained and reported. These were considered against the frequency listings in the summary table and safety reviews to identify any inconsistencies and specific data from informative studies presented.

Pivotal studies that assessed safety as a primary outcome

Not applicable.

Patient exposure

Many millions of women have been treated with mifepristone with prostaglandin for termination of pregnancy in the 23 years since mifepristone was first registered in France, although not all of these have had misoprostol. The most recent FDA Postmarketing Adverse Events Summary for mifepristone[16] estimated that approximately 1.52 million women had used mifepristone in the USA to April 2011; as the approved regimen for Mifeprex® includes 400μg misoprostol orally it is likely that the vast majority of these women have also taken misoprostol.

Over 22,000 misoprostol recipients are listed in the first trimester efficacy tables (see Mifepristone Linepharma AusPAR). While ascertainment and reporting varied between studies, most of them addressed safety and adverse events.

The application safety review presents tables reported to represent 190,000 women exposed to mifepristone, of whom 149,000 had regimens including misoprostol and the rest having mifepristone alone or with other prostaglandins.

Several reviews addressing safety were included in the current submission:

[16] FDA Postmarketing Adverse Events Summary for mifepristone.
http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM263353.pdf Accessed December 2011.

- Study 593, reporting on 95,163 procedures in the USA
- Study 543, reviewing 227,823 procedures in the USA
- Study 546, reporting on adverse events notified from around 80,000 procedures in the USA
- Study 541, a review addressing complications and safety and
- Study 628, which considers 46,421 medical abortions in reviewing infection.

The first four of these studies relate only to mifepristone/misoprostol regimens, while Study 628 included a broader group of women having medical abortion using a variety of regimens.

These large studies provide information on rare and serious events.

The Periodic Safety Update Reports (PSURs) cover approximately 130,000 packs of misoprostol.

Adverse events

All adverse events (irrespective of relationship to study treatment)

Pivotal studies

In Study 509 (1530 women):

- 5 women needed blood transfusions.
- More than 80% had abdominal pain.
- Nausea was frequent (>50%) but did not appear to differ in frequency before and after misoprostol administration.
- Vomiting occurred in fewer than 20% of women after misoprostol and with similar frequency before misoprostol was given.
- Diarrhoea was reported as "uncommon" occurring in 6.8-8.6% of women after misoprostol; significantly more frequently than before.

Study 528 (847 women) found over 90% of women had at least one adverse effect:

- nausea (63-75%)
- vomiting (39-48%)
- diarrhoea (33-43%)
- fever and/or chills (33-48%): significantly more frequent after buccal than oral misoprostol
- headache (31-41%)
- dizziness (29-39%)
- weakness (42-58%).

Three women in this study were admitted to hospital (for pulmonary embolus, ruptured ectopic pregnancy and right hip pain); there were two other admissions for unspecified reasons. Twenty-one women made emergency room visits, mainly because of pain and bleeding.

Other studies

Adverse events are tabulated in Table 12 (and also presented in the proposed PI). 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. It should be noted that it is not restricted to misoprostol but it is somewhat academic to try to separate out the effects of medical abortion itself and the effects of the drugs included in the regimens.

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 (GI) symptoms.

Specific groups of adverse events are considered under further subheadings using examples from the studies evaluated for efficacy.

Table 12: 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)**	**Uncommon (≥ 1/1000 to < 1/100)**	**Rare (≥ 1/10000 to < 1/1000) and very rare (< 1/10000)***
Gastro-intestinal disorders	Nausea Vomiting Diarrhoea 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 haemorrhage Endometritis Breast tenderness Heavy bleeding	Haemorrhagic shock Salpingitis	Bilateral adnexal mass Intrauterine adhesion Ovarian cyst rupture Breast abscess Haematosalpynx Uterine rupture
General disorders and administration site conditions	Fatigue Chill / fever	Fainting		Anaphylaxis Periorbital edema
Infections and infestations			Infection	Toxic shock syndrome
Vascular disorders			Hot flush	Superficial thrombo-phlebitis Hypotension
Cardiac disorders				Myocardial infarction Induced Adam-Stokes syndrome
Respiratory, thoracic and mediastinal disorders				Bronchospasm Induced bronchial asthma

Table 12 (continued): 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)	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 thrombo-cytopenic purpura Thrombocytopenia Induced systemic lupus erythematosus
Renal and urinary disorders				Renal failure
Neoplasms benign, malignant and unspecified				Elevated alpha-foeto protein Elevated carcinoembryonic antigen
Musculoskeletal and connective tissue disorders				Limb spasm
Eye disorders				Ophtalmoplegia
Psychiatric disorders				Mania

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 variably reported; where reported they occur in 80-98% of women but some studies do not mention them at all. Analgesia requirements vary enormously; in some studies the majority of women use no analgesia[507, 509, 515] while in others a majority will use

oral analgesia[513, 539]. It appears that few women prior to 49DA will need parenteral analgesia[507, 513, 515] 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[519, 520, 521, 526, 528]. 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.

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[507, 517, 518, 519,523] and 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 11-15 days, with a range up to 60 days, some of which may be spotting[507, 509, 513, 515, 517, 519, 522, 523, 539, 601]. Some studies have reported that it is usual for 2-3 days of bleeding to be considered heavier than normal menses.

Study 514 examined blood loss during and after medical abortion and surgical abortion and found a median loss of 84-101 mL (range 16-524 mL; mean 115-136 mL) with three different regimens using mifepristone and gemeprost. Loss with surgical abortion was reported as a mean of 53.2 mL (range 29-336 mL, mean 66.9 mL) but the authors noted that this was lower than other reports.

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

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

Treatment failure: 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 reported 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 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 (see below).

Gastrointestinal side effects

Nausea was reported in all the cited efficacy studies at rates around 20-60%: two studies which assessed nausea at a number of timepoints found that it decreased after misoprostol administration[507, 540] while another[509] found little difference.

Vomiting is reported in around 20-30% of women undergoing medical abortion but may be as low as 7%[523] or as high as 47%[528]; again two studies which assessed it serially found vomiting to decrease in frequency after misoprostol administration[507, 540] while another found little difference[509].

As nausea and vomiting are well recognised symptoms of pregnancy it is unsurprising that ending pregnancy would reduce these symptoms.

Diarrhoea was reported at very variable rates from around 5%[523] to 43%[528] with most studies reporting around 10-30%[513, 517, 518, 519, 520, 539, 540, 601], with some variation according to route (below). Unlike nausea and vomiting the rates were generally low prior to misoprostol administration, suggesting that diarrhoea is specifically related to treatment with misoprostol.

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.

Most of the clinical studies in the current submission did not specifically report infection rates, although cases of endometritis and/or antibiotic prescription were sometimes listed. Serious infections are considered further below.

Other adverse events

Fevers were reported in the reviewed studies at frequencies from 4%[539] to as high as 51%[526] with most around 15-30%. Some studies reported chills separately, while others grouped fevers with chills and two studies reported rigors at a rate around 3%[523, 539]. There may also have been some overlap with hot flushes, listed in the table as an uncommon adverse event. There is little information about methods of ascertainment.

Headache, dizziness and fatigue are all listed in Table 12 as very common, with frequencies greater than 10% consistent with the literature presented. In the studies reviewed rates of headache ranged from 13-49% but not all studies mentioned it. The ranges for fatigue and dizziness were similarly wide; breast tenderness and fainting are listed as 1-10% and were reported less consistently in the studies. These are also common pregnancy symptoms and the studies that assessed symptoms over time found dizziness, fatigue and breast tenderness to be less frequent after misoprostol administration than before although it is unclear to what extent the prior frequencies were cumulative rather than point prevalences.

Skin rashes and pruritus are listed with a frequency of 0.1-1%. These were uncommonly reported in the reviewed studies.

Rare and very rare events and case reports

Most of the events listed in this column of Table 12 are based on case reports; while many are serious most are unlikely to be causally related to mifepristone or misoprostol and given the now vast international experience with medical abortion, there can be a reasonable level of confidence that they are indeed very rare.

Adverse events in the bioequivalence study

These were appropriately reported and considered. There was one episode of nausea, two episodes of lower abdominal pain and four episodes of diarrhoea. There were no serious adverse events.

Treatment-related adverse events (adverse drug reactions)

This section includes only those adverse events likely to be related to misoprostol itself not those due to the procedure of abortion.

Pivotal studies

In Study 509:

- Nausea was frequent (>50%) but did not appear to differ in frequency before and after misoprostol administration.
- Vomiting occurred in fewer than 20% of women after misoprostol and with similar frequency before misoprostol was given.
- Diarrhoea was reported as "uncommon", occurring in 6.8-8.6% of women after misoprostol, significantly more frequently than before.

Study 528 found over 90% of women had at least one adverse effect, including:

- nausea 63-75%
- vomiting 39-48%
- diarrhoea 33-43%
- fever and/or chills 33-48% (significantly more frequent after buccal than oral misoprostol)
- headache 31-41%
- dizziness 29-39%
- weakness 42-58%.

Other studies

Findings are considered under the subheadings below.

Differences between different routes of administration

This application and evaluation have not fully explored all studies for all routes of administration of misoprostol, in particular experience with vaginal and sublingual administration. It is generally contended that there are greater frequencies of gastrointestinal side effects after oral than vaginal misoprostol, with the profiles for sublingual and buccal administration thought to be intermediate.

Among the studies that directly compared different routes of administration of misoprostol in randomised trials:

- One study[520] found a greater frequency of headaches after 800 μg misoprostol vaginally than 400 μg orally.
- Three studies found a greater frequency of fever and/or chills after vaginal than oral misoprostol[520, 528, 540].
- One large study[540] found greater frequencies of nausea and vomiting after oral than vaginal misoprostol but several others found no significant differences[518, 519, 520].

- The studies directly comparing buccal with vaginal[526] and buccal with oral misoprostol[528] did not establish differences in frequency of nausea and vomiting.
- Diarrhoea was significantly more common after oral than vaginal misoprostol in three studies which examined this; with frequencies of 18-36% in the oral groups and 9-19% in the vaginal comparators[518, 519, 520, 540]. No difference was found between buccal and oral administration[528] but diarrhoea was more frequent after buccal than vaginal administration of misoprostol[526].
- Study 909 found both dose and route dependent differences between 400 and 800 μg misoprostol given sublingually and vaginally, with nausea, vomiting, diarrhoea, fever and chills all more significantly more frequent in the sublingual than vaginal groups. There was no difference between frequencies of headache and abdominal pain.

Some 9%[526] and 24%[528] of women who took misoprostol buccally complained about the taste of the tablets.

Side effect profiles are important to consider in choice of misoprostol regimen due to the unpleasant if transient nature of these symptoms.

