Guide for Dispensing Mifegymiso® (MIFEpristone/MISOprostol) for Medical Abortion

Introduction

This guide is intended for use by community pharmacists dispensing medications for first trimester induced medical abortions (MA) to patients in community practice. The information in this guide and the accompanying checklist is in accordance with the SOGC and Health Canada guidelines for medical abortion with mifepristone (MIFE) and misoprostol (MISO), (Mifegymiso®); other drug regimens are outlined in the SOGC guidelines.

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1. Communication about Medical Abortion

Abortion is common in Canada: one in three females will have an abortion. Women and trans men, especially those who are younger, face a number of barriers to abortion access including stigmatization and lack of information. As a pharmacist, you are in a unique role to **provide a safe and supportive** environment for a patient coming in to pick up medications for a medical abortion, as well as **provide information and resources** about safe medical abortion practices.

1.1 Key actions for creating a safe and supportive environment

- Provide a private space for counselling and ensure confidentiality
- Demonstrate an openness to listen and address any concerns or feelings of unease
- Be ready to discuss the patient's personal and emotional needs, values and coping strategies *[resources for referrals provided on page 5]*
- Help the patient identify resources including: a) personal support system and b) community and emergency resources
- Help clarify any myths and misconceptions about abortion
- Use non-stigmatizing language

1.2 Use of language

SUGGESTED MESSAGES

- Abortion is a common medical procedure and requires informed consent
- Abortion is a legal and safe procedure
- All pregnant people have the right to make decisions about their bodies and decide if, when, and how to have a child
- Pregnant people are encouraged (but not required) to seek help from a supportive individual of their choice when accessing abortion services

NON-STIGMATIZING TERMS

Use this…	*Rather than this…*
End a pregnancy; have an abortion	Abort a child
Choose abortion; decide to end a pregnancy	Get rid of…
(Choose to) continue the pregnancy	Keep the baby/child
Service/abortion/healthcare provider	Abortionist
Pregnancy	Baby
Embryo (<10 weeks) or fetus (≥ 10 weeks)	Unborn baby or child / dead fetus
Pregnant person	Mother
Partner of pregnant person	Father
	Parent
Prevent/reduce unintended pregnancies	Reduce abortion
Anti-choice/anti-abortion	Pro-life
More than one abortion	Repeat/multiple abortion

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2. Criteria for a Medical Abortion with Mifegymiso®

2.1 Inclusion criteria

When a patient comes into your pharmacy with a Mifegymiso® prescription, they will have had an in-depth conversation with their prescriber who will have covered all options and confirmed eligibility for a medical abortion (MA) with Mifegymiso®, including:

1. MA involves using drugs to end a pregnancy.
2. MA with mifepristone 200 mg oral and misoprostol 800 mg buccal is considered as safe as surgical abortion before 63 days following last menstrual period (LMP) and is highly effective up to 70 days LMP.
3. MA is considered irreversible.
4. All drugs need to be taken as directed.
5. In the event of an ongoing pregnancy post-MA, a surgical abortion is recommended as the MA drugs are teratogenic.
6. Patients should have access to urgent medical care for the 7-14 days post-MA.
7. Risks include: bleeding, cramping/pelvic pain, gastrointestinal symptoms (nausea/vomiting/diarrhea), headaches, fever/chills, and pelvic/lower genital infection.
8. Special risks include a need for urgent surgical intervention if there is heavy bleeding, severe pain, ongoing pregnancy or retained products. The risk of mortality is 0.3 in 100,000, usually from infection or undiagnosed ectopic pregnancy. The mortality risk is similar to surgical abortion and lower than for a term pregnancy.

