MIFEGYMISO
(mifepristone, misoprostol)

EDUCATIONAL PROGRAM FOR HEALTH CARE PROFESSIONALS
Version 2.0
Date of revision: November 14th, 2017
### Revision History

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<tr>
<th>Version</th>
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<th>Summary of Changes</th>
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<tr>
<td>1.0</td>
<td>November 7(^{th}), 2017</td>
<td>Original version</td>
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<tr>
<td>2.0</td>
<td>November 14(^{th}), 2017</td>
<td>• Minor administrative changes involving grammar and punctuation;</td>
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<td>• The contraceptive options slide was added to the ‘Pre-Abortion Care’ section.</td>
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Overview of the Educational Program

- This Educational Program has been developed to train health professionals to ensure safe and effective use of MIFEGYMISO (mifepristone, misoprostol). It provides information on the use of MIFEGYMISO for the termination of early pregnancy in accordance with the approved Canadian Product Monograph (CPM).

- Additional pre- and post-abortion care information is also provided.

- The Educational Program is available to physicians, pharmacists and other health professionals.
Educational Program Topics

1. Introduction to MIFEGYMISO
2. Informed Consent
3. Assessing Patient Eligibility
4. Assessment of Gestational Age
5. Pre-Abortion Care
6. Administration of MIFEGYMISO
7. Post-Abortion Care (Follow-up)
8. Management of Complications
9. Frequently Asked Questions
1. INTRODUCTION TO MIFEGYMISO
1. INTRODUCTION TO MIFEGYMISO

Objective:

To describe the pharmacology and mechanisms of action of mifepristone (MIFE) and misoprostol (MISO), contained within each pack of MIFEGYMISO.

Introduction:

MIFE and MISO have been used for the termination of first trimester pregnancy since the 1980s and MIFEGYMISO is commercially available in Canada since January 2017.
1. INTRODUCTION TO MIFEGYMISO

**Mechanism of Action:**

MIFE is a synthetic steroid with antiprogestational action as a result of competition at the progesterone receptors.

When MIFE blocks progesterone receptors, the endometrium can no longer sustain the growing embryo. Without the effect of progesterone:

- the lining of the uterus breaks down, and
- bleeding begins.

MIFE also triggers an increase in prostaglandin levels and dilates the cervix, facilitating abortion.

MIFE induces uterine activity in virtually all women 36 and 48 hours after administration.

MISO is a synthetic analogue of prostaglandin E1. At the recommended dosage, misoprostol induces contractions of the smooth muscle fibers in the myometrium and relaxation of the uterine cervix. The uterotonic properties of MISO facilitates cervical opening and evacuation of intrauterine content.
1. INTRODUCTION TO MIFEGYMISO

Approved Indication:

MIFEGYMISO is indicated for medical termination of a developing intra-uterine pregnancy with a gestational age up to 63 days as measured from the first day of the Last Menstrual Period (LMP) in a presumed 28-day cycle.
1. INTRODUCTION TO MIFEGYMISO

Limitations of Use:

Mifegymiso is not intended for routine use as a contraceptive.

Prior to prescribing Mifegymiso, health professionals must:

- Ensure that patients have access to emergency medical care in the 14 days following administration of mifepristone;
- Schedule a follow-up 7 to 14 days after the patient takes mifepristone, to confirm complete pregnancy termination;
- Exclude an ectopic pregnancy and confirm the gestational age (GA) by ultrasound;
- Counsel each patient on the risks and benefits of Mifegymiso, including bleeding, infection and incomplete abortion;
- Obtain the patient’s informed consent to take the drug.

Mifegymiso should be prescribed by health professionals with adequate knowledge of medical abortion and/or who have completed a Mifegymiso education program.
2. INFORMED CONSENT
2. INFORMED CONSENT

- Objectives:
  
  To review the information a woman should receive in order to provide her informed consent for MIFEGYMISO (mifepristone, misoprostol).
  
  To highlight counselling points recommended before a woman decides on a termination and the method of termination.
2. INFORMED CONSENT

Informed Consent:

The health professional must ensure that the woman:

- Understands the MIFE\textsuperscript{GYMISO} medical abortion (MA) process and the potential risks and side effects of the treatment before she is asked to give consent;
- Understands that MA is irreversible, and that, owing to risk of teratogenicity, the patient is expected to complete the regimen in its entirety;
- Understands what to expect during the expulsion;
- Knows that surgical abortion is an alternative to MIFE\textsuperscript{GYMISO};
- The decision to use MIFE\textsuperscript{GYMISO} must be the voluntary decision of the patient alone;
- The woman must be given the opportunity to ask any questions and have them answered satisfactorily;
- Woman can decide against having MIFE\textsuperscript{GYMISO} at any time before it takes place;
- The woman must understand that if MIFE\textsuperscript{GYMISO} process fails to terminate the pregnancy, surgical termination is recommended because of the possibility of birth defects from the medication;
- The effect of MIFE alone on a foetus is not known;
- There are reports of foetal malformations after the administration of misoprostol.
2. INFORMED CONSENT

Informed Consent cont’d:

The health professional must also ensure that the woman understands:

- How and where MIFE and MISO tablets will be administered;
- The number of visits to the clinic/hospital required;
- The importance of a support person;
- That the follow-up is essential to confirm termination of pregnancy and exclude complications;
- How to access 24-hour emergency care in the event of a complication.
2. INFORMED CONSENT

Informed Consent cont’d:

The expected side effects and their difference with complications. The following symptoms require immediate medical attention:

- Soaking two or more maxi pads per hour for two consecutive hours;
- Sustained fever $> 38^\circ C$ (100.4°F) or onset of fever more than 24 hours after taking MISO;
- General malaise (including weakness, nausea, vomiting, or diarrhoea) with or without abdominal pain or fever, occurring $> 24$ hours after misoprostol administration;
- Vaginal bleeding accompanied by one-sided, severe lower abdominal pain, with dizziness, shoulder pain or shortness of breath, or other signs/symptoms suspicious for ruptured ectopic pregnancy.

If needed, download Informed Consent Forms from Celopharma website (www.Celopharma.com) or email info@Celopharma.com for printed copies.
2. INFORMED CONSENT

Risks and Side Effects:

The potential serious risks of MIFEGYMISO are:

- Continuing pregnancy;
- Incomplete abortion;
- Excessive bleeding;
- Infection (0.016% to 0.019%),\(^1\) including serious infection.

The potential serious risks may necessitate additional medical measures such as surgical abortion or blood transfusion.

The possible side effects of MIFEGYMISO: \(^2\)

- Bleeding and cramping are expected, and may require additional use of analgesics;
- Nausea (34-71%) and vomiting (26-40%);
- Diarrhoea (34-60%);
- Fever/chills (37-45%).

\(^1\) CAPS, \(^2\) Mifegymiso Canadian Product Monograph
2. INFORMED CONSENT

Patients Counselling and Resources:

Decision-making involves an exploration of all options available to the patient, including: continuing the pregnancy with the intention to be parent, to place the child for adoption, and abortion (medical or surgical).

- Women should be aware of the risks and benefits of each option.

Many women are certain of their decision at the time of consultation, and confirming the certainty of their decision is sufficient. In other cases, further counselling or referral may be beneficial.

Counselling and abortion care should be provided in a timely fashion, while allowing the patient adequate time to reach a decision. The woman should be informed of her gestational age and the gestational age limit for medical abortions or abortions services in her area.

As fertility is immediately restored after an MA, it is recommended that the woman’s future contraceptive options be considered during the counselling session.
3. ASSESSING PATIENT’S ELIGIBILITY
3. ASSESSING PATIENT’S ELIGIBILITY

Objective:
To identify which women are eligible - and not eligible - for MA with MIFEGYMISO.
3. ASSESSING PATIENT’S ELIGIBILITY

Eligibility Criteria:
A women is eligible to MA with MIFEGYMISO if:

- She has made an informed choice to have MA;
- Her pregnancy is no more than 63 days of gestational age since last menstrual period (LMP);
- She has no medical contraindications to MIFEGYMISO;
- It is safe for the woman to abort at home.
3. ASSESSING PATIENT’S ELIGIBILITY

Contraindications to MIFEGYMISO:

MIFEGYMISO should not be prescribed to patients who:
- have an ectopic pregnancy;
- have an intrauterine device (IUD) in place;
- have unconfirmed gestational age;
- have chronic adrenal failure;
- are on concurrent long term systemic corticosteroid therapy;
- have haemorrhagic disorders or are using concurrent anticoagulation therapy;
- have inherited porphyria;
- have uncontrolled asthma;
- have known hypersensitivity to mifepristone, misoprostol, other prostaglandins, or to any excipients used in MIFEGYMISO (see CPM).
3. ASSESSING PATIENT’S ELIGIBILITY

Other Considerations:

- Cramping, abdominal pain, or vaginal bleeding since LMP:
  - Consider ectopic pregnancy\(^1\) or spontaneous abortion.
- Contraceptive use:
  - If the pregnancy occurred while taking the contraceptive pill or other hormonal contraceptive, the date of LMP cannot be relied on for determining gestational age.\(^2\)
- Symptoms of pelvic infection:
  - Pelvic infection should be treated immediately and abortion can then be performed.\(^3\)
- The need for follow-up 7 to 14 days after mifepristone administration to confirm that the termination is complete and exclude complications.
- Access to 24-hour emergency care in the case of a complication.
- Based on the limited evidence available, women who have the following conditions can be offered MIFEGYMISO:\(^4\)
  - Obesity;
  - Uterine malformations, including fibroids, or previous cervical surgery.

\(^1\) SOGC 2016, \(^2\) Hunter 2009, \(^3\) WHO 2012, \(^4\) WHO 2014
3. ASSESSING PATIENT’S ELIGIBILITY

**Warnings:**

Due to the absence of specific studies, MIFEGYMISO is not recommended in patients with:

- **Severe anaemia:**
  - Heavy bleeding requiring curettage occurred in some patients in clinical trials;
  - Patients with anemia should be treated with caution;
  - Perform haemoglobin testing if there is a history or symptoms/signs suggestive of anaemia:
    - Hb of < 9.5 g/dL is a contraindication for MA.
- **Renal failure;**
- **Hepatic failure;**
- **Malnutrition;**
- **Cardiovascular disease.**

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1 Mifegymiso Canadian Product Monograph, 2 NAF 2017, 3 SOGC 2016
3. ASSESSING PATIENT’S ELIGIBILITY

- **Precautions:**
  If pregnancy occurs with an intrauterine device (IUD) *in situ*, ectopic pregnancy MUST be excluded, and the device should be removed before administration of MIFEYGMISO.²

  **Cardiovascular**
  - Rare cardiovascular accidents have been reported following administration of prostaglandins including MISO.
    - Women with risk factors for cardiovascular disease (hypertension, diabetes or women who are older than 35 years old and are heavy smokers) should be treated with caution.