Misoprostol for gastrointestinal indications

When used for gastrointestinal indications misoprostol is taken long term usually at doses of 800 μg daily. The Australian PI for Cytotec® lists diarrhoea, abdominal pain and loose stools as the most frequent adverse events, occurring in about one tenth of patients and usually self limiting. Other adverse events reported in clinical trials in 1-3% of patients were nausea, headache, flatulence, dyspepsia, vomiting, constipation and dizziness. Postmarketing surveillance noted anaphylactic reaction, chills and pyrexia.

The PI also lists a number of gynaecological disorders and pregnancy complications, which are related to the desired pharmacodynamic effects which are the subject of the present application and considered elsewhere in this evaluation. Birth defects are mentioned and also considered elsewhere.

The listings in this PI do not suggest relevant matters of concern not already covered elsewhere in the application and/or evaluation.

Deaths and other serious adverse events

Pivotal studies

These studies did not specifically list serious adverse events but Study 509 noted that 5 women needed blood transfusions and Study 528 reported three hospital admissions for reasons not related to treatment (one being a pulmonary embolus) and two other admissions for unspecified reasons.

Other studies

Findings from other studies are included under the headings below.

Deaths from infection

After an estimated 1.52 million medical abortions in the USA, the most recent FDA Postmarketing Adverse Events Summary[16] noted 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 application and discussed in the literature[520, 541, 543, 549]. Cohen et

al[17] and Meites et al report on further clostridial deaths after medical abortion including two cases positive for *Clostridium perfringens* but it is unclear whether any of these cases is additional to those reported by the FDA.

Fatal toxic shock syndrome associated with *Clostridium sordellii* has also been reported in association with childbirth, miscarriage and several other medical and surgical conditions[18].

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

Other deaths

The same FDA report included 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.

Serious infections

A number of reviews have considered infection rates in large treatment populations, generally found to occur at rates less than 1%[543, 593, 628]. Some explicitly focussed on serious infections (variously defined) while the international review of Shannon et al[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"[7] 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.

One of the Periodic Safety Update Reports (PSURs) includes a case report from the literature of septic shock with Klebsiella after early medical abortion.

Heavy bleeding, severe haemorrhage, and haemorrhagic shock

There is no clear definition of these terms but blood transfusion may be considered a marker 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 included under the heading of unsuccessful medical abortion.

The mifepristone evaluation estimated the blood transfusion rate at 0.1-0.2% for first trimester abortion, based on the transfusions reported in the studies presented in the application.

Acute myocardial infarction and other events

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

[17] Cohen AL, Bhatnagar J, Reagan S, Zane SB, D'Angeli MA, Fischer M, Killgore G, Kwan-Gett TS, Blossom DB, Shieh W, Guarner J, Jernigan JJ, Duchin JS, Zaki SR, McDonald LC,et al. Toxic Shock Associated With Clostridium sordellii and Clostridium perfringens After Medical and Spontaneous Abortion. Obstetrics & Gynecology 2007: 110(5): 1027-1033.

[18] 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.

the USA after misoprostol[546] and two more are referred to in the PSURs. A case report of "cryptogenic stroke" was found[19].

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 than related to medical abortion regimens.

Uterine hyperstimulation and rupture

These complications are extremely rare in the first trimester but the following case reports were found:

- A case of uterine rupture with attempted medical abortion at 9 weeks gestation using misoprostol 10 days after failed surgical abortion with uterine perforation[20]. The perforation was a likely contributor to the rupture.
- A case of uterine rupture following misoprostol treatment of miscarriage at 8 weeks gestation in a woman with a previous uterine rupture related to caesarean section scar[21].
- A case of uterine rupture after the use of misoprostol for cervical priming prior to curettage for miscarriage[22]. There was debate in the literature as to whether this may have been an interstitial ectopic pregnancy.
- A further case report included with the PSUR and said to be in the first trimester in fact occurred at 13 weeks gestation albeit in a woman with no identified risk factor.

In early pregnancy the challenge is usually to find a dose of misoprostol which is high enough to be effective but low enough to minimise unpleasant side effects. It is very difficult to overstimulate the uterus in the first trimester and in each of the early pregnancy cases listed above there is a contributing complication. Nevertheless, severe pain and/or deteriorating condition following misoprostol must always be considered seriously.

As pregnancy advances into the late second trimester and beyond the uterus becomes more responsive to prostaglandins and it is more possible to cause hyperstimulation which can result in fetal compromise and/or uterine rupture with possible haemorrhage and even maternal death. The risk of uterine rupture is greater in the presence of a uterine scar, such as following previous caesarean section.

[19]Patel N, S. R., Shatzmiller R Sanossian N, Sahai-Srivastava S. Cryptogenic stroke in the setting of intravaginal prostaglandin therapy for elective abortion. Clinical Neurology And Neurosurgery 2008: 110(5): 529-531.

[20]Lialios G, Kallitsaris A, Mademtzis J, Messinis IE. Uterine Perforation as a Rare Complication of Attempted Pregnancy Termination with Misoprostol: A Case Report. The Journal of Reproductive Medicine 2006. 51(7): 599-600.

[21]Khan S, Gain A. Uterine rupture at 8 weeks' gestation following 600 mg of oral misoprostol for management of delayed miscarriage. Journal Of Obstetrics And Gynaecology 2007. 27(8): 869-870.

[22]Kim JO, Han JY, Choi JS, Ahn HK, Yang JH, Kang IS, Song MJ, Nava-Ocampo AA. Oral misoprostol and uterine rupture in the first trimester of pregnancy: A case report. Reproductive Toxicology 2005. 20: 575–577.

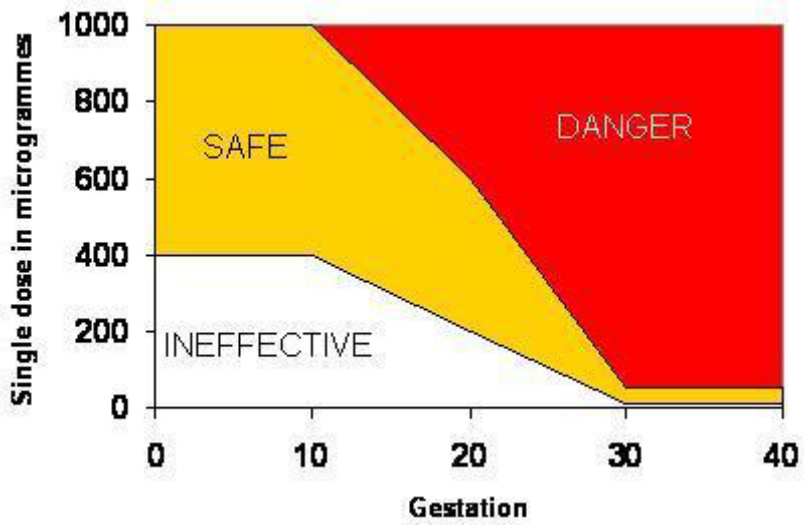
Dosage regimens beyond the first nine weeks of pregnancy are more complex, as repeat dosages will usually be required and the timing of the second trimester fall in dosage requirement can be difficult to predict for an individual woman.

Figure 8 is a pictorial representation of this dilemma, reproduced from a clinical consensus group's website[23]. While there is room for debate about the cut-off doses and gestations, the "in principle" depiction is apt. The relevance to the current indication (which ends at 7 weeks gestation) is only that if gestation is significantly underestimated an inappropriate dosage regimen may be used, resulting either in failure if the dose is too low or in uterine hyperstimulation if gestation is substantially more advanced. Doses as low as 25-50 μg, one eighth to one quarter of a misoprostol tablet have been advocated for induction of labour near term.

Error or misuse could give rise to uterine hyperstimulation. The sponsor's Clinical Overview reports a case where a woman was given misoprostol in error to treat uterine contractions, instead causing contractions and haemorrhage. Hypothetically a woman could defer taking misoprostol when prescribed and take it later in pregnancy or give it to someone else. For this reason the evaluator suggested an addition to the Consumer Medicine Information on the risk of harm if taken later in pregnancy. Errors and misuse seem more likely with off-label use of the currently registered preparation.

Figure 8: "Safe" dosage of misoprostol by gestation in weeks

Reproduced from misoprostol.org website[12].



Misoprostol toxicity

There are several reports over the last 20 years of misoprostol toxicity due to large doses taken either in error or without medical supervision, none of them in Australia.

Some very large doses have been remarkably well tolerated with rapid recovery but organ failure and mortality have occurred; brief summaries are included below:

- A 29 year old woman required intensive care after taking 8 mg (40 tablets) of misoprostol to induce early medical abortion. She developed rhabdomyolysis, acute renal failure and abnormal liver function. She made a full recovery, had a complete abortion and was discharged after nine days[24].

[23]http://www.misoprostol.org/ Accessed December 2011.

[24]Barros JG, Reis I, Graça LM. Acute misoprostol toxicity during the first trimester of pregnancy. International Journal Of Gynaecology And Obstetrics 2011. 113(2): 157-158.

- A 23 year old woman was admitted to hospital after taking 8.4 mg (42 tablets) of misoprostol over 3 days in an attempt to induce abortion. She presented with abdominal pain, vomiting and diarrhoe, which resolved in a few hours. Surgical abortion was performed and she was discharged after 2 days[25].
- A 21 year old woman took 4 g (20 tablets) of misoprostol and was admitted with diarrhoea, fever, rhabdomyolysis and haemolytic anaemia. She recovered fully and was discharged after 21 days[26].
- A teenager took 12 mg (60 tablets) of misoprostol over 2 days to induce early abortion. She developed severe upper gastrointestinal tract bleeding, acute renal failure, rhabdomyolysis, consumption coagulopathy and extensive necrosis of the gastric lesser curvature and distal oesophagus; she had several episodes of cardiac arrest and died despite active resuscitation efforts[27].
- A 19 year old woman at 31 weeks gestation took 6 mg (30 tablets) of misoprostol and other medication in a suicide attempt. Two hours later she complained of heat, chills and dyspnoea and the uterus was found to be tetanic, with the cervix 5 cm dilated. Fetal death was diagnosed and she delivered vaginally 1 h later. She also had rhabdomyolysis, metabolic acidosis and hypoxia which recovered over a day[28].
- A 25 year old woman took 6.6 mg (33 tablets) of misoprostol and developed hyperthermia (41.4° C), abdominal cramping and confusion within 3.5 h when fetal death was diagnosed. Caesarean section was undertaken and recovery was complete within 15 h[29].
- A 71 year old woman took 3 mg (15 tablets) of misoprostol in mistake for 15 fluoride tablets. She presented with nausea, abdominal cramps, fever and chills and recovered within 24 h[30].

