

PUBLIC SUMMARY DOCUMENT

Product: Mifepristone, tablet 200 mg, Mifepristone Linepharma™, and Misoprostol, tablet 200 microgram, GyMiso®

Sponsor: MS Health

Date of PBAC Consideration: March 2013

1. Purpose of Application

The submission requested Authority Required listings for use in women of childbearing age for the termination of an intra-uterine pregnancy of up to 49 days gestation.

2. Background

These products had not previously been considered by the PBAC.

3. Registration Status

Mifepristone Linepharma™ and Misoprostol (GyMiso®) were registered by the TGA on 29 August 2012.

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

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

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.

4. Listing Requested and PBAC's View

Authority Required

Termination of an intra-uterine pregnancy of up to 49 days gestation.

Notes:

Mifepristone must be prescribed and dispensed with misoprostol.

Prescribers of mifepristone and misoprostol under the PBS for termination of pregnancy must be registered with the MS2 Step™ Prescribing Program

Authority Required

Termination of an intra-uterine pregnancy of up to 49 days gestation.

Notes:

Misoprostol must be prescribed with mifepristone.

Prescribers of mifepristone and misoprostol under the PBS for termination of pregnancy must be registered with the MS 2 Step™ Prescribing Program.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Mifepristone is a synthetic steroid with an anti-progestational action which antagonises the endometrial and myometrial effects of progesterone, sensitises the myometrium to the contraction inducing action of prostaglandins and allows dilatation of the uterine cervix.

Misoprostol is a synthetic analogue of prostaglandin E1 which induces contraction of smooth muscle fibres in the myometrium and relaxation of the uterine cervix.

When used in the recommended sequential regimen, mifepristone and misoprostol will cause medical termination of pregnancy (MTO) and accelerate expulsion of the conceptus of pregnancy from the uterus.

Medical termination of pregnancy with mifepristone and misoprostol is proposed as an alternative to surgical termination of pregnancy of up to 49 days gestation.

For PBAC's view, see Recommendation and Reasons.

6. Comparator

The submission nominated surgical termination of pregnancy (STOP) by vacuum aspiration as the comparator. The PBAC accepted that this was appropriate.

7. Clinical Trials

The submission was based on pooled analyses of five head-to-head open label partially randomised studies comparing MTO using mifepristone and a prostaglandin analogue (misoprostol or gemeprost) with STOP. Supporting analyses comparing the efficacy of mifepristone 600 mg with mifepristone 200 mg (three head-to-head studies), and misoprostol or gemeprost via different administration regimens (seven head-to-head studies) were also presented.

The table below details the published trials and associated reports presented in the submission.

Trial ID/ First author	Protocol title/ Publication title	Publication citation
MTO vs STOP (mifepristone 200 mg + prostaglandin analogue)		
Robson et al	Randomised preference trial of medical versus surgical termination of pregnancy less than 14 weeks' gestation	<i>Health Technology Assessment</i> , 2009; 13(53): 1-124
Rorbye et al	Medical versus surgical abortion efficacy, complications and leave of absence compared in a partly randomized study	<i>Contraception</i> , 2004; 70(5): 393-399
Rorbye et al	Medical versus surgical abortion: Comparing satisfaction and potential confounders in a partly randomized study	<i>Human Reproduction</i> , 2005; 20(3): 834-838
Henshaw et al	Comparison of medical abortion with surgical vacuum aspiration: Women's preferences and acceptability of treatment	<i>British Medical Journal</i> , 1993; 307(6906): 714-717