  **Respiratory**
  - Because of the anti-glucocorticoid activity of MIFE, the efficacy of long-term corticosteroid therapy, including inhaled corticosteroids in asthmatic patients, may be decreased during the 3 or 4 days following the intake of MIFE.³
    - Corticosteroid therapy should be adjusted accordingly.
  - Bronchospasm may occur with some prostaglandins and prostaglandin analogues.
    - Caution should be exercised in patients with a history of asthma.

1 Mifegymiso Canadian Product Monograph, ² CAPS, ³ Sitruk-Ware 2006
3. ASSESSING PATIENT’S ELIGIBILITY

Precautions cont’d:¹

*Endocrine and metabolism*

- Patients with suspected acute adrenal failure were excluded from trials and therefore should be treated with caution. If treatment with MIFEGYMISO is required, therapy should be adjusted.

*Neurologic*

- Seizures have been rarely reported with prostaglandins or prostaglandin analogues administered by routes other than the oral route.²
  - This possibility should be considered when treating patients with a history of a seizure disorder and/or epilepsy.

¹ Mifegymiso Canadian Product Monograph, ² Misoprostol Tablets Canadian Product Monograph
3. ASSESSING PATIENT’S ELIGIBILITY

Use in Special Populations:

MIFEGYMISO is not indicated in prepubertal (<15 years old) and post-menopausal women. Refer to the CPM for details on the use of MIFEGYMISO in special populations.

Nursing women

Mifegymiso use should be avoided during breast-feeding for the following reasons:

- MIFE may be excreted in the mother’s breast milk and should be avoided during breastfeeding;
- MISO is metabolised by the mother to misoprostol acid, which is biologically active and excreted in breast milk;
- MISO should not be administered to breastfeeding mothers because the excretion of misoprostol acid may cause undesirable effects such as diarrhoea in breastfeeding infants.
3. ASSESSING PATIENT’S ELIGIBILITY

Potential Drug Interactions:

MIFE is metabolised by the hepatic cytochrome P450 enzyme CYP3A4.

- Ketoconazole, itraconazole, erythromycin, and grapefruit juice may theoretically inhibit metabolism of MIFE;
- Rifampicin, dexamethasone, St John’s Wort, and certain anticonvulsants (phenytoin, phenobarbital, carbamazepine) may theoretically induce MIFE metabolism;
- There is no evidence as yet for any of these potential drug interactions, nor any reports of complications resulting from these interactions;
- Caution should be exercised when MIFE is administered with drugs that are CYP3A4 substrates and have narrow therapeutic range, including some agents used during general anaesthesia;
- Due to the anti-glucocorticoid activity of MIFE, the efficacy of corticosteroid therapy, including inhaled corticosteroids, may be temporarily decreased following MIFE intake. Therapy should be adjusted.
3. ASSESSING PATIENT’S ELIGIBILITY

Potential Drug Interactions:

Limited studies investigating the metabolism of MISO were conducted in the rat. MISO was not found to affect hepatic drug metabolism.

No drug interactions have been attributed to MISO in extensive clinical trials.
4. ESTABLISHING GESTATIONAL AGE
4. ESTABLISHING GESTATIONAL AGE

Establishing Gestational age (GA) and Pregnancy Location:

- Pelvic ultrasound is considered the standard technique\(^1\) to assess GA and pregnancy location, and it should be used prior to MA, as per the CPM;\(^2\)
- Ectopic pregnancy (EP) must be excluded:
  - Confirmed\(^2\) or suspected EP are contraindications to MIFEGYMISO,\(^3,4\) as it is not an effective treatment;
  - In the event EP is diagnosed, it should be managed by a clinician experienced in the management of EP.
- Medical history, physical exam, ultrasound, and serial \( \beta \text{hCG} \) should be reviewed in the following scenarios:\(^1,5\)
  - Clinical symptoms of bleeding or pelvic pain;
  - Risk factors for EP;
  - Uncertainty about GA;
  - Unknown pregnancy location.
- If serum \( \beta \text{hCG} \) is planned to be used for follow-up, the initial serum \( \beta \text{hCG} \) should be obtained at the initial visit.\(^1,3\)

\(^1\) SOGC 2016, \(^2\) Mifegymiso Canadian Product Monograph, \(^3\) NAF 2016, \(^4\) ACOG 2014, \(^5\) NAF 2017
5. PRE-ABORTION CARE
5. PRE-ABORTION CARE

Objectives:

To describe the recommended approach to rhesus immune globulin prophylaxis, antibiotic prophylaxis, and analgesia.