Access to safe legal abortion and responsive health care is probably the best way to prevent most of these sad cases, although at least one occurred where legal abortion was an option. Given the dosage and packaging planned in the present application, such events are extremely unlikely to occur with GyMiso®. They would be more possible with the registered misoprostol preparation and packaging.

Congenital abnormalities

It is likely that exposure to misoprostol in a pregnancy which continues carries a risk of congenital abnormality and information about this needs to be provided prior to medical abortion and discussed with women who have a failed attempted medical abortion and

[25]Yaacov Bentov, Eyal Sheiner, Miriam Katz. Case report: misoprostol overdose during the first trimester of pregnancy. European Journal of Obstetrics & Gynecology and Reproductive Biology 2004. 115: 108–109.

[26] Filippini A, Villa G, Corrocher R, De Franceschi L. Acute Hemolytic Anemia With Acanthocytosis Associated With High-Dose Misoprostol for Medical Abortion. Annals of Emergency Medicine 2007. 50: 289-291.

[27]Henriques A, Lourenço AV, Ribeirinho A, Ferreira H, Graça LM. Maternal death related to misoprostol overdose. Obstetrics and Gynecology 2007. 109 (2 Pt2), 489-490.

[28]Bond GR, Van Zee A. Overdosage of misoprostol in pregnancy. American Journal of Obstetrics and Gynecology 1994. 171: 561-562.

[29]Austin J, Ford MD. Acute intravaginal misoprostol toxicity with fetal demise. The Journal of Emergency Medicine 1997. 15(1): 61-64. (Abstract only obtained.)

[30] Graber DJ. Acute misoprostol toxicity. Annals of Emergency Medicine 1991. 20: 549-551.

wish to consider continuing the pregnancy. Da Silva Dal Pizzol et al[31] conducted a systematic review and meta-analysis; they concluded that Möbius sequence and terminal limb reduction defects are more frequent in misoprostol exposed pregnancies. Many of the reported cases appear to follow self administration of misoprostol in attempts to induce abortion without medical supervision; extent of exposure is often unknown and wide dosage ranges have been reported.

Discontinuation due to adverse events

The proposed indication generally requires single dose use, with a second dose prescribed in a minority of cases. No discontinuation due to adverse events was reported although a few women in some studies decided on surgical abortion after taking mifepristone, possibly due to a mifepristone related adverse event such as vomiting.

Pivotal/ Other studies

None reported.

Laboratory tests

No specific studies were reported.

Liver/ Kidney function

Pivotal/ Other studies

Not reported.

Other clinical chemistry
Pivotal/ Other studies

Not reported.

Haematology

Pivotal studies

Not reported.

Other studies

Some studies[507, 513, 515, 601] noted a small average fall of haemoglobin following medical abortion but one found no change[517]. Any fall is likely to be related to blood loss rather than any direct drug effect.

Electrocardiogram

Pivotal studies

Not reported.

Other studies

Study 517 reported no medication related changes in electrocardiograph findings between traces before mifepristone and after prostaglandin.

[31]da Silva Dal Pizzol T, Knop FP, Mengue SS. Prenatal exposure to misoprostol and congenital anomalies: Systematic review and meta-analysis. Reproductive Toxicology 2006. 22: 666–671.

Vital signs

Pivotal studies

Not reported.

Other studies

Study 515 reported a slight decrease in systolic blood pressure at 2 and 4 h after misoprostol, with no change in diastolic blood pressure. This was accompanied by a significant fall in heart rate of 4-7 beats per minute. This study also noted an increase in body temperature of 0.3-0.6°C. For reports of fever see section *Other Adverse Events* above.

In Study 540, fewer than 20% of women had an increase in systolic blood pressure of at least 10 mmHg within 3 h of misoprostol administration and a similar proportion a 5 mmHg rise in diastolic pressure. Approximately 25% had a decrease in one or both parameters.

Study 601 noted that 6 of 505 women had a transient substantial decrease in blood pressure, which the authors considered to be attributable to vagal reaction to uterine cramps. Overall there was a slight decrease in the mean systolic and diastolic pressures at 4 h after misoprostol.

Post marketing experience

Information is presented from PSURs for GyMiso 200 mg tablets from October 2003-October 2010, except for the period February–October 2008. The estimated exposure was around 130,000 patients, the approved indications being for pregnancy termination before 49 days and for preparation of the cervix before first trimester surgical termination. The sponsor reported that 164,210 women had GyMiso from 2004 but this may include an additional reporting period.

There had been some supply for clinical studies conducted by Gynuity for medical abortion and for treatment and prevention of postpartum haemorrhage during which one death and three cases of disseminated intravascular coagulation were reported; these were considered to be unrelated to the use of misoprostol.

Serious case reports were:

- coronary artery spasm presenting with chest pain and cardiac arrest 1.5 h after 800 μg misoprostol of unknown brand administered vaginally for medical abortion at around 8 weeks gestation; recovered with neurological sequelae.

Other notifications:

- Vomiting.

Other case reports from the published literature were included as follows:

- coronary artery spasm with ischaemia but full recovery
- multiple fetal abnormalities after misoprostol in the second month of pregnancy
- a patient with two epileptic seizures during medical abortion
- two deaths from *Clostridium sordellii* infection
- a case of *Klebsiella* septic shock which recovered
- lichenoid drug eruption; later patch tested positive for misoprostol
- uterine rupture in first trimester (although this was at least 13 weeks gestation) and
- gestational trophoblastic disease with liver metastases after misoprostol abortion.

It was not considered that any changes to the PI were indicated by these cases and this seems reasonable.

Other safety issues

Safety in special populations

The indication includes adolescents, in whom no specific adverse event studies have been undertaken. Misoprostol is only used in women who have reached reproductive maturity as evidenced by their capacity to conceive and there is no reason to anticipate clinically important different responses in this group.

A small clinical study of 28 patients aged 14-17 years[576] reported good outcomes and a recent registry based study[32] found the incidence of reported adverse events to be similar or lower among adolescents than older women undergoing medical abortion, despite the fact that their pregnancies tended to be more advanced.

Safety related to drug-drug interactions and other interactions

Two randomised studies examined the co administration of non-steroidal anti-inflammatory drugs (NSAIDs) with misoprostol for medical abortion and found no difference in efficacy rates[629, 630]. An analysis of analgesia use with methotrexate and misoprostol regimens[715] found that use of NSAIDs did not interfere with the action of misoprostol.

Evaluator's overall conclusions on clinical safety

The safety of misoprostol in early medical abortion regimens has been well established in extensive international clinical use. Most of the issues are those discussed in the mifepristone evaluation and relate to the procedure of medical abortion rather than the particular drugs being used. Considerations specific to misoprostol (and likely other prostaglandins) are those of uterine hyperstimulation and/or rupture, toxicity and congenital abnormalities as well as some of the minor adverse events, namely fever and diarrhoea.

The risks of medical abortion must be considered in the context that abortion by any method carries some risk as do pregnancy and childbirth.

Abdominal pain and vaginal bleeding are intrinsic to the procedure of medical abortion; analgesia is commonly needed and vaginal bleeding may result in a need for surgical evacuation of the uterus, occasionally urgently. More serious bleeding requiring blood transfusion is estimated to occur in around 1-2/1000 women having early medical abortions.

There is a recognised failure rate of the procedure, with around 1% of women having continuing pregnancy and up to 7% women in total undergoing curettage following medical abortion up to 49DA although this has been as high as 11% in a few studies using oral misoprostol. Follow up must be arranged to exclude or diagnose and manage continuing pregnancy and to provide for prompt 24 h access to advice and care including surgical intervention as needed.

Infections occur following medical abortion, as they do after surgical abortion and childbirth. Serious infection is very rare but deaths from toxic shock syndrome have been

[32]Niinimäki M, Suhonen S, Mentula M, Hemminki E, Heikinheimo O, Gissler M. Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study. BMJ (Clinical Research Ed.) 2011 Apr 19: Vol. 342, pp. d2111.

reported. It has been suggested that these infections may be related to vaginal administration of misoprostol but this has not been established and similar deaths occur following miscarriage and childbirth.

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

Common adverse events are uncomfortable but self limiting and not serious. Nausea, vomiting, dizziness and fatigue are likely related to pregnancy itself and may improve with termination of the pregnancy following mifepristone administration; they remain common following misoprostol but may not be caused by it. Diarrhoea is common and appears to be causally related to misoprostol administration although reported rates vary widely (5-43%); it is more common after oral than vaginal misoprostol. Fever, chills and/or rigors are also specifically related to misoprostol and appear to be more common after vaginal than oral use. Further research may clarify differences in adverse event profiles between different regimens.

Four case reports of serious coronary and cerebral vascular events have been associated in time with misoprostol used for medical abortion.

In the event of continuing pregnancy after failed attempted medical abortion, fetal adverse effects are possible and misoprostol is a likely cause. Information about this should be provided prior to a decision for medical abortion and discussed if failure occurs and continuing the pregnancy is being considered.

Because of the pharmacodynamic action of misoprostol in directly stimulating uterine contractions there is a risk of uterine hyperstimulation and rupture, requiring careful dose modulation with advancing pregnancy, particularly beyond about 18 weeks gestation and in the presence of risk factors such as previous caesarean section or other uterine scarring. The early pregnancy cases described in the section *Uterine hyperstimulation and rupture* above were all complex clinical scenarios, which carried a higher than usual risk of uterine perforation with surgical evacuation of the uterus. Uterine hyperstimulation is extremely unlikely to occur in early medical abortion.

Misoprostol toxicity is reported but is extremely unlikely to occur with the proposed use and packaging of GyMiso.

The conclusions of the clinical overview are reasonable with the exception of the matter already referred to in that it cannot be assumed that buccal administration of misoprostol will prevent toxic shock syndrome from occurring.

First Round Benefit-Risk Assessment

Benefits

The benefits of GyMiso® misoprostol 200μg tablets in the proposed usage are:

- In combination with mifepristone it would provide access to an evidence based, safe, effective, approved regimen for medical abortion for Australian women.
- Access to this treatment option would allow women needing early abortion to have their choice of method; it is well established that many women prefer the medical method and that such choice improves satisfaction with treatment.
- At least 93% of women choosing medical abortion up to 49DA can expect to have a complete abortion without needing surgical evacuation of the uterus, provided a repeat dose is an option. With increasing clinical experience, good information and appropriate expectations this figure can increase to 95% or more.

- It would decrease the likelihood of off-label use of misoprostol for early medical abortion, either alone or in combination with methotrexate, methods with lesser efficacy than mifepristone and misoprostol combinations.
- From a population health perspective the introduction of medical abortion regimens does not appear to affect abortion rates but a shift to medical abortion over time moves a proportion of service provision from operating theatres to outpatient services.

