Mifepristone (Mifepristone Linepharma) followed by misoprostol (GyMiso)
for medical termination of pregnancy of up to 49 days’ gestation
(mi-fe-PRIS-tone and miso-PROS-tol)

KEY POINTS

Medical termination of pregnancy is an alternative to surgical termination
Mifepristone followed by misoprostol is a safe and effective method for medical termination
of pregnancy of up to 49 days’ gestation.

Mifepristone followed by misoprostol has efficacy and safety similar to those
of surgical termination of pregnancy
It may cause more bleeding and painful cramps.

Serious adverse events, such as infection, occur rarely
The woman must have access to 24-hour emergency care if required.

Ectopic pregnancy must be excluded and gestational age confirmed,
preferably by ultrasound, before prescribing
Ensure any intrauterine device is removed before termination is started.

Mifepristone followed by misoprostol can be prescribed only by a suitably
trained medical practitioner
Training is provided in Australia by MS Health, a subsidiary of Marie Stopes International.

PBS listing
Authority required
For the termination of an intrauterine pregnancy
of up to 49 days’ gestation.

Who can prescribe and dispense it?

- Medical practitioners who have registered
  with MS Health and received certification
  as prescribers following completion of an
  online training program and assessment
  (www.ms2step.com.au).¹
- Some medical practitioners do not require training but must request certification
  from MS Health. These include Fellows of
  RANZCOG, holders of an Advanced Diploma
  from RANZCOG (DRANZCOG), and TGA
  Authorised Prescribers.²
- Pharmacists are also required to request
  certification (as dispensers) from MS Health
  to purchase mifepristone and misoprostol.
  Pharmacists are required to confirm that
  medical practitioners are registered and
  certified with MS Health prior to dispensing.
  This can be done via the secure healthcare

What is it?
Mifepristone (also known as RU-486) is a
synthetic steroid and progesterone antagonist
that competes with progesterone and blocks
progesterone receptors.³
In pregnant women mifepristone’s action
on the uterus can induce abortion. It causes
dilatation of the cervix and increases the
sensitivity of the myometrium to the action
of prostaglandins.
Misoprostol is a synthetic analogue of prostaglandin E1 that induces contractions of the smooth muscle fibres in the myometrium and relaxation of the uterine cervix.4

Mifepristone is followed 36–48 hours later with misoprostol to terminate a developing intrauterine pregnancy.5

**Who is it for?**

The combination of mifepristone followed by misoprostol is indicated for medical termination of a developing intrauterine pregnancy within 49 days of the start of a woman’s last menstrual period.3,4

It is an alternative to surgical termination of early pregnancy that can be offered to women when it is suitable for them, for example, for women with no contraindications to mifepristone or misoprostol (see Safety issues).3,4

Candidates for medical termination of pregnancy must be able to adhere to the treatment regimen (including follow-up visits) and have access to a telephone and transportation to a medical facility in case of emergency.

**Where does it fit?**

Medical abortion became an alternative method of first-trimester pregnancy termination in the 1980s with the availability of prostaglandins and anti-progesterones.6

The efficacy and safety of mifepristone followed by misoprostol for medical termination of pregnancy is well established. This combination of medicines has been in use for up to 20 years in many countries, including France, China, the UK and US.7,8

Mifepristone has been available in Australia since 2006 through the TGA Authorised Prescriber Scheme and was included on the Australian Register of Therapeutic Goods (ARTG) in 2012.1

Misoprostol was registered in Australia in 2012 for use orally or buccally in combination with mifepristone for termination of pregnancy of up to 49 days’ gestation.4

**Proven efficacy for termination of pregnancy of up to 49 days’ gestation**

The efficacy and safety of mifepristone followed by misoprostol for termination of early pregnancy was established in four pivotal trials conducted in France, the UK and US. The overall rate of success was high, with complete termination of pregnancy achieved in 92–97% of women who were pregnant for up to 49 days.9–12

Subsequent clinical trials have demonstrated consistent efficacy of at least 93% with mifepristone (200 mg) followed by misoprostol (800 micrograms) 24–48 hours later.3,4,13

**Not approved in Australia for termination of pregnancy after 49 days**

In Australia medical termination of pregnancy using mifepristone followed by misoprostol is not approved by the TGA for use after 49 days of gestation. However, this combination of drugs is widely accepted and safely used overseas up to 63 days’ gestation.14

Termination of pregnancy after 49 days’ gestation using mifepristone followed by oral misoprostol has lower efficacy rates than termination up to 49 days — often less than 90%. A decline in efficacy was not observed using buccal misoprostol up to 63 days.3,4,13