To state when different types of contraception may be resumed after the termination.
5. PRE-ABORTION CARE

Rhesus Immunoglobulin Testing:

- Rhesus (Rh) factor testing is recommended before MIFEGYMISO treatment;
- To prevent Rh factor sensitisation, non-sensitized Rh-negative women should be administered Rh D immunoglobulin:
  - A minimum of 120mcg is sufficient before 12 weeks of gestation;\(^1\)
  - It should be administered within 72 hours of the induced abortion.\(^2\)

\(^1\) SOGC 2003, \(^2\) WINHRO SDF Product Monograph
5. PRE-ABORTION CARE

Screening for Lower Genital Tract Infections:

- Women should be screened for chlamydia and gonorrhoea before MIFEYMISO, using cervico-vaginal or urine testing:¹
  - Do not delay MA with MIFEYMISO until results are received;²
  - If positive, treat in accordance with local practice standards. Do not delay MA until treatment is completed.¹,²,³

- Further screening for STIs should be based on risk factors and at the discretion of the treating clinician.

¹ SOGC 2016, ² WHO 2012, ³ NAF 2017
5. PRE-ABORTION CARE

Prophylactic Antibiotics:

- Cases of serious bacterial infection have been reported following mifepristone-misoprostol treatment:
  - No causal relationship with mifepristone or misoprostol has been established.
- The Society of Obstetricians and Gynaecologists of Canada (SOGC),\(^1\) the World Health Organization (WHO),\(^2\) the American College of Obstetricians and Gynaecologists (ACOG)\(^3\) and Society of Family Planning (SFP)\(^3\) and the National Abortion Federation (NAF)\(^4\) do not endorse universal antibiotic prophylaxis for MA;
- Screen-and-treat is preferred;
- The risk of infection should always be kept in mind and prophylactic antibiotics prescribed if deemed appropriate:
  - e.g., in women at high risk of infection.
- Women should monitor signs and symptoms of infection in the week following MA.

\(^{1}\) SOGC 2016, \(^{2}\) WHO 2014, \(^{3}\) ACOG and SFP 2014, \(^{4}\) NAF 2017
5. PRE-ABORTION CARE

Pain Management:

- Counselling and reassurance are crucial to managing pain;
- Patients should be advised to:
  - Rest;
  - Use hot packs on the lower abdomen;
  - Massage the lower abdominal area;
  - Take pain relief medication as required.
- When women experience severe pain following MA, they must seek medical attention and infection and retained products should be ruled out;¹,²
- There is little evidence to guide the choice of a specific analgesic regimen, however:²
  - NSAIDs such as ibuprofen have been shown to be the most effective in reducing pain, and superior to acetaminophen:
    - Ibuprofen 200-400 mg every 8 hours; or
    - Naproxen 225-500 mg every 12 hours.

¹ Mifegyniso Canadian Product Monograph, ² SOGC 2016
5. PRE-ABORTION CARE

Pain Management cont’d:
- Prophylactic ibuprofen administration is not superior to as-needed administration in women undergoing abortion, for pain control management;¹
- Preparations in combination with mild opioid analgesics (codeine or oxycodone) may also be effective for significant cramping and severe pain;¹
- Women’s medical history and allergies should be considered in the choice of analgesics.

Anti-emetics:
- Nausea and vomiting may occur after taking MISO;
- An anti-emetic may be taken if needed, at the discretion of the treating doctor:
  - e.g., dimenhydrinate, pyridoxine-doxylamine (Diclectin), or ondansetron.¹
5. PRE-ABORTION CARE

**Contraception:**

Contraception should be started as soon as possible after the termination.

- Fertility can return < 3 weeks after an MA:¹
  - To avoid the potential exposure of a subsequent pregnancy to mifepristone and misoprostol, it is recommended that conception be avoided during the next menstrual cycle.
- Condoms can be used immediately;²
- There is no optimal timing for cervical caps or diaphragms;³
- Oral contraceptives, vaginal rings, injectable contraceptives, and contraceptive implants can be started once bleeding has begun after misoprostol administration (on the day of or the day after);³
- An IUD / IUS may be inserted once the termination has been confirmed as complete, i.e. the follow-up visit;³
- All methods may be started at the time of follow-up, provided possible repeat pregnancy is excluded.

¹ Schreiber 2011, ² Micks 2014, ³ SOGC 2016
6. ADMINISTRATION OF MIFEGYMISO
6. ADMINISTRATION OF MIFEGYMISO

- Objectives:
  
  To describe treatment protocol for MA with MIFEGYMISO.
  
  To list the information the woman needs to know before leaving the clinic/hospital.
6. ADMINISTRATION OF MIFEGYMISO

Dosage Form, Composition and Packaging:

The MIFEGYMISO process involves the use of two products:

- Mifepristone (green box): Supplied in a pack of 1 x 200 mg tablet;
- Misoprostol (orange box): Supplied in a pack of 4 x 200 mcg tablets.

Each product is supplied as part of the MIFEGYMISO box.

MIFEGYMISO box contains a Patient Information Card and a Patient Medication Information document. The Patient Information Card should be completed by the health professional.