Risks

The risks of misoprostol GyMiso® misoprostol 200μg tablets in the proposed usage are:

- Up to around 1% of women will have a continuing pregnancy; follow up must ensure this is diagnosed and managed. Fetal adverse effects are possible if this occurs.
- Up to 7% of women will need surgical evacuation of the uterus for continuing pregnancy, vaginal bleeding or missed or incomplete abortion; in some cases this will need to be done urgently.
- The option of a second dose of misoprostol is important to maximise efficacy. Information and packaging to support this option should be available.
- The general risks of abortion apply, including haemorrhage requiring blood transfusion, infection, rarely serious and missed ectopic pregnancy and its complications.
- Deaths from toxic shock syndrome have been reported: 8 notifications among an estimate of over 1.5 million medical abortions in the USA. It has been suggested that vaginal administration of misoprostol may contribute to this but it has been reported after buccal administration; in the evaluator's opinion the aetiology is unclear and may be related to the procedure rather than the drugs used.
- It is likely that mifepristone and misoprostol will be used beyond 49DG. The oral misoprostol dosage proposed is likely to have inadequate efficacy at later gestations with a higher failure rate.
- It is likely that mifepristone and misoprostol will be used off-label in the second trimester, which requires greater clinical adjustment of misoprostol regimens.
- It is likely that misoprostol will continue to be used off-label in the management of miscarriage but the currently registered preparation may be used for this purpose unless GyMiso is available separately from mifepristone.

Benefit-risk balance

The benefit-risk balance of GyMiso misoprostol 200 μg tablets, given the proposed usage, was considered to be favourable.

Extensive international experience with medical abortion using mifepristone and misoprostol regimens supports the safety and efficacy of this option of care. Careful assessment including confirmation of intrauterine pregnancy and accurate gestational assessment can the minimise risks. Good information and thorough informed consent can provide realistic expectations of the process and anticipated adverse events and confidence about when to seek advice or medical attention. Appropriate arrengements can provide for early recognition of complications and intervention when necessary.

Clear advice in the PI can contribute to minimising the risk of inadequate doses or uterine hyperstimulation with inappropriate use.

Recommendation Regarding Authorisation

The evaluator recommended approval of the application for registration of misoprostol (GyMiso) for use in adults and adolescents of childbearing age for the medical termination of a developing intrauterine pregnancy in sequential combination with Mifepristone Linepharma 200mg tablet, up to 49 days of amenorrhoea (DA).

The PI should make clear that:

- a repeat dose of misoprostol may be considered if abortion has not occurred within a defined period (1-14 days) after the initial dose
- the proposed dosage regimens are not suitable for use beyond 49days gestation for oral and 63 days gestation for buccal misoprostol.

List of Questions

Efficacy

There appear to be some errors and inconsistencies in some of the referencing and/or percentages in some tables included in the sponsor's submission. Could these please be corrected.

Sponsor Response: Errors and inconsistencies were corrected and updated versions submitted to the TGA.

Safety

The sponsor's Clinical Overview reports on about 85,000 doses of GyMiso to February 2008 and a further 24,409 from October 2009-October 2010 but does not appear to cover February 2008-October 2009. PSURs are provided for about 130,000 doses to October 2010 but missing February-October 2008, which would take it to about 148,000. The risk management plan reports on 164,210 doses. Caould the sponsor please provide the PSUR for the missing period and clarify the end date for the risk management plan report.

Sponsor Response: The PSUR 7 from October 2007 to October 2008 was inadvertently missed. Additional tables were submitted to the TGA for clarification.

Second Round Benefit-Risk Assessment

Benefits

After consideration of the responses to clinical questions above, the benefits of GyMiso in the proposed usage are unchanged from those identified above.

Risks

After consideration of the responses to clinical questions above, the benefits of GyMiso in the proposed usage are unchanged from those identified above.

Benefit-risk balance

The initial assessment remains unchanged.

Second Round Recommendation Regarding Authorisation

The initial assessment remains unchanged. The questions of the original evaluator have been satisfactorily addressed. The overall recommendation (see above) remains valid.

V. Pharmacovigilance findings

Risk Management Plan

The sponsor submitted a Risk Management Plan (RMP Ver 3.0 dated 7 November 2008) which was reviewed by the TGA's Office of Product Review (OPR).

Safety Specification

Subject to the evaluation of the nonclinical aspects of the Safety Specification (SS) by the Toxicology area of the of Scientific Evaluation (OSE) and the clinical aspects of the SS by the Office of Medicines Authorisation (OMA), the summary of the Ongoing Safety Concerns as specified by the sponsor is described in Table 13 below.

Table 13. Ongoing Safety Concerns

Identified risk	Bleeding Infection, Toxic shock syndrome Method failure Uterine contractions/cramping Uterine infection (endometritis, pelvic inflammatory disease) Nausea, vomiting* Diarrhoea* Hypotension* Skin rashes, urticaria
Potential risk	Inadvertent pregnancy exposure and risk of incomplete abortion with severe bleeding Inadvertent pregnancy exposure (risk of 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
Missing information	Inherited porphyria# Theoretical interaction with NSAIDs* Potential interaction with products interacting with the progesterone receptor# Use in Adolescents
Pharmacological class effect	Risks related to the use of prostaglandin*

*identified as safety concern associated with misoprostol

#identified as safety concern associated with mifepristone

Remainder safety concerns pertaining to both products

OPR reviewer comment

Delayed diagnosis of an ectopic pregnancy may occur as a result of use of the medical method in early pregnancy. It is accepted that 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 was asked to justify the omission of this potential risk from the safety specification. In response the sponsor concluded:

"*There is no evidence of relationship between use of mifepristone and misoprostol and an increased incidence of ectopic pregnancy. Therefore it is considered that the existing warnings in the Product Information, Consumer Medicine Information and RMP are adequate."*

The evaluator does not contend that mifepristone or misoprostol cause ectopic pregnancy. However, the nature of the medical method means that intrauterine pregnancy will not be absolutely confirmed in all cases prior to termination. As some of the symptoms of ectopic pregnancy could be confused with those expected with medical termination it is reasonable to expect that diagnosis of ectopic pregnancy may be delayed in some cases. Therefore, whilst it is an indirect effect it is recommended that "Missed ectopic pregnancy" should be included as an Important potential risk in the RMP (this was accepted by the sponsor; See *Response from Sponsor* below).

In response to a TGA request for information the sponsor added 'Use in adolescents' as Important Missing Information in the latest update to the RMP. As justification the sponsor stated that:

"Mifepristone Linepharma 200mg tablet and Gymiso 200µg misoprostol tablets are recommended for use in adults. There are limited data available in women below the age of 18 years...The sponsor is not aware of any available evidence indicating that risks might arise from such off-label use, beyond the risks documented herein."

The evaluator also highlighted that the proposed adolescent indication, treatment in this age group would not be considered as off-label use.

Pharmacovigilance Plan

This was a literature based submission and there were no ongoing or planned clinical trials for misoprostol identified by the sponsor in the RMP.

The sponsor proposed routine pharmacovigilance activities to monitor all the specified Ongoing Safety Concerns, with special attention in PSURs for all the specified Important potential risks, Important missing information and the Pharmacological class effect.

In a TGA requests for information the sponsor was asked to provide details of the routine pharmacovigilance activities. The sponsor considered that the supplied routine pharmacovigilance system were consistent with the activities outlined in the relevant EU guideline[33] and this was considered acceptable.

'Use in adolescents' was added as Missing Information in the most recent update of the RMP. The sponsor proposed that routine pharmacovigilance is sufficient for this safety concern. This was considered acceptable.

It was recommended that the sponsor include 'Missed ectopic pregnancy' as an Important potential risk. It was further recommended that this Ongoing Safety Concern be monitored by routine pharmacovigilance activities with special reference in the PSURs.

There is reasonable experience of using mifepristone and misoprostol for medical termination of pregnancy under the authorised prescriber scheme (and within the Marie Stopes framework) however, general registration of this method will be novel in Australia. Hence, there exists the potential for the medical method to be used outside of a more controlled clinical environment (like that found at Marie Stopes) and this may result in a different or unexpected safety profile. It was therefore recommended that consideration should be made to develop a Registry for the use of mifepristone and misoprostol to further determine the safety profile of this combination in a 'real-world' setting. It would

[33] 3.1.2 Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03

be expected that recruitment to such a registry would be linked to prescription or supply to ensure that all eligible participants could be captured. The evaluator noted that the registry mentioned by the sponsor was a prescriber registry not a patient registry and this was not considered to be a pharmacovigilance activity.

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

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 to ensure that the most up to date information is presented.

Risk Minimisation Activities

The sponsor did not provide specific comment regarding the need for risk minimisation in the RMP but does indicate (via Table 1.13-19 in the RMP) that it considers routine risk minimisation activities were sufficient.

However, in relation to the specified Ongoing Safety Concerns the following is noted:

"Note: the above items will be included in the Information Sheet and Patient Agreement document (Part of the MSIA M4 Med Ed Programme in Appendix 4) which will be finalised once the PI and CMI for both Mifepristone Linepharma 200 mg and GyMiso200 µg tablets are approved in Australia."

OPR reviewer comment

Tables in the RMP indicate that routine risk minimisation activities are sufficient to mitigate all the Ongoing Safety Concerns however additional risk minimisation activities are detailed in the RMP. The sponsor should amend the RMP to reflect the proposed use of additional risk minimisation activities outlined in sections on 'Informed Consent, Compliance to the Method and Follow-up' and 'Training of Medical Practitioners' of the RMP.

There is limited safety information in the RMP for the safe use in adolescents and this is now represented as Missing information. However, the evaluator noted that the current application is for the following proposed indication:

GyMiso is indicated in adults and adolescents of childbearing age for the medical termination of a developing intrauterine pregnancy in sequential combination with Mifepristone Linepharma 200mg tablet, up to 49 days of gestation.

The evaluator also highlighted that according to the proposed adolescent indication above, treatment in this age group would not be considered off-label use as it is described in the sponsor's justification in the RMP.

The evaluator was concerned that inconsistency in the description of gestational age amongst the PI, CMI, RMP and educational materials could potentiate confusion and therefore medication error. In response to a TGA request for information the sponsor has amended all associated documents to conform to a description of "Up to 49 days of Gestation". This was considered acceptable.

The use of a different trade name from other forms of misoprostol and having a particular package size for a single treatment are both acceptable as a means to reduce the potential for medication errors.

