

6.17 MIFEPRISTONE AND MISOPROSTOL, Pack containing 1 tablet mifepristone 200 mg and 4 tablets misoprostol 200 micrograms, MS-2 Step®, MS Health Pty Ltd

1 Purpose of Submission

- 1.1 The Category 3 submission requested a change to the Authority Required type of PBS-listed mifepristone and misoprostol (MS-2 Step®) from Authority Required to Authority Required (STREAMLINED) for the termination of an intrauterine pregnancy.
- 1.2 The submission claimed that the request for amendment is based on the following factors:
 - the prescribing frequency of MS-2 Step appears to be reasonably stable, with annual PBS prescription numbers consistently around 30,000 per year since 2019 (see Table 1).
 - clinicians have developed a high level of familiarity with the treatment and a less onerous administrative process to prescribe MS-2 Step would not be expected to influence the frequency with which it is prescribed.

2 Background

- 2.1 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.
- 2.2 When used in the recommended sequential regimen, mifepristone and misoprostol will cause medical termination of pregnancy and accelerate expulsion of the conceptus/foetus of pregnancy from the uterus.

Registration status

- 2.3 MS-2 Step was TGA registered on 4 June 2014 for the medical termination of an intrauterine pregnancy of up to 63 days of gestation in females of childbearing age. The TGA approved product information recommends that the duration of pregnancy (i.e., up to 63 days gestation) be confirmed by ultrasound and in the event that an ultrasound is not possible, recommends that extra caution should be exercised. It also advises that an ultrasound is useful to exclude ectopic pregnancy.

2.4 The PBAC Secretariat noted that MS Health submitted two submissions to the TGA in 2022 in relation to MS-2 Step, that are still under assessment, requesting the following changes respectively:

- Proposed changes to Product Information (PI) under Section 4.4 to remove the precaution regarding rhesus alloimmunisation to align with relevant Australian and international guidelines which have been updated in the time since MS-2 Step was first registered.
- Proposed changes to PI to amend the black box warning from referencing “medical practitioner” to “healthcare practitioner”; and in section 4.2, for the reference to “doctors” to be amended to “healthcare practitioners”.

2.5 These changes are not proposed in the current PBAC submission.

Previous PBAC consideration

2.6 In its March 2013 meeting, the PBAC recommended the listing of the components mifepristone 200 mg (Mifepristone Linepharma®) and misoprostol 200 microgram (GyMiso 200®) for termination of an intra-uterine pregnancy of up to 49 days gestation on the basis of non-inferior effectiveness and lower cost versus surgical termination of pregnancy (STOP). This listing was effective 1 August 2013.

2.7 In its July 2014 meeting, the PBAC recommended the listing of mifepristone and misoprostol composite pack (MS-2 Step) for the termination of an intra-uterine of up to 63 days’ gestation on the basis of non-inferior effectiveness against STOP, in line with the revised TGA-approved indication.

3 Requested listing

3.1 The submission requested the existing listing of MS-2 Step be amended from Authority Required (Telephone) to Authority Required (STREAMLINED).

3.2 Suggested additions are in italics and deletions are in strikethrough.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
MIFEPRISTONE (&) MISOPROSTOL					
Mifepristone 200 mg tablet [1] (&) misoprostol 200 microgram tablet [4], 1 pack	10211K	1	1	0	MS-2 Step
Restriction Summary New1 / Treatment of Concept: New2					
Concept ID (for internal Dept. use)	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required <input checked="" type="checkbox"/> Authority Required (Streamlined) New2				
8702	Indication: Termination of an intra-uterine pregnancy				
12247	Clinical criteria:				
12246	The condition must be an intra-uterine pregnancy of up to 63 days of gestation				

8704	Treatment criteria:
8703	Must be treated by a prescriber who is registered with the MS 2 Step Prescribing Program
7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised

4 Consideration of the evidence

Sponsor hearing

4.1 There was no hearing for this item.

Consumer comments

4.2 The PBAC noted that no consumer comments were received for this item.

Submission evidence

4.3 The submission claimed that given the current listing of MS-2 Step aligns with its TGA registered indications, there is no risk of use outside of its intended population.

4.4 The submission further claimed that the requested change in authority level would not increase use of MS-2 Step, given the maturity of the market, the year-to-year consistency of script numbers, and the familiarity of prescribers with the use of MS-2 Step. It is unclear if this assumption is reasonable. In addition, the submission claimed that the current expenditure on MS-2 Step is modest by comparison with other PBS-listed medicines. It is unclear what other PBS-listed medicines the submission is referring to, noting that no comparator was nominated for this submission and there are no other medicines PBS-listed for the termination of pregnancy.