2.2 Exclusion criteria

ABSOLUTE CONTRAINDICATIONS	RATIONALE
Ambivalence*	MA should only be initiated when the patient is certain of their decision.
Ectopic pregnancy	MA is not an appropriate treatment for a current ectopic pregnancy and the consequences of a missed diagnosis could be life threatening.
Chronic adrenal failure	MIFE is an anti-glucocorticoid and can impair the action of cortisol replacement therapy in those with adrenal insufficiency.
Inherited porphyria	MIFE can induce δ-aminolevulinic synthetase; the rate limiting enzyme in heme biosynthesis.
Severe uncontrolled asthma*	MIFE is an anti-glucocorticoid and can compromise control of severe asthmatic attacks.
Hypersensitivity to ingredients*	Allergic reaction is rare (<0.01%) *[refer to Non-medicinal Ingredients on page 4].*

RELATIVE CONTRAINDICATIONS	RATIONALE AND MANAGEMENT
Unconfirmed gestational age (GA)	If GA is uncertain, ultrasound should be performed or other methods to date the pregnancy should be undertaken by the prescriber.
Intrauterine device (IUD) in place*	Pregnancies with IUDs in situ are more likely to be ectopic, which must be excluded. If an ultrasound indicates an intrauterine pregnancy, the **IUD should be removed before MA**.
Long term corticosteroid use*	Steroid effectiveness may be reduced for 3-4 days post-MIFE and therapy should be adjusted.
Hemorrhagic disorders or current anticoagulant therapy	MA routinely results in blood loss. Precautionary measures may be appropriate.
Anemia with hemoglobin < 95 g/L*	In many studies, anemic women did not obtain MA; precaution may be appropriate.

* Can be directly identified or addressed by a pharmacist.

3. Pharmacology of Mifegymiso®

3.1 Mechanism of action

MIFE is a progesterone receptor modulator. It is a potent anti-progestin and also exhibits strong antiglucocorticoid and weak antiandrogenic properties. It blocks progesterone receptors in early pregnancy leading to **endometrial degeneration**, synthesis of prostaglandins, uterine contractility, and decline in beta-human chorionic gonadotropin (β-hCG) secretion. These events **promote the onset of bleeding**.

MISO is a potent synthetic prostaglandin E1 that **induces cervical ripening and uterine contractions** that expel a pregnancy.

3.2 Drug interactions

MIFE is **metabolized by CYP3A4** and is also an irreversible competitive inhibitor of CYP3A4 and, to a lesser extent, of CYPs 1A, 2B, 2D6, and 2E1. As MIFE binds CYP irreversibly and is slowly eliminated from the body, caution should be exercised when mifepristone is administered with drugs that are CYP3A4 substrates and have narrow therapeutic range. Drug interactions of importance in the clinical setting that may alter the metabolism of MIFE include:

- CYP3A4 inducers (glucocorticoids, macrolide antibiotics, rifampicin, carbamazepine, benzodiazepines, barbiturates, St. John's wort);
- CYP3A4 inhibitors (cimetidine, ketoconazole, erythromycin, chloramphenicol, spironolactone, secobarbital, grapefruit juice).

MIFE has antiglucocorticoid activity; may temporarily decrease the efficacy of corticosteroid therapy, including inhaled corticosteroids.

MISO: no known drug interactions. **Oral ingestion with food or antacids may decrease oral bioavailability**.

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3.3 Pharmacokinetics

MIFE taken orally shows non-linear pharmacokinetics. It is rapidly absorbed and distributed, reaching peak concentrations after 0.75 hours. It is 94-99% plasma-bound and is metabolized by CYP enzymes, mainly CYP3A4. Elimination is relatively slow with a half-life ranging from 83-90 hours.

MISO pharmacokinetic profiles vary substantially depending on the route of administration.

Buccal: time to first uterine contraction is 67 minutes, sustained for about 90 minutes and begins to decline at 5 hours after administration. The uterine response of appears similar to that of vaginal administration, with less inter-individual variability.
Vaginal: time to first uterine contraction is 98 minutes for moistened tablets and 82 minutes for dry tablets, sustained activity is attained at 128 minutes and 106 minutes, respectively, and uterine activity begins to decline at five hours after administration.
Sublingual: tablets are absorbed through the mucosa within 20 minutes and MISO reaches peak serum concentration at 30 minutes. First-pass metabolism is avoided.

3.4 Mifegymiso® non-medicinal ingredients

An allergic reaction to Mifegymiso® is rare. The following is a list of non-medical ingredients that may cause a hypersensitivity reaction in addition to the drug components of mifepristone and misoprostol:

- *MIFE:* colloidal silica anhydrous, magnesium stearate, maize starch, microcrystalline cellulose and povidone K30.
- *MISO:* hydrogenated castor oil, hypromellose, microcrystalline cellulose and sodium starch glycolate.