There is a potential for off-label use for misoprostol in conjunction with mifepristone. Medical termination of pregnancy using this product under the current Authorised Prescriber Scheme may occur up to 63 days of amenorrhoea. It is possible that prescribers will continue to apply this indication instead of the indication in the application (ie up to

49 days of gestation). It is recommended that the education programme should emphasise this difference to reduce the likelihood of inadvertent off-label use.

M4 Med Ed Programme

The following are excerpts from the sponsor's description of their educational program:

Following marketing approval for Mifepristone Linepharma 200 mg and GyMiso® 200 mcg tablets in Australia, MSIA also 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.

The M4 Med Ed plan has been drafted by the Marie Stopes International Medical Development Team based in the London Support Office 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 professionals and patients have access to appropriate information regarding the safe and effective administration of Medical Method.

MSIA has also 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. MSIA intends to monitor the use of the Medical Method in Australia to evaluate the effectiveness of this programme.

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 hours 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. *Follow up message to patients – Patients may also give consent and elect to receive a follow-up communication from the Sponsor 3 to 5 days following ingestion of mifepristone. This message will provide the 24 hour call centre contact telephone number and describe symptoms that are of concern in relation to infection, incomplete abortion and therapeutic failure that require medical follow-up.*
6. *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.

An eligible medical practitioner must:

- *Have completed the MSIA educational programme and passed the course evaluation;*

- *Have the ability to assess the duration of pregnancy accurately;*
- *Have the ability to diagnose ectopic pregnancies;*
- *Be able to provide, or arrange with another provider, surgical intervention in cases of incomplete abortion or severe bleeding, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary;*
- *Have read and understood the prescribing information for Mifepristone Linepharma and GyMiso tablets;*
- *Provide each patient with a ISPA and fully explain the procedure to each patient, provide her with a copy of the ISPA, give her an opportunity to read and discuss the ISPA, obtain her signature on the Patient Agreement and sign it as well*
- *Record the dose, batch number and expiry date of the mifepristone and misoprostol used*
- *Report all adverse events to the Sponsor, MSIA.*

MSIA 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 this 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 revised training manual for Australia (Version 4) was provided in to the TGA in a requests for information.

MSIA has also 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 Consumer Medicine Information (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 ISPA has therefore been evaluated in clinical practice.

MSIA 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.*

OPR reviewer comment

The Med 4 Ed programme is considered to be additional risk minimisation. It was recommended that the information contained in sections on 'Informed Consent, Compliance to the Method and Follow-up' and 'Training of Medical Practitioners' of the RMP be noted as additional risk minimisation in the 'Risk Minimisation Plan' section.

In general the principles of the Med 4 Ed programme were considered to be satisfactory however several outstanding issues are detailed below.

Access and Distribution

The sponsor apparently 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. If misoprostol is to be available in nominated pharmacies, it is unclear how the sponsor can prevent prescribers not registered in their scheme from prescribing misoprostol for the early pregnancy indication and prevent it from being dispensed.

The sponsor was asked to clarify this. In response the sponsor stated:

"With regard to the prescribers who might use a particular pharmacy to dispense mifepristone to a patient, the sponsor will strongly recommend that doctors participate in training before prescribing mifepristone and misoprostol. Doctors who are fellows or diplomates of RANZCOG would not be expected to require training as they will have specialised in obstetrics and gynaecology. Other than making a strong recommendation for doctors to participate in training it will not be possible for the sponsor to compel prescribers to undertake such training."

The sponsor has not provided any assurance in their response that prescribers of the medication obtained through nominated pharmacies have undergone appropriate training. It is the evaluator's view that the M4 Med Ed training should be a prerequisite for entry to the prescriber registry which then enables supply of GyMiso and Mifepristone Linepharma either by direct supply to the doctor or via a pharmacy. It was accepted that the sponsor cannot compel prescribers to undertake training but it can limit access to the medication to those who have undertaken sufficient training. Whilst it is accepted that fellows or diplomates of RANZCOG would be necessarily skilled to manage the complications of the medical method in general it is recommended that all prescribers be at least offered the prescriber education program as outlined in the RMP.

It is also 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. It is recommended that the sponsor clarify the exact proposed mechanism of supply to the doctor and patient including the safeguards in place to ensure prescriber compliance with training. This is discussed further in "Prescribing outside the MSIA clinic framework" below.

The education package:

A draft preparatory workbook (as used in the UK) and Instrument for Structural Policy for Pre-Accession (ISPA) was previously supplied by the sponsor in support of the application. In the sponsor's response to TGA requests for information an updated ISPA and Training Manual for Australia (version 4) was provided. With the assumption that the Training manual replaces the preparatory workbook previously supplied, it would appear that the current version is in general less comprehensive. Specifically there is no mention of course evaluation or assessment. It was recommended that the sponsor clarify how Australian prescribers who participate in the education programme will be assessed.

In the RMP and associated documents the ISPA form is described as having been 'evaluated in clinical practice'. The Sponsor was requested to provide data to support this statement. In their responses the sponsor stated that:

"*patients returning for follow up are asked about their experience, and provide feedback on the service provided by Marie Stopes...A high level of satisfaction is reported. It is therefore considered that comprehension of the content of the ISPA by clients has been assessed and found satisfactory*."

The evaluator considers that this justification is insufficient to make the claim that the ISPA has been specifically 'evaluated in clinical practice'.

The draft workbook also stated in 'Common misunderstanding 2' *"that 'while ultrasound is a useful tool both for gestational age dating and for identifying ectopic pregnancy, it is not essential".* This was considered to be a source of confusion as consent was sought for an ultrasound scan in the 'Medical Abortion – Mifepristone and Misoprostol Information Sheet'. It is noted however that the updated ISPA has removed mention of routine ultrasound and the training manual has been updated accordingly. Advice was sought from the Advisory Committee on the Safety of Medicines (ACSOM) at TGA who agreed that ultrasound was not necessarily useful or needed but was context dependent.

In the Draft Preparatory workbook, a urinary pregnancy test is recommended under a limited list of circumstances. ACSOM considered that *"use of urinary BHCG is adequate for assessment of early pregnancy. It was not considered appropriate to mandate other measures in the RMP, as this was considered a clinical practice issue".*

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. ACSOM considered that *"diagnosis of anaemia by clinical examination only (without mandating routine blood testing) was considered appropriate".*

Upon request from the evaluator it was confirmed by the sponsor that Rhesus testing is essential in all instances despite a statement in the preparatory workbook otherwise. The updated training manual makes this clear.

The evaluator noted a number of inconsistencies amongst the educational materials regarding the description of gestational age. The sponsor amended the description amongst all documents to a description of "up to 49 days of gestation".

The sponsor has provided an assurance that the educational materials 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 undertake to submit the updated educational materials to the TGA for review before they are used and distributed in Australia.

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 professionals caring for patients in this setting. The sponsor does not detail any particular education strategy for later pregnancy termination but this should be considered.

Prescription outside the MSIA clinic framework

In general the education programme outlined conforms to the MSIA framework. The evaluator accepts that MSIA has well established protocols to ensure safe provision of their services. However, 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 concluded that they

"cannot be responsible for clinicians who despite the MSIA training may chose (sic) to manage patients in different ways or prescribe mifepristone or misoprostol for other indications."

It was accepted that the individual prescriber should take responsibility for the management of their patients. However, it was recommended that appropriate safeguards be implemented to ensure that prescribers have undertaken appropriate training, follow-up procedures are in place and are in the position to avail their patients of emergency treatment if necessary.

The following is not specifically addressed:

- How the sponsor will ensure health professionals will only be able to prescribe the product after completing the education programme eg 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 programme 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 an 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. In no place in the ISPA is the patient directed to their local emergency department for emergency care if needed. A statement to this effect is recommended.

Summary of Recommendations

The evaluator provided a summary of the recommendations arising from this evaluation. These recommendations and the sponsor's responses to these are outlined in the section *Response from Sponsor* below. OPR provided 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 EU-RMP is applicable without modification in Australia unless so qualified.

The following recommendation was also made by the OPR:

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

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations which were presented to the Advisory Committee on Prescription Medicines (ACPM):

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

Quality

The quality evaluator noted that misoprostol is a PGE1 analogue which has four chiral centres. All four stereoisomers are present. GyMiso is a conventional immediate release tablet. The quality is considered to be acceptable for short term use, noting that GyMiso was developed to be bioequivalent foreign sourced (France) misoprostol (Cytotec) tablets. A shelf life of 9 months has been approved.

The bioequivalence study (Study No. JEI308) used only the oral not the buccal route of administration. The study compared GyMiso (test) misoprostol doses of 2 X 200 µg tablets to a (reference) product (sourced in France), Cytotec misoprostol 200 µg tablet in healthy fasted Taiwanese women. It was a conventional randomised, two period, two-sequence, cross over study with at least a 7 day washout period between doses. Nineteen of twenty enrolled volunteers finished the study.

The formulations met the criteria for bioequivalence (see Table 14 below).

Table 14. 90% CI A versus B

Variable	Method	Lower Limit	Upper Limit	CV
AUC_{0-t}	ANOVA-log	89.4	101	9.569
$AUC_{0-\infty}$	ANOVA-log	90.4	102	9.440
C_{max}	ANOVA-log	83.4	105	23.115

The median T_{max} was 15 minutes for both the test and reference products.

The study determined a plasma elimination half-life of 35 minutes, a fact that the evaluator considered should be mentioned in the PI document.

The evaluator concluded that:

- Both Cytotec (France) and GyMiso misoprostol 200 µg tablets showed similar, rapid absorption of misoprostol acid (misoprostol T_{max} of 15 minutes).
- The Cytotec and Gymiso misoprostol 200 µg tablet formulations are bioequivalent with respect to C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

The evaluator notes that the Cytotec's bioavailability is affected by food which will reduce the C_{max}. No study involving the effect of food was submitted in this submission.

The evaluator asked what was known of the formulations of misoprostol that were used in the clinical studies that were included in the literature based submission. The evaluator concluded:

"The applicant has not been able to provide quantitative data of the formulation of the reference products used in the clinical trials referred to in the submission. However, additional analysis of the products referenced in the literature studies has been performed (ff. 216-218). This includes the identity of the reference product by brand or company name (when it has been stated), the country in which the study was performed in the case where the brand of misoprostol was not stated and the formulation excipients present in the identified products.

Of the 68 literature studies referred to, 20 specifically report use of Cytotec, these include product sourced from the USA, UK, Australia, Denmark and France. Cytotec appears likely to have been used in 14 of the remaining studies (based on the observation that no generic misoprostol product was available in the country in question at the time the particular study was conducted). The brand of misoprostol used in the remaining 34 of the 68 studies is not clear, but the sponsor concludes that these should be therapeutic equivalent to Cytotec."