Patients should be advised to take their Patient Information Card with them if they visit an emergency room or another health professional who did not prescribe Mifegymiso, so that the health professional will be aware that the patient is undergoing a medical abortion.

- Patient Information Card and Patient Medication Information document are available to download or order through Celopharma’s website.

MIFEGYMISO should be stored between 15-25°C in its original outer carton in order to protect from light.
6. ADMINISTRATION OF MIFEGYMISO

▶ Step 1 - Mifepristone:

200 mg of mifepristone (1 tablet) should be taken orally, followed 24-48 hours (1 to 2 days) later by the administration of misoprostol.

MIFE should be administered as directed by the prescribing health professional.

▶ Step 2 - Misoprostol:

24-48 hours later, 800 mcg of misoprostol (4 tablets, each tablet containing 200 mcg) should be placed between the cheek and the gum for 20-30 minutes before any remaining fragments are swallowed with water.

It is important that all patients be followed-up with their health professional 7 to 14 days after taking MIFE to confirm safe and complete pregnancy termination.
6. ADMINISTRATION OF MIFEGYMISO

Information Woman Needs to Know:

Before leaving the clinic, the woman should be informed of:

- Normal range of symptoms and side effects;
- Possible complications and warning signs;
- Who to contact with any questions or concerns;
- The importance of follow-up appointment (7 to 14 days after taking MIFE, even if no adverse events have occurred);
- The date and time for the follow-up;
- How to access 24-hour emergency care in the case of a complication:
  - How to access 24-hour emergency treatment;
  - Clinics offering 24-hour nurse after-care/hot-line can give their information.
Emergency Treatment:

Treatment with MIFEGYMISO should only be undertaken by the health professional when the patient has access to 24-hour emergency treatment for:

- Haemorrhage;
- Incomplete abortion.

Access to treatment may be onsite or through an arrangement with another health facility or medical service (i.e. on-call coverage, emergency department backup).
6. ADMINISTRATION OF MIFEGYMISO

Patient Educational Tools:

The following documents are available to download on Celopharma website (to order printed copies, email info@celopharma.com):

- MIFEGYMISO Canadian Product Monograph;
- MIFEGYMISO Patient Medication Information document (Part III of the CPM);
  - The package insert is also located inside the MIFEGYMISO box.
- Informed Consent Forms;
- Patient Information Card:
  - The Card is also located inside the MIFEGYMISO box;
  - The Card should be completed by the health professional and contains the agreed date and time of the treatment, follow-up details and contact information in case of emergency.
6. ADMINISTRATION OF MIFEGYMISO

Ordering MIFEGYMISO:

*Prescribers:*

- To place an order contact: `celopharma@lsu3pl.ca` / Fax: 1-844-552-8085 / or Phone: 1-877-230-4227 #2.
- Health professionals prescribing and stocking MIFEGYMISO may dispense the medication directly to the patient, where permitted under provincial/territorial law.

*Pharmacists:*

- Pharmacy orders can be placed with your wholesaler.
- For direct Pharmacy orders contact: `celopharma@lsu3pl.ca`.
7. POST-ABORTION CARE AND FOLLOW-UP
7. POST-ABORTION CARE AND FOLLOW-UP

Objectives:

To counsel about, identify and manage side effects and adverse events related to MA and MIFEGYMISO.

To describe how completion of the abortion may be confirmed.

To state when different types of contraception may be resumed after the termination.
7. POST-ABORTION CARE AND FOLLOW-UP

Signs and Symptoms of Possible Complications:

The patient should immediately return to the clinic or seek medical attention for:

- Heavy vaginal bleeding:
  - Soaking 2 (or more) sanitary pads per hour for 2 consecutive hours or large (fist-size) clots.
- Prolonged heavy bleeding or severe cramping:
  - Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical (blood transfusion) or surgical intervention may be needed;
  - Persistent bleeding should be monitored closely for a decrease in hemoglobin concentration, hematocrit and red blood cell count.
- Cramping which is not improved by pain relief medication;
- Sustained fever or chills (lasting 6 hours or more);
- General malaise (including weakness, nausea, vomiting, or diarrhoea) with or without abdominal pain or fever, occurring > 24 hours after misoprostol administration;
- Any abnormal vaginal discharge;
- Severe abdominal pain.
7. POST-ABORTION CARE AND FOLLOW-UP

Signs and Symptoms of Possible Complications:
Clinicians should have a low threshold to consider infection, particularly when there is:
- Abdominal or pelvic pain;
- Foul-smelling vaginal or cervical discharge;
- Prolonged vaginal bleeding or spotting;
- Fever or chills (more than 24 hours after MISO);
- Uterine or adnexal tenderness;
- Elevate white blood cell count.
7. POST-ABORTION CARE AND FOLLOW-UP

Signs and Symptoms of Possible Complications cont’d:

Signs and Symptoms of clostridial infection/toxic shock:

➢ General malaise with weakness, nausea, vomiting, and diarrhoea;
➢ Absence of fever (or mild fever);
➢ Minimal abdominal pain;
➢ Flu-like symptoms;
➢ Tachycardia;
➢ Hypotension;
➢ Oedema;
➢ High white blood cell count;
➢ High hemoglobin level (haemoconcentration).
Follow-up:

Patients must have a follow-up 7 to 14 days after taking MIFEGYMISO in order to:

- Confirm the completion of the abortion;
- Assess for possible complications;
  - Reasons for failure requiring a surgical termination of pregnancy include persistent non-viable pregnancies, continuing pregnancies, and persistent heavy vaginal bleeding.
- Answer any final questions from the patient;
- Review contraceptive options and contraception plan.
7. POST-ABORTION CARE AND FOLLOW-UP

Follow-up cont’d:

The follow-up can be provided as an in-person visit or via telephone, video-conference or any other means deemed appropriate by the health professional.