4. Administration of Mifegymiso®

4.1 Indication and clinical use

MIFE200/MISO800 is indicated by Health Canada for pregnancy termination up to 63 days as measured from the first day after the last menstrual period (LMP) in a presumed 28-day cycle. The SOGC indicates safe use up to 70 days LMP. There is no absolute lower gestational age limit and robust clinical data supports the use of MIFE200/MISO800 as an effective regimen up to 70 days.

4.2 Clinical efficacy of MIFE200/MISO800

MIFE 200 mg oral and **MISO 800 µg buccal/vaginal/sublingual regimens** are considered as effective and safe.

GESTATIONAL AGE	CLINICAL EFFICACY OF MIFE200/MISO800*	RISK OF ONGOING PREGNANCY
Up to 49 days	95.2 – 98%	0.5 – 0.9%
Up to 70 days	87 – 98%	3.5%

*Clinical efficacy refers to completion without further intervention required.

Pharmacist Check of Prescription Written Date

The pharmacist should review the written date on the prescription. If the prescription was written 7 days or more from when the prescription was brought to the pharmacy, the pharmacist may wish to follow-up with the prescriber.

4.3 Drug dosing and directions

In Canada, the approved MIFE/MISO combination product consists of oral MIFE 200 mg and buccal MISO 800 µg, taken 24 to 48 hours after MIFE administration. Each package of Mifegymiso® contains two coloured boxes. According to SOGC guidelines, routine prophylactic antibiotics are not required; screen-and-treat is the preferred management strategy and is performed by a prescriber.

ADMINSTRATION INSTRUCTIONS	
Day 1: MIFE200 (green box label)	Take one MIFE 200 mg tablet orally and swallow it with water.
Day 2-3: MISO800 (orange box label)	24-48 hours after taking MIFE, place 4 MISO tablets (single 800 µg buccal dose) between the cheeks and gums (two on each side of the mouth) and leave in place for 30 minutes then swallow any leftover fragments with water. MISO absorption may be decreased if administered with food and/or antacids.
Day 7-14: Prescriber Follow-up	Follow-up must take place to verify that expulsion has been completed.

4.4 Administration considerations and recommended schedule

Due to the expected effects of inducing a medical abortion including vaginal bleeding and abdominal pain, it is important to consider the timing of medication administration in order to ensure patient comfort and the least strain on activities of daily living.

RECOMMENDED ADMINSTRATION *(For a typical 9-5 working schedule)*	
Day 1: Thursday	Take MIFE in the morning. Minimal vaginal bleeding may occur; be prepared with panty liners.
Day 2: Friday	**If possible, it is recommended to take the day off work.** Take MISO in the morning. Expect heavy bleeding and cramping to start within 4 hours and last throughout the day. Be prepared with large sanitary pads.
Day 3-4: Saturday & Sunday	Bleeding is expected to continue through Saturday. Take the weekend to rest.

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5. Management and Monitoring for Mifegymiso®