There are no objections to the registration of GyMiso misoprostol 200µg tablet blister pack with regard to chemistry, quality control and biopharmaceutic aspects.

Comments:

1. 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.
2. The PSC also noted the risk of variable bioavailability with differences in timing of doses in relation to food.
3. As mentioned, no study on the effect of food was submitted. This is manageable because (i) the intake of misoprostol can be planned and (ii) planning can take meals into account. GyMiso should not be taken within 2 h of a meal.
4. It has not been established that French Cytotec is the same as Cytotec as sold elsewhere. However, the bioequivalence study does demonstrate that GyMiso is of acceptable quality and bioequivalent to a product that is likely to have been used for the purpose in the EU.
5. The buccal route has not been studied but the applicant has claimed that the two routes are equiefficacious. This will be discussed below in connection with Study 528.

Nonclinical

The data that were submitted was comprised entirely of published literature; many papers were deficient in details. "… none were GLP compliant".

With regard to pharmacodynamics, misoprostol preferentially binds prostaglandin E2 prostanoid subtype 3 receptors (EP3), over other EP subtypes, with higher affinity of the mouse and human EP3 receptor than the rat EP3 receptor. Efficacy in producing uterine contractions increased with the duration of gestation and abortion (when following the administration of mifepristone) was shown in guinea pigs and rats.

Misoprostol is rapidly converted by de-esterification to its free acid which possesses significant pharmacological activity. There are further active metabolites that are prostaglandin F analogues. The metabolites are excreted in the urine. Misoprostol does not share metabolic pathways with mifepristone.

Maternal toxicity included emesis, diarrhoea and gastric mucous cell hypertrophy. Chronic toxicities included gastric and intestinal mucosal hyperplasia.

Some teratogenic potential (skeletal abnormalities) was shown.

Some changes to the PI document and the CMI document were suggested.

Registration was not opposed on nonclinical grounds.

Clinical

The evaluator observes that the proposed dose of misoprostol in GyMiso is not higher than that of Cytotec, "The proposed regimen for GyMiso® involves a single dose of 800 μg taken in order to induce termination of pregnancy. The approved regimen for Cytotec® for gastrointestinal indications involves a total daily dose of 800 μg, taken in divided doses for periods of 14 days up to 12 months or even longer."

Misoprostol has a practical advantage over other prostaglandins because it is stable and does not require refrigeration.

Pharmacodynamics

Published studies are cited to support an increase in uterine tone that occurs at means of around 8 minutes for oral, 10-12 minutes for sublingual, 17-27 minutes for vaginal and 41 minutes for buccal administration of 400 μg misoprostol.

Uterine contractions in Studies 901 and 910 peaked by 5 h post dose, when Study 910 ended.

Dose finding has been empirical; the evaluator is of the view that the availability of a 200 μg tablet has influenced the selection of the doses used: "Studies as early as 1993 reported high efficacy rates with mifepristone followed by 400 μg misoprostol orally and subsequent studies have largely used doses of 400-800 μg via several routes". "The current application proposes buccal administration as an alternative to the oral route and several relevant references have been added to this application." See the clinical evaluation for a discussion of the ranges of doses used in studies of efficacy: "These results suggest that acceptable efficacy rates can be achieved with all the regimens presented. They appear be more consistent with 800 μg doses given orally or buccally when a repeat dose is an option; the wide variation in other groups may reflect variations in practice."

The interval between doses of the two drugs is also discussed in the clinical evaluation. There are insufficient data to make a recommendation about intervals lower than 24-48 h between mifepristone and oral or buccal misoprostol and evidence to suggest that concomitant administration or dosing with misoprostol 6-8 h after mifepristone.

Bioequivalence

The evaluator mentions three corporate sponsors (Searle, Pharmacia, Pfizer) of the reference product, Cytotec. These names represent successive corporate owners of the product.

The bioequivalence Study JEI308 [also referred to above] was conducted in 2004. It tested GyMiso® against a reference product Cytotec® (Pharmacia SAS) that was purchased in France but manufactured by Pharmacia UK. GyMiso and Cytotec have qualitatively similar formulations. The study enrolled 19 non pregnant, fasted Taiwanese women in a conventional randomised, double blind, two-sequence, two-period crossover study. The oral and not the buccal route was used.

As reported, bioequivalence was established within acceptance limits (see Table 2).

No study was conducted to study the *effect of food* on the rate and extent of absorption of misoprostol after oral dosing. The evaluator makes some inferences about the effect of

food in the report but no specific data are available. The evaluator concludes, "*There is not enough information to make a recommendation about food intake and oral administration of misoprostol; it is probably not important to overall efficacy but a contribution to variation of response cannot be ruled out*."

The evaluator also concludes, "*While there are clearly some pharmacokinetic differences between the various routes of administration, which are likely to contribute to the observed differences in efficacy and adverse effect profiles, it is reasonable on pharmacokinetic grounds to consider oral, sublingual, buccal and vaginal routes of administration of misoprostol for gynaecological indications*."

Comments: The foreign provenance of the reference tablets of Cytotec is of less concern in the context of this application as the point of the bioequivalence study is more to relate GyMiso to published studies that are in connection with use with mifepristone and not to register a generic medicine. However, the absence of a food study is somewhat problematical[34]. The evaluator's tabulation suggested that vaginal absorption is lower and less extensive that buccal or sublingual administration but this suggestion is somewhat confounded by incomplete and short duration of sampling of all of the studies except the Bioequivalence Study JEI308.

The evaluator concludes, *"…it is reasonable on pharmacokinetic grounds to consider oral, sublingual, buccal and vaginal routes of administration of misoprostol for gynaecological indications*". However, the report stated, "The studies reported in references 901 and 910 found the first increase in uterine tone to occur at means of around 8 minutes for oral, 10-12 minutes for sublingual, 17-27 minutes for vaginal and 41 minutes for buccal administration of 400 μg misoprostol."

Comment: These differences between sublingual, buccal and oral absorption are counterintuitive as far as buccal administration is concerned and consistent with dissolution under the tongue and swallowing (= oral administration with a slight delay) as far as sublingual administration is concerned. The evaluator cannot reasonably conclude it is reasonable on *pharmacokinetic grounds* to consider oral, sublingual, buccal and vaginal routes of administration of misoprostol for gynaecological indications but would be entitled to do so on the empirical basis of published studies that report efficacy and safety.

Phase III Studies

Two studies were considered to be pivotal in terms of the proposed dose, route and indication, Studies 509 and 528.

Study 509 was conducted for the WHO and was published in 2000. It was of an acceptable design (multicentric, double blind, parallel group, randomised controlled trial comparing the abortifacient efficacy and side effects of two single doses of mifepristone (200 versus 600 mg) followed 48 h later by an *oral* dose of 400 μg of misoprostol in women with an early pregnancy.) The main efficacy variables were:

- completeness of abortion at day 15 follow-up;
- need for emergency or elective curettage prior to first menstruation
- failure of attempted abortion (continuing pregnancy at follow-up at Days 15 and 43).

The study was adequate in terms of statistical power; the intention was to be able to detect a difference in efficacy of 4% between the doses of mifepristone (92% versus 96%). Results were comparable between the two doses although efficacy was less than expected: 89.3% versus 88.1%

[34] Sponsor comment: The following statement has been included in the approved PI: *Misoprostol should be taken 2 hours before or 2 hours after a meal*.

The study authors concluded that the regimens including misoprostol were less effective than those they had previously investigated using gemeprost as the prostaglandin (94% efficacy with 95% CI 91-96%). Efficacy was inversely correlated with gestational age, with 49 days of amenorrhea set as the limit. Expulsion of uterine contents occurred at about 3 h after misoprostol.

Aggregate analysis revealed that efficacy is inversely related to gestational age, declining from 90.7% for the earliest gestational ages (≤ 49 DA) to 80.3% at the latest (between 56 – 63 DA).

In Study 509 some safety data were reported. Of 1530 women:

- 5 women needed blood transfusions.
- More than 80% had abdominal pain.
- Nausea was frequent (>50%) but did not appear to differ in frequency before and after misoprostol administration.
- Vomiting occurred in fewer than 20% of women after misoprostol and with similar frequency before misoprostol was given.
- Diarrhoea was reported as "uncommon", occurring in 6.8-8.6% of women after misoprostol, significantly more frequently than before.

Study 528 was conducted in the USA and was used to support the registration of mifepristone there but not by Linepharma. [It was therefore conducted to acceptable regulatory standards.]

The study was open label, randomised, multicentric in design. It differed in design from Study 509 because it was open label and it used one dose of mifepristone (200 mg) and it tested one fixed dose of misoprostol (800 μg not 400 μg) but it compared oral versus buccal dosing (randomised 1:1), doses were given 24-36 h after mifepristone. The study also differed in the selection of sufficient numbers of women who were at 57-63 days of amenorrhoea. Follow-up took place 1-2 weeks later. Enrolment was discontinued after 966 women when 265 women in the 57-63 days of amenorrhoea band had been randomised, ensuring at least 210 analysable cases. Unfortunately, 9.5% of participants were lost to follow up after administration of misoprostol.

The primary outcome variable was successful medical abortion, defined as a complete abortion without surgical intervention at any point regardless of the number of doses of misoprostol taken. The secondary outcome variable was the effect of a second dose of misoprostol. The results of the study favoured the buccal route, including for later gestational age (see Table 7 and Figure 7).

In regard to the secondary endpoint, fourteen women treated with buccal misoprostol and 12 with oral misoprostol had a second dose of misoprostol at the follow up visit, of whom 92.9% and 50.0% respectively (p=0.026) achieved a successful outcome, improving the success rate for buccal by 3.1% and for oral misoprostol by 1.5%.

In Study 528, some safety data were reported. Of 847 women > 90% had at least one adverse effect:

- nausea (63-75%)
- vomiting (39-48%)
- diarrhoea (33-43%)
- fever and/or chills (33-48%): significantly more frequent after buccal than oral misoprostol
- headache (31-41%)

- dizziness (29-39%)
- weakness (42-58%).

Of serious events, three women were admitted to hospital (pulmonary embolus, ruptured ectopic pregnancy and right hip pain); there were two other admissions for unspecified reasons. Twenty-one women made emergency room visits, mainly because of pain and bleeding.

Comment: This study is particularly relevant to this application because it used the regimens proposed for registration in Australia. It is of note that the buccal route was more effective, even in the context of a second dose. It is unclear to what extent a food interaction might have been involved. The results of this study make the pharmacodynamic study results reported for the oral versus buccal routes even less credible than on their face value. The discussion of the efficacy of buccal versus other routes of the report is of note; the tendency for buccal administration to be more effective than the vaginal route or the oral route including towards 63 days of amenorrhoea. The very high rate of adverse event reporting provides reassurance that some adequate sensitivity in respect of data collection prevailed. Pulmonary embolus and ectopic pregnancy are not likely to be related to treatment but rather to pregnancy and its complications.