- The health professional should assess if the following are present:
  - Continuing pregnancy;
  - Ectopic pregnancy;
  - Incomplete abortion;
  - Persistent heavy bleeding;
  - Signs of infection.

- Ultrasound may be useful to assess clinical signs and symptoms, such as persistent bleeding, pain or continuing signs of pregnancy.
7. POST-ABORTION CARE AND FOLLOW-UP

Determining the Outcome of the MA:

As per the MIFEGYMISO CPM, follow-up must take place within a period of 7 to 14 days after administration of MIFEGYMISO to verify that expulsion has been completed (clinical examination, ultrasound scan or βhCG measurement).¹

- **History of clinical events** (including resolution of pregnancy symptoms and absence of persistent heavy bleeding):
  - Minimal or no bleeding after MISO is highly suggestive of ongoing pregnancy/incomplete abortion (retained products of conception);²,³,⁴
  - Bleeding heavier than a period, with associated cramping and resolution of pregnancy symptoms is highly suggestive of a complete MA. Such history combined with a normal pelvic examination are useful to confirm complete MA;²,³
  - History alone is highly predictive of pregnancy termination but inadequate to identify treatment failure.³,⁴

¹ Mifegymiso Canadian Product Monograph, ² SOGC Training Program 2016, ³ SOGC 2016, ⁴ CAPS
Determining the Outcome of the MA cont’d:

- **Clinical examination:**
  - History and physical examination (bimanual exam) can be helpful in determining the likelihood of completion,\(^1\) however they are insufficient to rule out ongoing pregnancy;
  - If a woman states she has had minimal pain or bleeding, this is highly suspicious for ongoing pregnancy.

- **Ultrasound scan:**
  - Ultrasound provides definitive evidence of MA completion, but no evidence shows that routine ultrasound is superior to other methods\(^1\);
  - When woman experiences unexpected pain, prolonged, heavy bleeding or inadequate bleeding, ultrasound is helpful;
  - More details on pelvic ultrasound may be found in the most recent SOGC Medical Abortion Guidelines.

\(^1\) SOGC 2016
Determining the Outcome of the MA cont’d:

- **βhCG measurement:**
  - Urine pregnancy test:
    - A high-sensitivity human chorionic gonadotropin (hCG) urine pregnancy test may be positive 30 days after the termination;
    - When used 14 days after MIFE, negative tests were highly correlated with completion abortion, however, false negative are common.
Determining the Outcome of the MA cont’d:

- BhCG measurement cont’d:
  - Serum BhCG determination:
    - Significant decline in serum BhCG levels - a greater than 80% decrease in serum BhCG levels measured pre and post abortion (8-16 days after taking mifepristone) has been found to be predictive of success;
    - Serum BhCG 50% drops are observed within 24 hours of pregnancy expulsion.

In summary, pelvic ultrasound (when pre-procedural ultrasound was obtained) or serial serum BhCG are the preferred methods of confirmation of completion of the abortion.

1 SOGC 2016
7. POST-ABORTION CARE AND FOLLOW-UP

**Contraception:**

Contraception should be started as soon as possible after the termination.

- Fertility can return < 3 weeks after an MA:\(^1\)
  - To avoid the potential exposure of a subsequent pregnancy to mifepristone and misoprostol, it is recommended that conception be avoided during the next menstrual cycle.
- Condoms can be used immediately:\(^2\)
- There is no optimal timing for cervical caps or diaphragms:\(^3\)
- Oral contraceptives, vaginal rings, injectable contraceptives, and contraceptive implants can be started once bleeding has begun after misoprostol administration (on the day of or the day after):\(^3\)
- An IUD / IUS may be inserted once the termination has been confirmed as complete, i.e. the follow-up visit:\(^3\)
- All methods may be started at the time of follow-up, provided possible repeat pregnancy is excluded.

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\(^1\) Schreiber 2011, \(^2\) Micks 2014, \(^3\) SOGC 2016
8. MANAGEMENT OF COMPLICATIONS
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Objective:

To identify and manage the possible complications and side effects associated with MIFEGYMISO.
8. MANAGEMENT OF COMPLICATIONS

- **Continuing Pregnancy:**
  - Reported in the literature it occurs in 0.2% to 2.7% of cases;
  - May be suspected on history and physical examination, or confirmed by ultrasound examination or rising serum βhCG levels;
  - Women with continuing symptoms of pregnancy or clinical signs of failed abortion should be offered a uterine evacuation procedure as expeditiously as possible;
  - Surgical termination is recommended because of the possibility of birth defects from the medications;
  - The possibility of an ectopic or heterotopic pregnancy should be investigated in the setting of increasing or rebounding hCG levels.
8. MANAGEMENT OF COMPLICATIONS