Table 1: PBS Script volumes (2015-2021)

Year	2015	2016	2017	2018	2019	2020	2021
Total PBS scripts processed	9,373	15,092	19,236	18,735	29,207	27,239	31,067

Source: Mifepristone misoprostol PBS script volumes 2015-2021

Table 2: PBS Expenditure (2015-2021)

Year	2015	2016	2017	2018	2019	2020	2021
Total Benefit processed (\$)	2,661,385	4,223,378	5,395,935	5,266,062	8,155,219	7,530,687	8,885,119

Source: Mifepristone misoprostol PBS expenditure 2015-2021

4.5 The submission stated that the treatment criteria would remain the same, including no change to the requirements for prescribers to be registered with the MS-2 Step Prescribing Program.

4.6 MS-2 Step is currently an Authority Required (Telephone) listing which require prescribers to either call or apply for authority approval to prescribe MS-2 Step using Services Australia’s Online PBS Authorities (OPA) system. Services Australia (SA) noted prescribers are required to answer questions either in a phone call to an SA officer or

via an e-form through the OPA system to declare that they are registered for MS-2 step prescribing program and that the patient's pregnancy is up to 63 days of gestation.

- 4.7 The submission claimed that the change in Authority required type would reduce administrative burden for clinicians. Mifepristone 200 mg was considered as part of Tranche 1 of the Post-Market Review (PMR) of Authority Required PBS Listings (the Review). The submission claimed that the Review arose from the realisation that "Authority Required listings caused significant regulatory burden to prescribing", leading to a comprehensive consideration of all listings "to ensure that restrictions appropriately reflect the level of monitoring required to manage the quality use of medicines and the identified risks". The Review Reference Group did not recommend a change to the authority level of mifepristone at that time because of the recency of its listing. The submission argued that as prescribers are now highly familiar with the use of the drug on the PBS, changing the Authority required type to Authority Required (STREAMLINED) would be unlikely to result in higher prescribing rates or increased costs to the PBS. The submission's claim of greater convenience and reduced administrative burden for prescribers is justifiable in the scenario where prescribers opt to call SA because of the time taken for prescribers to call. However, the submission's claim of reduction in administrative burden for the prescriber when the authority is assessed via the OPA system is unclear as the OPA system allows prescribers to obtain immediate authority approval (following confirmation of eligibility), without direct contact with SA. The Pre-PBAC response argued that although the OPA system would result in reduction in waiting time for prescribers, the process is not seamless. The response noted that the time required to log onto the system with 2-factor authorisation where the system is not integrated with prescribing software, search for the medicine, complete the Q&A process and retrieval of the approval code still consumes a proportion of the time allocation for consultation. The response therefore asserts that streamlining of MS-2 Step would produce a benefit for prescribers in terms of administrative burden.
- 4.8 The change in Authority type to an Authority Required (STREAMLINED) benefit would result in no validation of the above two criteria by SA and prescribers would be responsible for ensuring all criteria are met for patients to access MS-2 Step. SA would also have no oversight of when prescribers apply to prescribe MS-2 Step and data would only be collected when prescriptions are dispensed at pharmacies. A streamlined authority may present an increased risk that prescribers who are not registered with the MS-2 Step Prescribing Program may prescribe MS-2 Step this could present a QUM issue. The Pre-PBAC response argued that the prescriber's obligation to acquire the knowledge and skill to prescribe a drug safely is a fundamental aspect of their practice, regardless of whether the PBS approval process requires demonstration of that knowledge. The response further reiterated that prescribers must have undertaken appropriate education and training to fulfil their professional obligations before the administration of a drug (e.g. testing, monitoring or other

activity that must occur before administration of a drug; obtained informed consent and providing follow-up care as needed). The response further noted that there were adequate training resources available to support prescribers on the safe prescribing of MS-2 Step.

Estimated PBS usage and financial implications

- 4.9 The submission stated that the change of authority type would likely have no impact on the uptake of MS-2 Step, noting that the clinical criteria and indication would remain the same. The submission therefore did not provide any financial estimates to support the requested change. The change in authority level could result in increased utilisation in that it may increase the risk of use outside the restriction. The Pre-PBAC response acknowledged that there may be an increase; however, recalled that the March 2013 recommendation for MS-2 Step recognised that the use of medical termination of pregnancy (MTO) would be cost-saving over STOP and reiterated that the statement remains that MTO is a less costly procedure than STOP and the use of MS-2 Step over STOP would result in a cost-saving to the Commonwealth and State health budgets.
- 4.10 An analysis of the utilisation of mifepristone and misoprostol (item 10211K) was undertaken by the DUSC Secretariat using 100% data extracted from the PBS and Authorities data maintained by Department of Health and Aged Care, processed by Services Australia. The PBS data was extracted based on the date of supply; the analyses were conducted on 8 February 2023. Referring to Table 3, the number of prescriptions dispensed and benefits for mifepristone and misoprostol had increased between 2021 and 2022. There was also growth in the number of initiating patients (Table 3). The utilisation of mifepristone and misoprostol is dependent on the number of medical practitioners and pharmacists registered to prescribe and dispense MS-2 Step[®]. There was a large increase in the number of PBS prescribers in 2022 compared to prior years (Table 4). The growth in utilisation in 2022 could also relate to restrictions on medical abortions being lifted in South Australia from July 2022 and the introduction of permanent telehealth services from January 2022. The Pre-PBAC response argued that any increase in patient or prescription numbers would be driven by the patient's decision between a medical or a surgical termination. The PBAC recalled its March 2013 advice that the availability of MTO is unlikely to result in an increase in overall terminations of pregnancy.