Other Data

The sponsor's experience in Australia (through the supply of authorised prescribers) is described in the clinical evaluation. The protocol described is 200 mg mifepristone orally followed 24-48 h later by 800 µg misoprostol administered buccally by the woman at home. The patient may return to the centre for a further dose of misoprostol if no bleeding has occurred within 24 h of the misoprostol dose; otherwise a follow up visit is scheduled 2 weeks later. Efficacy (complete abortion without surgery) was reported as 96.7%, with 0.6% continuing pregnancies amongst 12,830 women. [On 16 March 2012, Marie Stopes stated that. "*Since August 2009, mifepristone has been used for termination of first trimester pregnancy in Marie Stopes Clinics in Australia under the Therapeutic Goods Administration's (TGA) Authorised Prescriber programme. Over 18,000 women have been treated with mifepristone in our clinics...".* There has been one sepsis related death in Australia.

Safety

In the introductory remarks, the evaluator comments 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. Reporting and ascertainment of adverse events vary between studies.

In terms of postmarketing data, "*The most recent USA Food and Drug Administration (FDA) Postmarketing Adverse Events Summary for mifepristone estimated that approximately 1.52 million women had used mifepristone in the USA to April 2011; as the approved regimen for Mifeprex includes 400 µg misoprostol orally it is likely that the vast majority of these women have also taken misoprostol*."

Recommendations of Clinical Evaluator

The evaluator found that the bulk of the literature supported the superior efficacy vaginal route (which has not been requested) and the buccal route over the oral route, although the last still has acceptable efficacy. In regard to dosing, "*In the evaluator's opinion, 800 µg misoprostol administered orally 36-48 h after 200 mg mifepristone is an acceptably effective regimen for medical abortion up to 49 days gestation, particularly with provision for a repeat dose if needed. The evaluator further consider buccal administration of 80 0µg to be an equally effective alternative, with the advantage that its efficacy does not decrease to the same extent with increasing gestation*."

There are no robust data to support the suggestion that oral or buccal administration will reduce the risk of toxic shock that has rarely been reported after the vaginal administration of misoprostol.

Supplementary Clinical Evaluation Report

The applicant has addressed a few concerns of the clinical evaluator.

The supplementary clinical evaluation has no material impact upon the original findings.

Other 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 Table 15. 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

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 SA and those endorsed by the Queensland Clinical Trials Network Inc Human Research Ethics Committee (QCTN HREC) 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 by state and territory

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

Risk Management Plan

The version available at the time of consideration by the ACPM was evidently not fully satisfactory. Aspects of concern were numerous and they included:

- Risks/potential risks such as continuing pregnancy, delayed diagnosis of ectopic pregnancy, use of misoprostol beyond 49 days of gestation which risks excessive uterine contractions/ hyperstimulation; and,
- Inadequate instruments to mitigate risk such as adequacy of professional training and accreditation; informed consent and availability of follow-up to patients; and,
- Inadequate pharmacovigilance.

Some concerns were outlined in the OPR evaluation report. It is evident that there has been some lack of clarity about the proposed indication and whether use in adolescents is contemplated or not.

There was no agreed version of the Risk Management Plan at the time of the Delegate's Overview. See *OPR Summary of Recommendations* (above) and *Response from Sponsor* (below) for outstanding matters.

Applicant's Response to Clinical Evaluation Reports:

In brief, the clinical evaluator's recommended revisions to the PI and CMI were noted and considered acceptable to the sponsor; the nonclinical evaluator's recommended revisions to the PI were noted and considered acceptable to the sponsor; the changes to the RMP were acceptable but there was some disparity concerning a patient registry (not requested by the clinical evaluator who did not support a patient registry).

In regard to the quality evaluation, "...considers that it is necessary for GyMiso to be registered separately, independent of the composite pack presentation, to enable " a repeat dose of misoprostol ..... if abortion has not occurred within a defined period (1-14 days) after the initial dose". The availability of GyMiso® alone (4 tablet carton) would preclude the potential off-label use of Cytotec® (supplied as 120 tablets per container.)"

Risk-benefit analysis

Delegate considerations

The proposed indication, "GyMiso is indicated in adults and adolescents of childbearing age for the medical termination of a developing intrauterine pregnancy in sequential combination with Mifepristone Linepharma 200 mg tablet, up to 49 days of gestation" is anti-competitive and will become outdated should a generic ever be registered. A more acceptable form is, "GyMiso is indicated in adults and adolescents of childbearing age for the medical termination of a developing intrauterine pregnancy in sequential combination with a mifepristone 200 mg tablet, up to 49 days of gestation".

It will be necessary for the applicant to address the matters that are listed under *Summary of Recommendations* in the RMP report. This reply should be included in the Pre Advisory Committee on Prescription Medicines (ACPM) response.

There are no quality or nonclinical reasons to withhold approval. The bioavailability issues concerning buccal administration were not adequately addressed by the published studies submitted.

The implementation of an RMP satisfactory to the TGA will be imposed as a condition of registration.

Questions Addressed to the ACPM

Without wishing to limit or constrain the Committee's discussion or general advice, the following specific questions are 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. Although improbable on pharmacokinetic grounds, the evidence from the best available study supports the buccal route of administration. Does the Committee agree that the buccal use of misoprostol can be permitted?

Proposed Actions

The application by Marie Stopes International Australia to register GyMiso® uncoated tablets containing misoprostol 200 microgram should be approved.

The registered indication should be

GyMiso is indicated in adults and adolescents of childbearing age for the medical termination of a developing intrauterine pregnancy in sequential combination with a mifepristone 200 mg tablet, up to 49 days of gestation.

The PI and CMI documents and risk management activities should be negotiated to the satisfaction of the TGA.

Submitted for advice.

Response from Sponsor

A. Concerning the RMP Evaluation

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 will 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 was evident that there had 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 women and adolescent girls 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 the RMP that was submitted with their reponse to a TGA request for information.

3. RMP Issue: Missed Ectopic Pregnancy

- The RMP Evaluator recommended that "Missed ectopic pregnancy" be included in the RMP as an Important potential risk.

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

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 TGA.

5. RMP Issue: Use of Additional Risk Minimisation Activities

- The RMP Evaluator recommended revision to the table *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 (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 undertakes 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 notes 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 DRANZCOG will be offered training even though they will have specialised 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 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 is seeking accreditation for this program from RANZCOG, and will 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 noted that 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 specialised 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 undertakes 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 (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 has provided the following elements to ensure that medical practitioners as well aspatients have access to information and aftercare that are designed to improve compliance with guidelines. The elements of this programme are shown in Table 16 below.

Table 16: Education program

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

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. Such a registry was recommended by the RMP Evaluator.

The sponsor considered 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 by the RMP Evaluator would require registration and follow up of every patient. The sponsor respectfully requests that the specific need for this type of Patient Registry, as well as the detailed requirements for its implementation, be considered very carefully in the setting of medical termination of pregnancy in Australia and be weighed against the logistical and other pragmatic issues that would surround such a detailed programme. The following are important considerations:

- *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, over 1.5 million women have been treated in the US alone according to post marketing 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.in 'real life' settings.*
- *Abortion services are very well established in Australia and are provided by a small number of experienced medical practitioners, most of whom have worked with mifepristone under the Authorised Prescriber programme (APP) since 2006. These practitioners have therefore gained experience on the safe and efficacious use of the produc, and are aware of the need for follow up. The sponsor is aware of at least two significant databases that document the APP: (i) the South Australian experience with over 1,300 patients was published by Mulligan and Messenger in 2011; and (ii) the MSIA experience; its suburban clinic network has treated over 20,000 women under the APP since 2009. A report on the first 13,345 women 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 these experiences constitute a defacto "patient registry", and that a post marketing Patient Registry in Australia will not provide clinically relevant new information beyond what is already available and/or published in the literature.*
- *From a pragmatic perspective, the reality is that abortion is a sensitive issue and patients demand privacy. A mandated registry for mifepristone users will be adetraction 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 APP experience, one third of women opt not to return to the clinic for follow up and of this number, only half of these patients can be reached by telephone. MSIA considers that it goes to great lengths to follow up clients and contends that this reflects the real world where clients 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 sponsor suggests 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 above discussion notwithstanding, the sponsor will negotiate as appropriate with the RMP evaluators at the TGA, to agree a mutually acceptable way forward.*

B. Concerning GyMiso® Evaluation

- The Delegate noted that the RMP was not fully satisfactory. One issue related to risks/potential risks surrounding the use of misoprostol beyond 49 days of gestation (excessive uterine contractions/hyperstimulation).

The sponsor has addressed items relating to the RMP above. With respect to use of misoprostol beyond 49 days, the draft PI has been amended in accordance with the recommendations of the clinical evaluator. This includes warnings on use of misoprostol in the second trimester (the need to reduce dose due to the risk of hyperstimulation) and that oral misoprostol is less effective after 49 days of gestation. The sponsor undertakes to add this information to the medical education programme.

The Delegate also noted the RMP Evaluator required adequate pharmacovigilance in relation to safety concerns.
These items are all covered in the RMP Issues 1-7 above.

Advisory Committee Considerations

The submission seeks to register an extension of indications for a currently registered product.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered this product to have an overall positive benefit–risk profile for the indication:

> *For use in females of child bearing age for the medical termination of a developing intrauterine pregnancy in sequential combination with mifepristone 200 mg tablet, up to 49 days of gestation.*

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

- a more comprehensive statement in the *Precautions* section to ensure the accurate reflection of teratogenic risk should the treatment fail.

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 patients.

The ACPM did not support the inclusion of a patient registry as an appropriate strategy; however, it recommended that the sponsor be required to conduct and submit a further phase IV study 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 this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of GyMiso oral tablet containing misoprostol 200 microgram, for the indication:

> *"GyMiso® is indicated in females of childbearing age for the medical termination of a developing intrauterine pregnancy in sequential combination with a mifepristone 200 mg tablet, up to 49 days of gestation."*

Specific Conditions Applying to these Therapeutic Goods

10. The implementation in Australia of the GyMiso (misoprostol) Risk Management Plan (RMP), version: 28 August 2012 and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

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 #

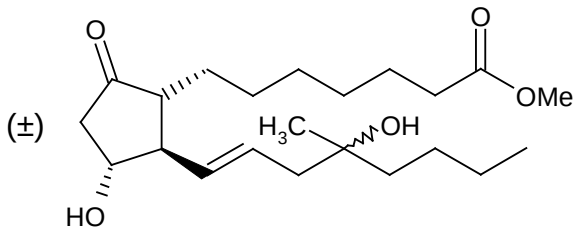
PRODUCT INFORMATION - GyMiso®

Name of the Medicine

GyMiso®, misoprostol 200 microgram tablet

Australian Approved Name (AAN): Misoprostol

Chemical Structure:



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

The CAS Registry Number: 59122-46-2

Description

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

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

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

Pharmacology

Pharmacodynamic properties

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

Misoprostol is a synthetic analogue of prostaglandin E1. At the recommended dosages, misoprostol induces contractions of the smooth muscle fibers in the myometrium and relaxation of the uterine cervix. The uterotonic properties of misoprostol should facilitate cervical opening and evacuation of intrauterine debris.