Medical termination of pregnancy after 49 days’ gestation is associated with slightly more adverse events, including bleeding, pain and a higher rate of complications.15

**An alternative to surgical termination of pregnancy**

Women can choose their preferred option if both alternatives for termination of pregnancy are suitable and available. Having a choice of method for termination of pregnancy may improve a woman’s psychological outcome.16

In a UK study the most frequent reason for choosing medical abortion was to avoid some aspects of the operative process, particularly the anaesthetic (61%), or because women viewed the process as simpler and more natural (32%). Women who chose surgical termination of pregnancy generally wanted to avoid the awareness and involvement in the process of termination (49%) and were concerned about the pain (16%) or emotional impact (14%) of medical termination.17
Legal and regulatory requirements for termination of pregnancy
Termination of pregnancy by any method needs to be conducted in accordance with the legal and regulatory requirements of the jurisdiction where it occurs. Relevant law varies between Australian States and Territories.

Refer to the Children by Choice Fact Sheet: Australian abortion law and practice⁶ for a summary of current Australian legislative provisions relevant to abortion.

Prevention of future unintended pregnancy is a priority
Medical practitioners have an important role in prevention of unintended or unwanted pregnancy, through taking up opportunities for individual counselling and population health promotion about relationships, safe sex and contraceptive use.⁹

How does it compare?
The most effective regimen for medical termination
The most widely researched drugs for medical termination of early pregnancy are:⁶

- mifepristone with prostaglandins (misoprostol or gemeprost)
- prostaglandins alone
- mifepristone alone
- methotrexate alone
- methotrexate with prostaglandins.

Evidence suggests that combined regimens such as mifepristone followed by misoprostol are more effective than single agents.⁹ A combined regimen of mifepristone followed by misoprostol is faster and more effective than a combination of methotrexate followed by misoprostol.²⁰

Different prostaglandins can be used with mifepristone for medical abortion, such as gemeprost, but misoprostol is superior because it is more cost effective, does not require refrigeration and offers different routes of administration.⁶

Buccal administration of misoprostol is absorbed more slowly than oral administration, but appears to induce higher overall uterine activity. Efficacy rates for mifepristone followed by misoprostol administered either orally or buccally are comparable for women at 43–49 days (94.7% vs 96.4%, respectively).⁴

Similar efficacy to that of surgical termination
Different surgical methods for termination of early pregnancy are available, with various levels of efficacy:

- dilatation and curettage
- power-operated vacuum aspiration
- manual vacuum aspiration or hysterotomy (not commonly used).²¹

A Cochrane review found insufficient data to make recommendations about which surgical methods are favoured for early termination of pregnancy.²¹

In general, medical termination of early pregnancy is considered to have similar efficacy to that of surgical termination.²²,²³ For example, vacuum aspiration, which is a common method for surgical terminations of early pregnancy, has similar efficacy to medical termination of pregnancy using mifepristone followed by misoprostol.²²

However, surgical termination of early pregnancy appears to have higher rates of complete abortion, with less than 2–4% failure rate.²⁵–²⁷
Patient experience after termination of pregnancy
Satisfaction with both medical and surgical methods for termination of early pregnancy is high.27-29 The health outcomes appear to be similar with both methods, but many women have a strong preference for one approach.27,30

Recovery after medical and surgical termination of early pregnancy is estimated to be the same. For example, even though women who underwent vacuum aspiration required more time off work than those who underwent medical abortion (2.4 vs 1.3 days), the time taken for return to normal daily activities was similar for both groups.22

Choice of the method for termination
Medical termination of early pregnancy is an alternative to surgical termination and ideally both methods should be offered to ensure the woman understands that she has a choice.

For a woman the choice between surgical and medical abortion involves balancing the benefits and risks of both methods (Table 1). The risk of surgery and anaesthesia is balanced against the risk of a medical method with a slightly lower efficacy, involving more pain and bleeding.

Some women may feel more in control using a medical method, but this method may be perceived a more unpleasant option by others.

Safety issues
Expected consequences of medical abortion using mifepristone followed by misoprostol are heavy uterine bleeding and painful uterine contractions or cramps.7 Cramps are similar to those experienced during a menstrual cycle or labour. For most women the pain is adequately managed with OTC analgesics.19

Many of the side effects experienced during medical abortion are associated with misoprostol use. Common transient side effects from these drugs include:3,4,19

- nausea: experienced by about 40–70% women
- vomiting: experienced by about 10–45% women
- diarrhoea: experienced by about 10–30% women
- headache, fever, chills and fatigue.