5.1 Common side effects and recommended management

SIDE EFFECT	WHAT TO EXPECT	MANAGEMENT AND MONITORING
Vaginal Bleeding + Discharge	Vaginal bleeding occurs in almost all cases and is **not proof of complete expulsion**. **Prolonged heavy bleeding can be a sign of incomplete expulsion**. Immediate: typically starts 4 to 48 hours after taking misoprostol and lasts 2-4 hours; heavier than regular menses with **potential to pass clots**. Lasts on average 10 to 16 days. Prolonged: light bleeding may continue for 30 days post-pregnancy termination or until next menstrual period.	• Ensure patient is prepared with maxi pads for immediate bleeding. • Liners may be recommended for prolonged bleeding that may occur post-pregnancy termination. • Advise to not use tampons. ***Advise patient to seek help if*:** a. They soak > 2 maxi pads per hour for > 2 consecutive hours, or if they feel dizzy, lightheaded, or have a racing heartbeat; b. They have prolonged heavy bleeding or cramping > 16 days; c. They notice abnormal or foul-smelling vaginal discharge.
Pelvic or Abdominal Pain	Some pain and cramping is expected before and at the time of expulsion. Typically starts within 4 hours of misoprostol administration; usually greater than typical menstrual period. Usually lasts no longer than 24 hours. Factors associated with more pain: • Young age • Advanced gestational age • Nulliparous status • Previous abortion	• Most cases, NSAIDs (e.g. standard dosing of ibuprofen or naproxen) can be used to manage pain as needed with no requirement for prophylactic dosing. • Mild opioid analgesics (e.g. codeine or oxycodone) can be prescribed to be taken as needed for significant cramping or severe pain. • Acetaminophen is not as effective alone at reducing pain as NSAIDs but may be taken in combination with opioids analgesics. ***Advise patient to seek help if*:** severe pain during abortion is not controlled by analgesics.
Other Side Effects	Are fairly common; nausea, vomiting, diarrhea, dizziness, headache, chills/fever.	• Nausea can be treated with OTC dimenhydrinate. Alternatively, prescription ondansetron or Diclectin® are also options. • Gastrointestinal side effects can be reduced by taking misoprostol after a small snack. Diarrhea, fever and chills are usually self-limiting and can be managed with OTC medications. ***Advise patient to seek help if*:** they present with fever > 38°C lasting more than 6 hours, especially after the day of misoprostol administration, and if they feel weakness/faintness, nausea, vomiting, or diarrhea in the days after abortion.

5.2 Frequency of occurrence of adverse events

- Very common (≥ 10%): nausea (30%), vomiting (21%), diarrhea (58%); dizziness (13%), headache (13%), chills/fever (45%), fatigue; gastric discomfort, abdominal pain; vaginal bleeding, spotting, uterine contractions or cramping
- Common (1-10%): fainting; gastrointestinal cramping, light or moderate; prolonged post-abortion bleeding, severe hemorrhage, endometritis, breast tenderness, heavy bleeding with or without requiring surgical termination of pregnancy
- Uncommon (0.1-1%): arrhythmia; hemorrhagic shock, salpingitis, heavy bleeding requiring IV fluids or blood transfusion; infection; hot flush, hypotension; bronchospasm; skin rash/pruritus

5.3 Teratogenicity

MIFE: data are limited. A prospective case series from France of 38 continuing pregnancies exposed to MIFE only reported two unrelated major malformations.

MISO: congenital anomalies associated with MISO use in the first trimester have been reported including limb abnormalities and Moebius syndrome, which affects cranial nerve development and leading to impaired swallowing, sucking, expression of emotion, speech, and motor development. Even though terminal transverse limb defects may be detected with ultrasound, the facial components of Moebius syndrome cannot be assessed by ultrasound prenatally.

5.4 Signs of complications

- Some of the key complications of medical abortion include: retained products of conception, post-abortion infection, and toxic shock syndrome in addition to ongoing pregnancy. Below are listed some signs and symptoms that are suggestive of these events.

COMPLICATION	SYMPTOMS		SIGNS UPON LAB EXAMINATION
Retained Products (3 – 5%)	• Unexpected heavy/prolonged bleeding and cramping OR • Failure to have expected bleeding		
Infection (<1%)	• Abdominal or pelvic pain • Foul-smelling vaginal or cervical discharge • Prolonged vaginal bleeding or spotting	• Fever or chills (more than 24 hours after misoprostol) • Uterine or adnexal tenderness	• High white blood cell count
Toxic Shock Syndrome (very rare)	• General malaise with nausea, vomiting, and diarrhea • Absence of fever (or mild fever) • Minimal abdominal pain	• Weakness • Flu-like symptoms • Tachycardia/hypotension • Edema	• High white blood cell count • High hemoglobin level

- Adverse reaction reporting to Health Canada: Complete a report online at https://webprod4.hc-sc.gc.ca/medeffect-medeffet/index-eng.jsp or call Canada Vigilance Regional Office at 1-866-234-2345.

5.5 Missed doses

Both **mifepristone and misoprostol are embryotoxic** and have been associated with fetal abnormalities. As such, once the treatment is started, there is a risk of embryotoxicity if the pregnancy is not terminated.