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

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

Pharmacokinetic properties

Absorption

When administered orally, misoprostol is rapidly absorbed and metabolized. Peak concentrations around 1.1 ng/mL were reached about 15 minutes after a 400 microgram dose in the fasting state. Plasma concentrations of its main degradation metabolite, misoprostol acid, reach their peak of 2 - 2.5 ng/mL after a 2 microgram/kg oral dose within approximately 30 minutes and rapidly decline thereafter. As a result, uterine contractility increases and then plateaus after about one hour. Absorption is almost complete, measured at levels between 64 - 73% from urinary data. While not compared directly with oral administration, buccal administration has been found to result in peak concentrations comparable to those following vaginal administration, which have been found in turn to be lower and later than those for oral administration.

Distribution

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

Metabolism and excretion

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

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

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

Clinical trials

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

A study of 966 patients with pregnancies up to 63 DA, randomized to 200 mg mifepristone followed 24-36 hours later by 800 micrograms of misoprostol orally or buccally, reported efficacy rates of 91.3% for the oral and 96.2% for the buccal group (RR 0.95, 95%CI 0.92-0.98, p=0.003). When patients at 43-49 days gestation were considered, efficacy rates were not significantly different according to route of administration, 94.7% for the oral and 96.4% for the buccal group. This study allowed a repeat dose of misoprostol if abortion had not occurred by 7 to 14 days.

Clinical trials have reported efficacy rates varying from 89-98% with oral misoprostol in doses of 400 to 800 micrograms 24-48 hours after mifepristone. Varying results are likely due in part to varying follow up and intervention practices. Some studies reported higher efficacies when a repeat dose of misoprostol was offered at a varying time interval (1-14 days) after the first dose.

For patients up to 49 days gestation clinical trials have consistently reported efficacy rates of at least 93% using 800 micrograms misoprostol orally in single or divided doses or 800 micrograms buccally 24-48 hours after 200 mg mifepristone, when a follow up dose could be used.

Most studies that have reported mifepristone and oral misoprostol regimens in women after 49 days gestation have found significantly lower efficacy rates at later gestations, often less than 90%; for this reason oral misoprostol should not be used in medical abortion regimens after 49 days gestation. Such a decline has not been observed using buccal misoprostol to 63 days.

Indications

GyMiso® is indicated in females of childbearing age for the medical termination of a developing intrauterine pregnancy in sequential combination with a mifepristone 200 mg tablet, up to 49 days of gestation.

Contraindications

- Known hypersensitivity to misoprostol (or any prostaglandin) or to any of the excipients;
- Contraindication to medical abortion (see Product Information of Mifepristone Linepharma 200 mg tablet) including:
    - Known or suspected hypocoagulation diseases, treatment with anticoagulants;
    - Uncertainty about pregnancy age;
    - Suspected ectopic pregnancy;
    - Contraindication to mifepristone.

Precautions

Misoprostol (or mifepristone) should not be administered if an intrauterine contraceptive device is present: it should be removed first.

Because of its abortive properties, GyMiso® should not be used by a woman with a viable pregnancy and who intends to carry that pregnancy to term. Uterine hyperstimulation and rupture have been reported beyond the first trimester when much lower dosage of misoprosotol may be required.

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

Epileptic seizures have been reported with prostaglandins and prostaglandin analogues administered by routes other than oral and this possibility should be borne in mind in patients with a history of epilepsy.

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

Special warnings and precautions for use

Special warnings and precautions for use related to the combination of GyMiso® with Mifepristone Linepharma, should also be followed (see Mifepristone Linepharma 200 mg tablet Product Information).

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 Mifepristone Linepharma
- The need for follow-up within 14 to 21 days after intake of Mifepristone Linepharma and GyMiso® in order to confirm that the abortion is complete
- The non-negligible risk of failure (see Clinical Trials) of the medical method which may require termination by another method.
- On discharge from the treatment centre all women should be provided with appropriate medications as necessary and be fully counseled regarding the likely signs and symptoms she may experience and have direct access to the treatment centre by telephone or local access.

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 7% of cases, 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 and GyMiso® intake) which may be heavy. Bleeding occurs in almost all cases and is not in any way proof of complete expulsion. Persistent bleeding can be the consequence of incomplete expulsion. Bleeding can be large enough to necessitate a blood transfusion 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.

Follow-up must take place within a period of 14 to 21 days after administration of Mifepristone Linepharma and GyMiso® to verify by the appropriate means (clinical examination, ultrasound scan, or beta-hCG measurement) that expulsion has been completed and that vaginal bleeding has stopped. In case of persistent bleeding (even light) beyond this follow-up, the disappearance of bleeding should be checked within a few days.

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

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

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

- **Infection**

As with other types of abortion, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of mifepristone and misoprostol. No causal relationship between these events and the use of mifepristone and misoprostol has been established. Treating doctors evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event. In particular, a sustained fever of 38C or higher, severe abdominal pain, or pelvic tenderness in the days after a medical abortion may be an indication of infection.

A high index of suspicion is needed to rule out sepsis (from e.g. *Clostridium sordellii* or other species e.g. Streptococcus) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhea) 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, hemoconcentration, and general malaise. Most of these deaths occurred in 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%.

Effects on fertility

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

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

Use in pregnancy

Use of misoprostol has been associated with birth defects. In a few cases where misoprostol was self-administered (orally or vaginally) in order to induce an abortion, the following deleterious effects of misoprostol have been suggested: malformations of limbs, of foetal movements and of cranial nerves (hypomimia, abnormalities in suckling, deglutition, and eye movements). To date, a risk of malformation cannot be excluded.

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

Consequently:

- 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, she should be appropriately counseled as to the risk of birth defects. In that event of continuation of the pregnancy, careful ultra-sonographic monitoring of the pregnancy should be carried out.

Use during lactation

Misoprostol is rapidly metabolized in the mother to misoprostol acid, which is biologically active and is excreted in breast milk. GyMiso® should not be administered to breastfeeding

mothers because the excretion of misoprostol acid could cause undesirable effects such as diarrhoea in breast feeding infants.

Paediatric use

Limited data are available for use of misoprostol in women under 18 years of age. There is no relevant use of misoprostol in the prepubertal paediatric population in the indication.

Use in the elderly

There is no relevant use of misoprostol in the elderly population in the indication.

Genotoxicity

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

Carcinogenicity

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

Effect on laboratory tests

There are no known effects of misoprostol on laboratory tests.

Interactions with other medicines

The serum protein binding of misoprostol acid was not affected by indomethacin, ranitidine, digoxin, phenylbutazone, warfarin, diazepam, methyldopa, propranolol, triamterene, cimetidine, paracetamol, ibuprofen, chlorpropamide and hydrochlorothiazide. With salicylic acid (300 microgram/mL), the protein binding of misoprostol was lowered from 84 to 52% which is not considered clinically significant since the binding of misoprostol acid is not extensive and its elimination half-life is very short.

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

Adverse effects

The most frequent undesirable effects which are observed during treatment with misoprostol are the following:

- Gastrointestinal disorders: nausea (transient and mild), vomiting, diarrhea, abdominal pain.
- Reproductive system disorders: very frequent uterine contractions observed in the hours following misoprostol intake; vaginal bleeding, sometimes heavy and prolonged when used with mifepristone for medical termination of pregnancy (see Special Warnings and Precautions for Use).
- General disorders: headache, dizziness, and chills and fever.

Because castor oil is an excipient, digestive symptoms (nausea, vomiting, abdominal pain) can be observed.

The adverse events reported with mifepristone and a prostaglandin analogue, 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 breast	Vaginal bleeding Uterine spasm	Prolonged post-abortion bleeding Spotting

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)**
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" (≥ 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" (≥ 1/10000 to < 1/1000) and "Very Rare" (<1/10000*) are summarized as shown below:

- Gastro Intestinal Disorders: Gastric 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

- 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: Ophtalmoplegia
- Psychiatric Disorders: Mania

*Including occasional case reports

Bleeding is an almost constant part of the procedure, whatever the prostaglandin analogue used, and at any pregnancy term, although it is usually more abundant when pregnancy age increases. It can occur after mifepristone alone. When heavy, it usually reflects incomplete abortion and is observed in approximately 3 to 12% of cases, depending on the pregnancy age and the prostaglandin analogue used, and needs specific treatment. It can necessitate a blood transfusion in 0.5 to 1 percent of cases. 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 and GyMiso® 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 extremely 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 general malaise. 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.

The issue of the outcome of persisting pregnancy in the case of failure of the medical method remains incompletely solved; a risk of malformation attributable to mifepristone or to prostaglandin analogues such as misoprostol cannot be excluded, and women should be adequately 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 the method does not appear able to terminate an ectopic pregnancy.

Dosage and administration

Medical termination of early pregnancy of up to 49 days of gestation, in combination with Mifepristone Linepharma 200 mg tablet.

- GyMiso® must be administered 36 to 48 hours after the oral intake of mifepristone.
- GyMiso® dosage is 800 micrograms, i.e. 4 tablets in a single intake, orally, or if preferred taken as two doses of 400 micrograms, i.e. two tablets taken orally followed two hours later by another two tablets. GyMiso® tablets may be taken buccally i.e: kept between the cheek and the gum for 30 minutes before any fragments being swallowed with water.
- A repeat dose of misoprostol may be offered after 1-7 days if abortion has not occurred.

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

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

Refer also to Contraindicatons, Precautions and Special Warnings and Precautions For Use.

Overdosage

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

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

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

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

Presentation and storage conditions

GyMiso®, misoprostol 200 microgram tablets are packaged in dual-faced aluminium blisters and presented in a box of four white, round, flat tablets with ML on one side and 200 on the other side.

Keep out of the reach of children.

Do not use after the expiry date printed on the outer packaging.

Store below 25°C in the original packaging.

Name and address of the sponsor

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

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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

PRODUCT INFORMATION - GyMiso®

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