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Henshaw et al	A comparison of medical abortion (using mifepristone and gemeprost) with surgical vacuum aspiration: Efficacy and early medical sequelae	<i>Human Reproduction</i> , 1994; 9(11): 2167-2172
Henshaw et al	Psychological responses following medical abortion (using mifepristone and gemeprost) and surgical vacuum aspiration: A patient-centered, partially randomised prospective study	<i>Acta Obstetrica et Gynecologica Scandinavica</i> , 1994; 73(10): 812-818
Howie et al	Medical abortion or vacuum aspiration? Two year follow up of a patient preference trial	<i>British Journal of Obstetrics and Gynaecology</i> . 1997; 104(7): 829-833
Cameron et al	Early pregnancy termination: A comparison between vacuum aspiration and medical abortion using prostaglandin (16,16 dimethyl-trans-(Delta)(2)-PGE(1) methyl ester) or the antiprogesterone RU 486	<i>British Journal of Obstetrics and Gynaecology</i> , 1988; 95(3): 271-276
Woldetsadik et al	Client preferences and acceptability for medical abortion and MVA as early pregnancy termination method in Northwest Ethiopia	<i>Reproductive Health</i> , 2011; 8:1 Article 19
WHO 1993 Van Look et al	Termination of pregnancy with reduced doses of mifepristone.	<i>British Medical Journal</i> , 1993; 307(6903): 532-537
Misoprostol 800 mcg vaginally vs gemeprost		
Bartley et al	Double-blind randomized trial of mifepristone in combination with vaginal gemeprost or misoprostol for induction of abortion up to 63 days gestation.	<i>Human Reproduction</i> , 2001; 16(10): 2098-2102.
	Vaginal misoprostol was more effective than gemeprost after mifepristone for medical abortion up to 63 days gestation.	<i>Evidence-based Obstetrics and Gynecology</i> , 2002; 4(3): 132-133.
Misoprostol 800mcg buccally vs misoprostol 800 mcg vaginally		
Middleton et al	Randomized trial of mifepristone and buccal or vaginal misoprostol for abortion through 56 days of last menstrual period.	<i>Contraception</i> , 2005; 72(5): 328-332.
Misoprostol 800 mcg orally vs misoprostol 800 mcg vaginally		
Jyothi et al	Medical abortion by mifepristone with oral versus vaginal misoprostol	<i>Journal of Obstetrics and Gynecology of India</i> , 2006;56(6):529-31
Schaff et al	Randomized trial of oral versus vaginal misoprostol 2 days after mifepristone 200 mg for abortion up to 63 days of pregnancy.	<i>Contraception</i> , 2002;66(4):247-250.
Schaff et al	Randomized trial of oral versus vaginal misoprostol at one day after mifepristone for early medical abortion	<i>Contraception</i> , 2001; 64(2): 81-85

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Misoprostol 800 mcg orally vs misoprostol 800 mcg buccally		
Winlkoff et al	Two distinct oral routes of misoprostol in mifepristone medical abortion: A randomized controlled trial	<i>Obstetrics and Gynecology</i> . 2008; 112(6): 1303-1310.
Gemeprost 500 mcg vaginally vs gemeprost 1,000mcg vaginally		
WHO 2001 Templeton et al	Lowering the doses of mifepristone and gemeprost for early abortion: A randomised controlled trial	<i>British Journal of Obstetrics and Gynaecology</i> , 2001; 108(7): 738-742.
Rodger et al	Induction of early abortion with mifepristone (RU486) and two different doses of prostaglandin pessary (gemeprost)	<i>Contraception</i> , 1989; 39(5): 497-502

For PBAC's view, see Recommendation and Reasons.

8. Results of Trials

The clinical and patient relevant outcomes for benefits and harms were:

- Proportion of women reporting failure of termination of pregnancy (TOP) requiring surgical intervention;
- Proportion of women with complications or adverse events related to the termination, (including duration and extent of haemorrhage, distress or depression);
- Unplanned admission to hospital or unplanned consultation with a general practitioner;
- Acceptability (i.e. proportion of women who would opt for that procedure again if necessary);
- Time to return to work or normal activity.

The results of the five head-to-head trials for proportion of patients with failure of TOP are presented in the table below.

Proportion of patients with failure of TOP (MTOP vs STOP)

Trial ID	MTOP n/N (%)	STOP n/N (%)	Risk difference* (95% CI)	Odds ratio* (95% CI)
Robson 2009	41/985 (4.16%)	6/892 (0.67%)	3.5% (2.2, 5.0)	6.41 (2.71, 15.18)
Rorbye 2005	24/386 (6.22%)	17/711 (2.39%)	3.8% (1.4, 6.9)	2.71 (1.44, 5.10)
Henshaw 1993	10/172 (5.81%)	4/191 (2.09%)	3.7% (-0.3, 8.5)	2.89 (0.89, 9.38)
Cameron 1988	1/19 (5.26%)	1/28 (3.57%)	1.7% (-13.5, 21.8)	1.50 (0.09, 25.55)
Woldetsadik 2011	13/251 (5.18%)	7/139 (5.04%)	0.1% (-5.3, 4.5)	1.03 (0.40, 2.65)
Pooled result risk difference			3.0% (2.0, 5.0)	
Pooled result odds ratio				2.64 (1.37, 5.10)
Chi-square for heterogeneity: P=0.08; I ² = 51%				

Abbreviations: TOP = termination of pregnancy; MTOP = medical termination of pregnancy; STOP = surgical termination of pregnancy.