- Incomplete Abortion:
  - Reported in the literature it occurs in 1.1% to 4.2% of cases;
  - If evident from persistent heavy bleeding or cramping, surgical aspiration or dilation and curettage is usually required;
  - If clinically suspected from less severe clinical signs and symptoms:
    - Explain that tissue may be expelled during subsequent vaginal bleeding or with the next menstrual period;
    - Carry out surgical aspiration or dilation and curettage (if this is the patient’s preference).
  - Professionals are encouraged to refer to their associations’ Medical Abortion Guidelines for the management of incomplete abortions.
8. MANAGEMENT OF COMPLICATIONS

- **Vaginal Bleeding:**
  - Bleeding occurs in all cases, but is not a proof of complete expulsion:
    - Follow-up assessment is necessary to confirm termination of pregnancy.
  - Bleeding usually start within 4 hours of taking MISO:
    - Expulsion occurs within 4 hours (60%) or 24 to 72 hours (40%) following MISO intake;
    - Bleeding can range from light to heavy, usually exceeds the typical levels of menstrual bleeding;
    - Bleeding is heavier for more advanced pregnancy;
    - Bleeding is heavier during pregnancy expulsion (associated with passage of clots) and decreases after;
    - Bleeding may sometimes occur after MIFE but before MISO:
      - MISO should still be taken as directed at the recommended time.
    - Women should be informed of prolonged vaginal bleeding (average of 11.4 days), which may be heavier than normal period for 2.2 days;
    - Light bleeding can continue for 30 days or more but does not normally go beyond the first period.
8. MANAGEMENT OF COMPLICATIONS

Vaginal Bleeding cont’d:

- Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed:
  - If soaking through two maxi-pads per hour for two consecutive hours OR experience large (fist-size) clots;
  - If experiencing orthostatic symptoms such as faintness, dizziness or tachycardia.
- Prolonged heavy bleeding may require surgical termination if the patient has a clinically significant haemorrhage;
- Aspiration due to bleeding occurs in 0.65% to 2.49% of cases and increases with GA;
- Persistent bleeding should be monitored closely for a decrease in haemoglobin concentration, haematocrit and red blood cell count, hypovolaemia or orthostatic hypotension:
  - Haemorrhage requiring a transfusion occurs in 0.1% of cases.

Hamoda 2010, Raymond 2013, SOGC 2016
8. MANAGEMENT OF COMPLICATIONS

▶ Cramping and Pain:

- Cramping can start within 4 hours of taking MISO tablets;
- Cramping can range from mild to severe and is usually more than typical menstrual period:
  - Significant cramping should diminish once the pregnancy is expelled and does not usually last more than 24 hours.
8. MANAGEMENT OF COMPLICATIONS

- Risk of Infection and Sepsis:
  - Cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of MIFEGYMISO:
    - Occurrence is low and varies in the literature:
      - 0.016% to 0.019% or 0.18% to 1.56% of cases.
    - Risk of death is 1/100,000.
  - Signs and symptoms include:
    - A sustained fever of 38°C or higher;
    - Severe abdominal pain;
    - Pelvic tenderness;
    - General malaise more than 24 hours after taking MISO:
      - Weakness, nausea, vomiting, diarrhoea.
  - Some patients presented without fever, with or without abdominal pain, but with leucocytosis with a marked left shift, tachycardia, haemoconcentration, and general malaise.

CAPS, Shannon 2004, Creinin 2006, Mifegymiso Canadian Product Monograph
8. MANAGEMENT OF COMPLICATIONS

Risk of Infection and Sepsis cont’d:

- Sepsis (from e.g. *Clostridium sordellii* or other species e.g. *Streptococcus*) should be highly suspected if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhoea) more than 24 hours after taking misoprostol;¹

- Possibility of sepsis should be considered in all women who present with nausea, vomiting, diarrhoea and weakness with or without abdominal pain or fever. Strong consideration should be given to obtaining a complete blood count in these patients:
  - Significant leucocytosis with a marked left shift and haemoconcentration may be indicative of sepsis.

- Post-abortion infections:²
  - Treatment should be individualized and usually consists of broad-spectrum therapy. Oral antibiotics can be used in mild cases.

- Severe infection, women is unresponsive to treatment or suspected sepsis:²

¹ Mifegymiso Canadian Product Monograph, ² SOGC 2016
8. MANAGEMENT OF COMPLICATIONS

Infection - Atypical Symptoms:

- Women with sepsis might not present with typical symptoms of sepsis; a high index of suspicion is needed to rule out sepsis (e.g., from *Clostridium sordellii* or other species such as Streptococcus);

- The possibility of sepsis should be considered in all women who are undergoing medical termination and who present with nausea, vomiting, or diarrhoea and weakness with or without abdominal pain more than 24 hours after taking misoprostol;

- Strong consideration should be given to obtaining a complete blood count in these patients;

- Doctors should consider immediately initiating treatment with antibiotics that includes coverage of anaerobic bacteria such as *Clostridium sordellii*;

- If severe infection or sepsis is suspected: Hospitalisation for treatment.
8. MANAGEMENT OF COMPLICATIONS