- *If **MISO is forgotten** and > 48 hours has passed since MIFE:* advise patient to take MISO as soon as possible and to inform their prescriber about the delay at their scheduled follow-up. Studies most strongly support using MISO between 24 to 48 hours after MIFE; however, MISO still works when taken earlier or later and using it is much more effective than not.
- *If **vomiting occurs**:*
  - ***Less than 1 hour after swallowing MIFE**:* contact prescriber for assessment. The dose of MIFE may need to be repeated and taken with an antinauseant medication.
  - ***During buccal absorption of MISO**:* contact prescriber for assessment. If there is not any bleeding within 48 hours of MISO administration, another dose may be required.
  - *After swallowing MISO fragments 30 minutes after buccal administration:* no action required; medication has already been absorbed.
- *If MISO is swallowed before 30 minutes have passed:* MISO is safe and effective to swallow. There may be more gastrointestinal side effects when MISO is taken orally compared to buccally or vaginally.

5.6 Psychological support

There is **no evidence that early medical abortion is associated with an increase in psychological problems** such as depression, anxiety, or suicidality. A range of emotions following an abortion is normal and pregnant people who are concerned about their emotional response should be are encouraged to talk with their prescriber. Additionally, you can refer them to Exhale, a free, after-abortion Talkline *[refer to Canada-Specific Abortion Resources on page 6].*

6. Contraception Plan

Fertility can return as rapidly as 8 days after a medical abortion; patients should discuss a contraceptive plan at initial visit with the prescriber. Refer patients seeking more information about contraception options to the SOGC Sex and U webpage *[refer to Canada-Specific Abortion Resources on page 6].*

METHODS	WHEN TO INITIAL	SPECIAL CONSIDERATIONS
Intrauterine device/system (IUD/IUS)	• after MIFE/MISO administration and abortion completion	• Insert at the prescriber follow-up appointment recommended
Hormonal contraceptives	• As soon as possible after MISO administration Note: There is some evidence that shows progestin-containing contraceptives may reduce the effectiveness of progestin receptor modulators such as MIFE, and vice versa. Currently, the available clinical data does not justify delaying hormonal contraception after MIFE administration.	• Ensure to counsel on appropriate barrier methods for first 7 days of use
Condoms and spermicides	• can be used immediately	
Cervical cap or diaphragm	• Delay initiation until bleeding stops	

7. Prescriber Follow-up Appointment

- A **follow-up appointment with the prescriber is required to confirm termination of pregnancy.** This appointment should be scheduled 7-14 days after administration of mifepristone.
- The patient should be aware of who to consult or where to go in case they have further questions or is experiencing complications. This can include:
    - Contact information for a prescriber or clinic
    - Knowledge of the closest emergency department

8. Canada-Specific Abortion Resources

- **Canadian Abortion Providers Support:** www.caps-cpca.ubc.ca
    - Includes "Ask an expert", an online forum for sharing cases, and resources and support for prescribers, pharmacists, and their healthcare teams
    - Provides locations of pharmacies dispensing Mifegymiso® in Canada
- **Action Canada for Sexual Health and Rights:** www.sexualhealthandrights.ca
    - National 24-hour Access Line: 1-888-642-2725 (provide information on reproductive and sexual health and referrals on pregnancy options)
    - Website has list of service providers that provide clinical or educational services, surgical or medical abortion, etc
- **National Abortion Federation:** www.nafcanada.org
    - Toll-Free: 1-800-772-9100 (M-F: 7:00 AM – 11:00 PM EST; Sat & Sun: 9:00AM – 9:00PM EST)
        - Answers to questions about abortion, unintended pregnancy, or related issues (including financial assistance)
    - For referrals to quality abortion providers: 1-877-257-0012
- **Sex and U by the Society of Obstetricians and Gynecologist of Canada:** http://www.sexandu.ca/pregnancy/
    - Broad overview of pregnancy options and links to resources
    - Full website has supplementary information on sexuality, sexual health, and contraception options
- **Fédération du Québec pour le planning des naissances (FQPN):** www.fqpn.qc.ca *(Québec specific)*
    - For referrals to quality abortion providers in Québec: 514-866-3721
- **Exhale:** www.4exhale.org or 1-866-439-4253
    - Free, after-abortion Talkline that provides emotional support, resources, and information

9. References

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