* Random effects. Statistically significant results in bold.

The following table summarises the results for the proportion of women with failure of termination, stratified by gestational age, as the requested listing restricts use of MTOP to gestational age of ≤ 49 days. There was no statistically significant difference in the proportion of women with failure of termination of pregnancy between MTOP and STOP in this population (pooled RD 1.6%, 95% CI -0.6%, 5.3%; OR 2.77, 95% CI 0.69, 11.10).

Proportion of patients with failure of TOP by gestational age

Trial ID	MTOP n/N (%)	STOP n/N (%)	Risk difference* (95% CI)	Odds ratio* (95% CI)
Gestational age ≤ 49 days				
Rorbye 2005	5/193 (2.6%)	2/279 (0.7%)	1.9% (0.4, 5.3)	3.68 (0.59, 38.96)
Henshaw 1993	1/51 (2.0%)	1/59 (1.7%)	0.3% (-7.3, 8.8)	1.16 (0.01, 92.61)
Pooled result ≤ 49 days gestation			1.6% (-0.6, 3.8)	2.77 (0.69, 11.10)
Gestational age > 49 days				
Rorbye 2005	19/193 (9.8%)	15/432 (3.5%)	6.4% (2.3, 11.6)	3.04 (1.42, 6.57)
Henshaw 1993	9/121 (7.4%)	3/132 (2.3%)	5.2% (-0.1, 11.6)	3.46 (0.83, 20.23)
Pooled result > 49 days gestation			5.9% (2.4, 9.3)	3.14 (1.69, 5.83)

For PBAC's view, see Recommendation and Reasons.

The results for the proportion of women who would opt for the same method of termination of pregnancy again are presented in the table below.

Proportion of women who would opt for the same method of TOP again

Trial ID	MTOP* n/N (%)	STOP* n/N (%)	Risk difference* (95% CI)	Odds ratio** (95% CI)
Robson 2009	542/688 (78.8%)	597/622 (96.0%)	-17.0% (-21.0, -14.0)	0.16 (0.10, 0.24)
Rorbye 2005	241/356 (67.7%)	659/900 (73.2%)	-6.0% (-11.0, 0.0)	0.77 (0.58, 1.01)
Henshaw 1993	138/166 (83.1%)	159/179 (88.8%)	-0.06% (-13.0, 2.0)	0.62 (0.32, 1.20)
Woldetsadik 2011	236/251 (94%)	137/159 (86%)	8.0% (2.0, 10.0)	2.53 (1.20, 5.41)

Source: Table Bi.6.3, p.70 of the submission.

Note: Statistically significant results in bold.

* Combined preferred and randomised arms.

** Random effects model.

The acceptability of MTOP and STOP varied between studies, but was consistently high for both procedures in all studies (67.7-96%).

Women undergoing MTOP reported more nausea, vomiting, diarrhoea, dizziness and abdominal pain or cramping compared to women undergoing STOP. These differences were statistically significant in four of the five studies. Women undergoing MTOP also reported more heavy, severe or excessive bleeding, and bleeding over a longer duration than women undergoing STOP.

Mulligan and Messenger (2011)¹ described the results of a South Australian audit of medical and surgical terminations up to 9 weeks gestation for the two years; January 2009 to 31 December 2010. The likelihood of admission to hospital (STOP 23/5823, 0.4%; MTOP 54/947, 5.7%) or requiring surgical intervention (STOP 12/5823, 0.2%; MTOP 53/947, 5.6%) for the evacuation of retained products of conception was significantly higher following early MTOP compared to STOP ($p < 0.001$).

¹ Mulligan E & Messenger H. Mifepristone in South Australia: The first 1343 tablets. *Australian Family Physician*, 2011; 40(5): 342-345.

The TGA has issued a boxed warning in the mifepristone Product Information document that states: “*It is important that all patients receiving this medication are followed up by a medical practitioner, preferably the prescriber, to ensure that the medication has been effective. Even if no adverse events have occurred all patients must receive follow-up 14 to 21 days after taking mifepristone.*”

For PBAC’s view, see Recommendation and Reasons.

9. Clinical Claim

The submission described medical termination of pregnancy using mifepristone and misoprostol as equivalent in terms of comparative effectiveness and equivalent in terms of comparative safety over surgical termination of pregnancy up to 49 days gestation.

The PBAC considered that the clinical claim was adequately supported by the data provided.

For PBAC’s view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost analysis of the MTOP and STOP procedures, including Commonwealth and State government costs.