- Undiagnosed Ectopic Pregnancy:
  - The possibility of an undiagnosed ectopic pregnancy should be kept in mind:
    - Some of the expected symptoms of an MA (e.g., pain and bleeding) may be similar to those of a ruptured ectopic pregnancy;¹
    - Ultrasound may be useful in diagnosing ectopic pregnancy.
  - MIFEGYMISO is not effective for an ectopic pregnancy.
8. MANAGEMENT OF COMPLICATIONS

- **Allergic Reactions to Misoprostol:**
  - Uncommon but severe;
  - Symptoms include:
    - Skin rash, urticaria;
    - Difficulty breathing, chest pain or tightness;
    - Swelling of the mouth, face, lips, and tongue;
    - Black and tarry stools;
    - Severe vomiting.
  - Angioedema of the face, lips, tongue, and/or larynx, including cases of anaphylaxis have been reported in post-market surveillance with the use of MIFEGYMISO;
  - Angioedema associated with upper airway swelling may be life threatening;
    - If the tongue, hypopharynx, or larynx has been involved, appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided.
8. MANAGEMENT OF COMPLICATIONS

- Long-Term Side Effects:
  - Psychological sequelae:
    - The best current evidence suggests that it makes no difference to a woman’s mental health whether she chooses to terminate or continue with the pregnancy;
    - The most reliable predictor of mental health problems after a termination is a history of mental health problems before a termination;
    - However, a small proportion of women may experience adverse psychological sequelae after a termination.
  - Premature delivery of subsequent pregnancies:
    - Termination may be associated with a small increase in the risk of subsequent pre-term birth;
    - This risk increases with the number of terminations;
    - No significant difference between the medical and surgical methods of termination in the risk of pre-term birth has been reported.

8. MANAGEMENT OF COMPLICATIONS

- Long-Term Side Effects cont’d:
  - Possible teratogenicity of misoprostol:
    - Congenital abnormalities have been associated with foetal exposure to misoprostol:
      - Lower limb;
      - Upper limb;
      - Central nervous system, including Möbius’ syndrome;
      - Skeletal.
    - The majority of cases resulted from self-prescribed, self-administered, and non-validated use of misoprostol.
9. FREQUENTLY ASKED QUESTIONS
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Vomiting:

Q: What happens if a patient vomits the dose of mifepristone?

A: The peak of concentration for single dose of 200 mg mifepristone is reached after 0.75 hour.

Vomited more than 1 hour after taking the dose of mifepristone does not require the patient to return to her prescriber as the medication will have been absorbed.

If she had vomited less than 1 hour after taking the dose of Mifepristone then she should return to her prescriber to get a new prescription for the medication along with an anti-nausea medication.
9. FREQUENTLY ASKED QUESTIONS

**Vomiting cont’d:**

**Q:** What happens if a patient vomits the dose of misoprostol?

**A:** While we understand that a normal symptom of the misoprostol includes vomiting (as well as low-grade fever, chills, nausea), the question is what if a patient vomits immediately (or almost immediately) after taking the misoprostol (for example, it hasn’t been 30 mins yet since she placed it in her cheek, or it’s immediately after she swallowed any remaining fragments at the 30-minute mark).

The cut off time is 1 hour after misoprostol intake because the peak of concentration for misoprostol is reached after 0.5 hour.
Vomiting cont’d:

**Q:** What actions should the patient take if she vomits before the cut-off time (for example, should she get another prescription for misoprostol?)?

**A:** If the patient vomits before the cut-off time, it is advised to take another dose of misoprostol.

**Q:** What actions should the patient take if she vomits after the cut-off time?

**A:** No action is required.
9. FREQUENTLY ASKED QUESTIONS

Sexually Transmitted Infection:

Q: What is considered “best practices” for treating sexually transmitted infections (STI) in patients who will be using MIFEGYMISO.

A: STI Screening for chlamydia and gonorrhea using either cervicovaginal or urine testing is recommended.

There is no strong evidence supporting routine antibiotic prophylaxis for medical abortion. If screening testing is positive routine antibiotic prophylaxis for chlamydia and gonorrhea are acceptable to mitigate this risk.
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SOGC Medical Abortion Training Program. 2016


WHO. Clinical practice handbook for safe abortion. 2014

WHO. Safe abortion technical and policy guidance for health systems. 2012
IMPORTANT CONTACT INFORMATION

- General Information: [www.celopharma.com](http://www.celopharma.com) and [info@celopharma.com](mailto:info@celopharma.com)
- To place an order contact Celopharma:
  - By email: [celopharma@lsu3pl.ca](mailto:celopharma@lsu3pl.ca)
  - By fax: 1-844-552-8085
  - For direct Pharmacy orders contact: [celopharma@lsu3pl.ca](mailto:celopharma@lsu3pl.ca)
- To report side effects:
  - Online at [MedEffect](http://MedEffect)
  - By calling 1-866-234-2345 (toll-free);
  - By completing a Consumer Side Effect Reporting Form and sending it by:
    - Fax to 1-866-678-6789 (toll-free),
    - Mail to: Canada Vigilance Program
      Health Canada, Postal Locator 0701E
      Ottawa, ON, K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.