Most women find the side effects acceptable. The rate of any serious adverse event or complication after medical termination of early pregnancy is low.8

Table 1.
Advantages and disadvantages of medical and surgical abortion31

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Medical abortion</th>
<th>Surgical abortion</th>
</tr>
</thead>
<tbody>
<tr>
<td>▶ Avoids surgery and anaesthesia</td>
<td>▶ Faster</td>
<td>▶ Invasive procedure</td>
</tr>
<tr>
<td>▶ More acceptable to some women (feels like menses)</td>
<td>▶ Takes place in a healthcare centre, clinic or hospital</td>
<td>▶ Small risk of cervical or uterine injury</td>
</tr>
<tr>
<td>▶ No risk of cervical or uterine injury</td>
<td>▶ Fewer failures</td>
<td>▶ Risk of postoperative infection</td>
</tr>
<tr>
<td>▶ Can take place at home</td>
<td>▶ Gestation up to 14–24 weeks (depending on State laws)</td>
<td>▶ Adverse effects from anaesthetic</td>
</tr>
<tr>
<td>▶ Lower risk of infection</td>
<td>▶ Sterilisation (if chosen for contraception) can be concurrent</td>
<td></td>
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<table>
<thead>
<tr>
<th>Disadvantages</th>
<th>Medical abortion</th>
<th>Surgical abortion</th>
</tr>
</thead>
<tbody>
<tr>
<td>▶ Bleeding, cramping, nausea, diarrhoea and pain occur</td>
<td>▶ Invasive procedure</td>
<td></td>
</tr>
<tr>
<td>▶ Risk of failure and need for surgical abortion</td>
<td>▶ Small risk of cervical or uterine injury</td>
<td></td>
</tr>
<tr>
<td>▶ More clinic visits required</td>
<td>▶ Risk of postoperative infection</td>
<td></td>
</tr>
<tr>
<td>▶ Gestation of up to 49 days</td>
<td>▶ Adverse effects from anaesthetic</td>
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Persistent bleeding for longer than 16 days occurs rarely
Bleeding associated with medical termination of pregnancy usually occurs within 4–6 hours of misoprostol administration in > 95% of women.3,4 Some vaginal bleeding may continue for an average of 10–16 days after mifepristone administration.3,4
Advise women experiencing heavy bleeding for > 2 days after misoprostol administration to seek medical advice. In 0.1–0.2% of women terminating pregnancy up to 49 days’ gestation, the bleeding is heavy enough to cause anaemia and may require a blood transfusion.3,4
If persistent bleeding (even if light) is reported at the follow-up visit at 14–21 days, arrange a further appointment within a few days to assess cause. Persistent bleeding can be a consequence of incomplete abortion or an unnoticed extrauterine pregnancy and may require surgical intervention.3,4

Pelvic infection
As with other types of abortion, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported after use of mifepristone followed by misoprostol.3,4 Overall serious infection rates after medical abortion are estimated to be < 1%.2 The US FDA estimates reports of fatal sepsis are about 1 in 100,000.32
Fever, severe abdominal pain, nausea, vomiting or pelvic tenderness in the days after a medical abortion may indicate presence of an infection.3
There is currently insufficient evidence to recommend the use of prophylactic antibiotics for women having a medical abortion.32

Failures requiring surgical intervention
The overall failure rate of mifepristone followed by misoprostol is about 2–7%.3,4,13 Failure can be caused by incomplete abortion (about 2–4% of failures) or ongoing pregnancy (about 1% of failures).13
Surgical intervention is undertaken in < 5% of women undergoing medical abortion for continuing viable pregnancy or, more commonly, incomplete abortion.19

The frequency of surgical evacuation of the uterus is reported to decrease with increasing experience of the clinical team with the medical method.33,34

Follow-up is essential due to risk of failure
Follow-up is essential 14–21 days after mifepristone administration to verify that expulsion has completed, vaginal bleeding has stopped and to exclude complications such as infection.3
If medical termination fails and ongoing pregnancy is confirmed with an ultrasound, offer termination of pregnancy by a surgical method.3
There is unknown risk to the foetus after exposure to mifepristone, but use of misoprostol is associated with birth defects.3

Long-term risks associated with termination of pregnancy
There does not appear to be an association between termination of pregnancy and risk of miscarriage, preterm birth or placenta praevia in subsequent pregnancies.19
Evidence does not support an association between termination of pregnancy and infertility, ectopic pregnancy or breast cancer.19
It appears that after one medical versus one surgical termination of pregnancy the obstetric risks for delivery in subsequent pregnancies are similar.35