Table 3: Utilisation of mifepristone and misoprostol by incident and prevalent patients, scripts dispensed and benefits paid

Year	Incident patients	Prevalent patients	Annal growth in prevalent patients	Scripts dispensed	Annual growth in scripts dispensed	Benefits paid	Annual growth in benefits paid
2015	9594	9594	Nil	9859	Nil	\$2,797,910	Nil
2016	14215	14738	54%	15305	55%	\$4,283,072	53%
2017	17475	18599	26%	19342	26%	\$5,425,683	27%
2018	20673	22613	22%	23546	22%	\$6,602,981	22%
2019	22549	25318	12%	26259	12%	\$7,332,542	11%
2020	24381	28016	11%	29111	11%	\$8,059,428	10%
2021	25657	30101	7%	31356	8%	\$9,014,260	12%
2022	29511	35221	17%	36701	17%	\$11,675,313	30%

Table 4: Number of prescribers for PBS mifepristone and misoprostol

Year	Number of PBS prescribers
2015	324
2016	440
2017	570
2018	727
2019	961
2020	1242
2021	1462
2022	1893

4.11 Data from Services Australia shows that all approved authorities for mifepristone and misoprostol had valid answers in relation to: (1) the treating prescriber being registered with the MS 2 Step Prescribing Program; and (2) that the application was for an intra-uterine pregnancy of up to 63 days of gestation.

4.12 As shown in Table 5, the majority of prescribers were general practitioners.

Table 5: The number of scripts of mifepristone and misoprostol supplied by prescriber type from first listing to 31 December 2022

Prescriber type	Number of scripts dispensed	Proportion
General practitioner	171,168	89.4%
Obstetrics and Gynaecology	14,774	7.7%
Sexual Health Medicine	1,960	1.0%
Public Health Medicine	410	0.2%
Other	423	0.2%
Not specified	2,744	1.4%
Total	191,479	100.0%

For more detail on PBAC's view, see section 5 PBAC outcome.

5 PBAC Outcome

- 5.1 The PBAC recommended a change to the restriction level of mifepristone and misoprostol from Authority Required to Authority Required (STREAMLINED) for the termination of intrauterine pregnancy.
- 5.2 The PBAC noted that regardless of the authority level, prescribers are required to prescribe in accordance with the PBS restriction and agreed with the view presented in the sponsor’s pre-PBAC response that the prescriber’s obligation to acquire the knowledge and skill to prescribe a drug safely is a fundamental aspect of prescribing practice.
- 5.3 The PBAC considered that, in addition to the MS-2 Step Prescribing Program, there were adequate resources such as the electronic Therapeutic Guidelines and training resources offered by MS Health available to educate prescribers on the safe prescribing of MS-2 Step.
- 5.4 While the PBAC considered that the change in authority level is unlikely to increase utilisation of MS-2 Step, it considered that any increase in utilisation may signal improved access for those currently experiencing access challenges, such as people in remote communities. The PBAC noted that no financial estimates were provided.
- 5.5 The PBAC also recalled from its March 2013 consideration that MTOP was less costly than STOP under all the realistic sensitivity analyses presented. The PBAC retained the view that MTOP is less costly than STOP to the whole of health budget (both Commonwealth and State hospital and community costs). Thus, improving access to MTOP may reduce health system costs where STOP would otherwise be used.
- 5.6 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

6 Recommended listing

- 6.1 Amend existing listing:

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Restriction Summary [New1] / Treatment of Concept: [New2]					
Concept ID (for internal Dept. use)	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required (Streamlined) [New2]				

8702	Indication: Termination of an intra-uterine pregnancy
12247	Clinical criteria:
12246	The condition must be an intra-uterine pregnancy of up to 63 days of gestation
8704	Treatment criteria:
8703	Must be treated by a prescriber who is registered with the MS 2 Step Prescribing Program
7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

7 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

8 Sponsor's Comment

The sponsor had no comment.