The submission derived the number and proportions of private and public patients undergoing TOP from the count of MBS item 35643 and casemix AR-DRG-O05z separations. The submission used a variety of sources to estimate the population likely to be eligible for MTOP using mifepristone and misoprostol.

The results of the cost analysis showed MTOP to be cost saving compared to STOP. The cost analysis was most sensitive to changes in the price of mifepristone, choice of anaesthesia and the proportion of women as private patients admitted to hospital or day-hospital facilities.

For PBAC’s view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The PBAC agreed with DUSC and ESC that the availability of MTOP will allow a choice for women who have decided to undergo a termination, and is unlikely to result in an increase in overall terminations of pregnancy. Rather, MTOP will replace STOP in a proportion of cases.

The likely number of patients per year was estimated in the submission to be between 10,000 and 50,000, assuming MTOP accounts for 45% of all terminations of pregnancy in Year 5. The estimated net cost per year to the PBS was less than \$10 million in Year 5. The overall financial implication to all governments of the requested listing was estimated in the submission to be a cost saving per year of less than \$10 million in Year 5.

The relatively high price of mifepristone offered in the submission compared to overseas markets was noted. The PBAC accepted that the additional cost is related to provision of the Risk Management Plan and noted that at the price proposed the listing on the PBS was cost saving to the whole of health budget.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC recommended the listing of mifepristone and misoprostol for termination of an intra-uterine pregnancy of up to 49 days gestation on the premise of non-inferior effectiveness against STOP.

In making this decision, the PBAC took into account the Australian observational data provided, relevant to its consideration. The PBAC considered the observational data provided a reliable indication of the likely safety in Australian clinical practice.

With regard to the requested listing, the PBAC noted the submission requested an initial supply of 200 mg mifepristone and 800 mg misoprostol, and one repeat of 800 mg misoprostol. The repeat of misoprostol is available for use from 1-7 days after the initial dose of mifepristone plus misoprostol where indicated for failure of termination of pregnancy. The PBAC considered that there was uncertainty about the practicality of managing follow-up in specific situations such as failure of termination and management of adverse events. The PBAC noted that education programs are available and follow-up appointments at 14 days are part of the treatment plan. The PBAC considered that the education of those health practitioners providing the repeat was important for safe management of this product and good quality use of medicines.

The PBAC noted that in clinical practice, outlined in the clinical management algorithm, the decision between MTOP and STOP comes only after a woman has made the decision to undergo a termination. For this reason, the PBAC considered that the availability of mifepristone + misoprostol through the PBS is not likely to increase the overall number of procedures undertaken. This was supported by utilisation data from other countries.

Some limitations in relation to the evidence from the presented trials were noted by the PBAC. The extent of randomisation varied as some patients had the opportunity to select treatment of choice and the treatments were not blinded. Older studies used different doses and formulations of the prostaglandin inhibitor. The PBAC did not consider these significantly affected the interpretation of comparative effect in the five head to head studies considered. The PBAC also noted the experience of the registered doses of mifepristone and misoprostol in Australia and noted that the submission included supporting observational studies that used the doses registered for use in Australia.

The clinical and patient relevant outcomes for benefits and harms were:

- Proportion of women reporting failure of TOP requiring surgical intervention;
- Proportion of women with complications or adverse events related to the termination, (including duration and extent of haemorrhage, distress or depression);
- Unplanned admission to hospital or unplanned consultation with a general practitioner;
- Acceptability (i.e. proportion of women who would opt for that procedure again if necessary);
- Time to return to work or normal activity.

The PBAC noted in the subgroup analyses of women by gestational age, the rates of failures with MTOP were lower (absolute failure rates were 2.0-2.6%) in the subgroup of women with gestational age \leq 49 days than in the subgroup of women with gestational age $>$ 49 days (absolute failure rates 7.4-9.8%). The PBAC noted that effectiveness of MTOP decreased as gestational age increased, and that the TGA registration limited MTOP to gestational age less than 49 days, consistent with the proposed PBS restriction.

The PBAC noted that an observational study in Australia reported higher rates of hospital admission after MTOP than recorded in clinical trials using similar doses. The Mulligan and Messenger (2011) analysis of the results of a retrospective observational audit of all medical and surgical early terminations of pregnancy in South Australia (up to 9 weeks gestation), for the period 1 January 2009 to 31 December 2010, reported 5.7% hospital admissions from MTOP compared to 0.4% from STOP. The PBAC noted the sponsor's comment in the pre-PBAC response, and the limitations of this observational study. The PBAC considered that this represented a 'worst case scenario' in the context of new prescribers commencing use of the PBS-listed MTOP. The PBAC agreed with the sponsor that the hospital admissions were likely to decrease over time, with increasing expertise in prescribing MTOP.