Similar safety profile compared with that for surgical termination
Women who choose medical termination using mifepristone followed by misoprostol over surgical termination are more likely to experience adverse events such as bleeding, abdominal pain, nausea and vomiting.23,24,27,36
There is a low and comparable incidence of serious complication rates with surgical and medical methods for termination of pregnancy.8,37,38 A Cochrane systematic review reported no significant difference in the rate of complications between surgical and medical methods of abortion in the first trimester, although there were few sufficiently powered randomised studies to identify different rates for rare events.38
A large registry-based cohort study of more than 42,000 women in Finland compared complication rates after medical and surgical termination of early pregnancy and reported that both methods were safe.37

The incidence of haemorrhage or incomplete abortion was higher in women undergoing medical termination, while complications requiring surgical treatment were more common after surgical termination of pregnancy. The rates of infection and serious morbidity did not differ between the groups.37

**Contraindications to mifepristone and misoprostol**

Contraindications to mifepristone and misoprostol medical abortion include:

- chronic adrenal failure
- severe disease requiring steroid administration
- hypocoagulation diseases
- anticoagulant therapy
- allergy to mifepristone, misoprostol or other prostaglandin.3,4

This regimen is not recommended in women with anaemia, renal failure, hepatic impairment, malnutrition or cardiovascular disease.3,4

Before prescribing mifepristone and misoprostol ensure ectopic pregnancy is excluded, gestational age is confirmed as no more than 49 days and any intrauterine device is removed before treatment.3,4

For information about reporting adverse reactions to the TGA, or to report suspected adverse reactions online, see the TGA website (www.tga.gov.au/safety/problem.htm#medicine) or use the ‘Blue Card’ distributed three times a year with Australian Prescriber.

**Reason for PBS listing**

The PBAC recommended listing of mifepristone followed by misoprostol for medical termination of an intrauterine pregnancy of up to 49 days’ gestation on the basis of similar effectiveness and cost compared with surgical termination of pregnancy.19

**Dosing issues**

**Before mifepristone administration**

Discuss pain relief using paracetamol or OTC analgesics. Evidence supports the pre-emptive use of ibuprofen for pain relief.40

In all instances, the use of mifepristone requires prior rhesus determination.3

**Mifepristone administration**

A single mifepristone tablet (200 mg) should be swallowed with water. Evidence suggests that 200 mg of mifepristone is as effective as higher doses (600 mg).41 In about 3% of pregnancies the products of conception will be expelled before misoprostol is administered.3

**Misoprostol administration**

(36–48 hours after mifepristone)

Misoprostol should be taken 36–48 hours after mifepristone administration. Acceptable regimens for oral or buccal administration of misoprostol tablets (200 microgram tablet) are:

- 800 micrograms (four tablets) in a single dose
- 400 micrograms (two tablets) to be repeated after 2 hours.4

Advise the woman to stay at home and rest for 4–6 hours after taking misoprostol tablets or until the expulsion process is complete. Some women choose to be in the clinic for this part of the treatment. It is highly desirable that a support person is present who knows how to access emergency care if it is required.

**Additional misoprostol dose**

(1–7 days after initial misoprostol)

If abortion has not occurred after the initial dose of misoprostol, an additional dose of misoprostol (up to 800 micrograms) can be prescribed from 1 to 7 days later.3

**Follow-up examination is essential**

(14–21 days after mifepristone)

Advise the woman to return to the clinic 14–21 days after mifepristone administration to ensure termination of pregnancy is complete.3,4
Information for patients

If a woman chooses to terminate pregnancy using mifepristone followed by misoprostol, provide specific and clear instructions for this method. Discuss the mifepristone and misoprostol Consumer Medicine Information (CMI) leaflets with her. Provide a written list of the symptoms women may experience during medical termination of pregnancy and those that require urgent medical consultation.

Advise a woman undergoing medical termination of pregnancy as follows.

- It is highly desirable to have a support person present who will stay with you until the abortion process is complete.
- Take mifepristone and oral misoprostol tablets with water 2 hours before or 2 hours after a meal.
- If using buccal administration of misoprostol, keep the tablet between the cheek and the gum for 30 minutes before swallowing any remaining fragments with water.
- After taking misoprostol tablets, stay at home and rest for 4–6 hours or until the expulsion process is complete.
- Vaginal bleeding will usually occur and the products of conception may be expelled within a few hours of taking misoprostol or during the next few days.
- Bleeding may last up to 10–16 days but should not be heavy for > 2 days.
- Ensure access to emergency care and a 24-hour phone service.
- Follow-up is essential within 14–21 days after taking mifepristone to confirm that the pregnancy is terminated.
- If ongoing pregnancy is confirmed, surgical termination of pregnancy is required due to risks of teratogenic effects from one or both drugs.
- Consider contraceptive options and, when appropriate, start contraception after the abortion process.

References

REFERENCES Continued