The PBAC considered that the submission's clinical claim that MTOP using mifepristone and misoprostol was equivalent in terms of comparative effectiveness and safety over STOP, up to 49 days gestation was adequately supported by the data provided.

The PBAC noted the economic analysis provided a comparison of the costs associated with MTOP and STOP. The results showed that MTOP is less costly than STOP to the whole of health budget (both Commonwealth and State hospital and community costs). The estimate of the number of women undergoing STOP was based on the number of benefits paid for the relevant MBS listed item in 2011, extrapolation of NHDCD Cost Reports for AR-DRG O05z separations (2006-2009) for public patients, and removing duplication where private patients were treated in the public sector. The submission further assumed all women undergoing STOP will have a general anaesthetic (usually a twilight sedation) and that all women undergoing MTOP will have follow up medical consultation and pregnancy test to ensure successful termination and evacuation of the conceptus of pregnancy.

The PBAC considered that the assumptions used in the comparative costing of MTOP and STOP were generally reasonable, and that the costings appropriately accounted for expected differences such as the higher rate of complications with MTOP, patients having ultrasound and all patients attending a follow-up appointment after the procedure.

The PBAC noted that MTOP remained less costly than STOP under all realistic sensitivity analyses presented during the evaluation, including when the rates of hospital admission for complications for MTOP and STOP were adjusted to match the observational data (MTOP 5.7% and STOP 0.4%). The PBAC considered that this represented an extreme estimate and further experience would reduce these rates to those closer to the clinical trial complication rates. The PBAC also considered that uncertainty raised about the appropriateness of assigning costs for anaesthesia to all STOP patients had been adequately resolved in the sponsor's Pre-Sub-Committee response. The PBAC accepted that it was reasonable to assume that the majority of patients undergoing STOP would do so under twilight sedation.

The PBAC agreed that the best available sources of data had been used to estimate likely use of mifepristone and misoprostol. The utilisation estimates were considered reasonable, with the main uncertainty being the proportion of women who will choose medical rather than surgical termination of pregnancy.

The PBAC noted that the availability of MTOP would enhance patient choice. The PBAC considered that the availability of mifepristone + misoprostol through the PBS was not likely to increase the overall number of procedures undertaken, noting the international evidence in relation to this.

The PBAC acknowledged the proposal by the Sponsor for an educational program for prescribers and dispensers of this product and considered this would be important for the appropriate use of MTOP. Furthermore, the PBAC considered that it would be important to include an educational program for health workers other than prescribers and pharmacists for remote communities.

The PBAC considered that mifepristone and misoprostol should not be included in the list of PBS medicines for prescribing by nurse practitioners.

The PBAC noted the consumer comments received in relation to the submission.

Recommendation:

Recommended

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
MIFEPRISTONE Mifepristone 200 mg, tablet	1	0	Mifepristone Linepharma™	MS Health
Condition/Indication:	Termination of an intra-uterine pregnancy			
Restriction:	Authority Required			
Treatment criteria:	Must be treated by a prescriber who is registered with the MS 2 Step™ Prescribing Program			
Clinical criteria:	The condition must be an intra-uterine pregnancy of up to 49 days of gestation. The treatment must be in sequential combination with misoprostol 800 micrograms.			
Prescriber Instructions	An authority prescription for misoprostol 200 microgram tablets must be sought at the time of authority application.			
Administrative Advice	No increase in the maximum quantity or number of units may be authorised No increase in the maximum number of repeats may be authorised			

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
MISOPROSTOL Misoprostol 200 micrograms, tablet	4	1	GyMiso® MS Health

Condition/Indication:	Termination of an intra-uterine pregnancy
Restriction:	Authority Required
Treatment criteria:	Must be treated by a prescriber who is registered with the MS 2 Step™ Prescribing Program
Clinical criteria:	The condition must be an intra-uterine pregnancy of up to 49 days of gestation. The treatment must be in sequential combination with mifepristone 200 mg.
Prescriber Instructions	An authority prescription for mifepristone 200 mg tablet must be sought at the time of authority application.
Administrative Advice	No increase in the maximum quantity or number of units may be authorised No increase in the maximum number of repeats may be authorised

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor has no comment.