Important Information on
MIFEGYMISO (mifepristone and misoprostol tablets)
Canadian Distribution and Administration Program

2017/05/18

Audience
Healthcare professionals, including obstetricians/gynaecologists, family physicians, hospital pharmacy chiefs, pharmacists, and nurses, and associations and colleges of Canadian physicians, pharmacists, and nurses.

Key messages

This Health Product Risk Communication for MIFEGYMISO:

- **clarifies the implementation of the Distribution and Administration Program for MIFEGYMISO.**
- **provides information on the MIFEGYMISO Education Program that is available to physicians who wish to prescribe Mifegymiso, as well as pharmacists.**
- **describes the educational and information tools that should be provided by prescribers to their patients: the Patient Medication Guide, the Patient Information Card, and the Patient Consent Form.**
- **highlights that the MIFEGYMISO box labels and package inserts that are currently being distributed may not accurately reflect the information found in the updated Product Monograph.**

What is the issue?
Celopharma, in collaboration with Health Canada, is issuing this communication to healthcare professionals to clarify the different requirements and steps to follow in order to prescribe, order, stock, and/or dispense MIFEGYMISO, as outlined in the Distribution and Administration Program that is associated with MIFEGYMISO's approval in Canada.

Products affected

Manufacturer	Distributor	Product	DIN
Linepharma International Limited	Celopharma Inc.	MIFEGYMISO (mifepristone 200 mg and misoprostol 200 mcg tablets)	02444038

Background information

MIFEGYMISO (mifepristone tablet/misoprostol tablets) is a composite pack containing one mifepristone 200 mg tablet for oral use and four misoprostol 200 mcg tablets for buccal use. MIFEGYMISO is indicated for medical termination of a developing intra-uterine pregnancy with a gestational age up to 49 days as measured from the first day of the Last Menstrual Period (LMP) in a presumed 28-day cycle.

There have been serious safety concerns identified with the use of MIFEGYMISO including the risks of infection and/or sepsis, heavy bleeding, and embryo toxicity for an ongoing pregnancy (treatment failure) or any immediate subsequent pregnancy. These risks are described in a Serious Warnings and Precautions Box in the MIFEGYMISO Canadian Product Monograph. As a result, all patients should be followed up by a physician 7 to 14 days after taking mifepristone to confirm complete pregnancy termination and to verify that there is no excessive bleeding or infection. Compliance with the drug regimen, follow-up, access to a 24-hour support line, and access to emergency care are important to ensure the safe and effective use of MIFEGYMISO for Canadian patients.

Distribution and Administration Program and other post-marketing requirements

As part of the initial review and approval process, Linepharma International Limited submitted a Risk Management Plan (RMP) to Health Canada. The RMP includes details regarding the following risk mitigation measures:

- a Distribution and Administration Program;
- an Education and Registration Program for MIFEGYMISO prescribers;
- a Canadian Phase IV observational study of MIFEGYMISO safety;
- a 24-hour support-line in both English and French for patients taking MIFEGYMISO;
- a Patient Consent Form to be provided to each patient by the prescriber;
- a Patient Medication Guide and a Patient Information Card to be provided to each patient by the prescriber.

In order to clarify the terms of the implemented Distribution and Administration Program, this risk communication outlines the steps that need to be taken by healthcare professionals who wish to prescribe, order, stock, and/or dispense MIFEGYMISO. It also provides further details regarding the product and additional resources.

Information beyond what is below is considered to be practice of medicine / pharmacy and will vary by province as it falls under the jurisdiction of the provincial professional colleges.

Revised Patient Medication Information

Please note that the box labels and package inserts currently being distributed may have been printed prior to revisions made, and therefore may not accurately reflect the terms of the revised **Product Monograph**. Part III (Patient Medication Information) of the Product Monograph was revised in October 2016, allowing flexibility for the prescriber, and now reads as follow:

"Take MIFEGYMISO
- *As directed by your doctor or as given to you by medical staff*

Step 1:
As directed by your doctor or a member of the medical staff.

(Green box label)
Take the Mifepristone tablet
• Swallow tablet with a glass of water

24 to 48 hours after taking the Mifepristone tablet, you must do Step 2.

Step 2:
(Orange box label)
• Place the 4 Misoprostol tablets (as a single 800 mcg buccal dose) in your mouth
• Keep the 4 tablets between your cheeks and gums for 30 minutes
• Then, swallow any fragments that are left with water

Plan to rest for 3 hours after taking the Misoprostol tablets."

The boxes and package inserts will be updated in the next production run. The approved Product Monograph contains the administration instructions set out above and is available on the Celopharma website or on the Health Canada Drug Product Database website.

New MIFEGYMISO submission under review by Health Canada
Linepharma has presented a new submission for MIFEGYMISO to Health Canada. This new submission proposes to extend the indication for medical termination of a developing intra-uterine pregnancy with a gestational age up to 63 days, as well as to update the current Distribution and Administration Program. Should the review of the submission lead to changes to the current MIFEGYMISO indications or Distribution and Administration Program, a follow-up communication will be issued to inform healthcare professionals and patients of these changes.

Information for consumers
MIFEGYMISO is a combination product containing two drugs (1 mifepristone tablet and 4 misoprostol tablets) used for abortion, meaning ending a pregnancy less than 49 days from the start of the last menstrual period.

Physicians should complete a training program prior to prescribing MIFEGYMISO. Before getting MIFEGYMISO, the patient will be asked by the prescriber to review and sign a consent form and Patient Information Card.

The Patient Information Card contains the following information:

- The follow-up appointment location, date and time;

- Contact information in case the patient needs to call the doctor or clinic;
- Where the patient should go in case of an emergency;
- The manufacturer's 24 hour support line 1-877-230-4227. The patients can call this number when they need assistance but they cannot reach their own doctor or clinic.

The prescriber will also give the patient a printed copy of the Patient Medication Guide, a document that includes detailed information on MIFEGYMISO.

Patients should contact a healthcare professional if they are experiencing a side effect related to MIFEGYMISO use or if they wish to obtain additional information on the use of MIFEGYMISO and its safety.

Follow-up is important to confirm whether the pregnancy has completely ended and to verify that there is no prolonged heavy bleeding or infection.

Information for healthcare professionals

Practice of medicine and pharmacy may vary by province. In addition to the information below, different healthcare professional associations, such as the College of Physicians and Surgeons of British Columbia, the College of Pharmacists of British Columbia, as well as the College of Physicians and Surgeons and the College of Pharmacists of Ontario, have issued communications to their members regarding the associations' recommended approach for the dispensing of MIFEGYMISO.

Prescribing Physicians

An Education Program developed by Society of Obstetricians and Gynaecologists of Canada (SOGC) in collaboration with the College of Family Physicians of Canada (CFPC) and the Canadian Pharmacists Association (CPhA) is available to prescribing physicians.

Prescribing physicians should complete Module 5 of either the Accredited (paid access) OR Non-Accredited (free access) Medical Abortion Training Program, available on the SOGC Online courses website, before prescribing, ordering, stocking (if applicable), and/or dispensing MIFEGYMISO. Completion of Module 5 takes less than an hour.

- Upon completion of Module 5, the physician will receive information on how to order Patient Consent Forms, printed copies of the Patient Medication Guide, and Patient Information Cards, directly from Celopharma. Information can also be obtained on how to order MIFEGYMISO.
- Prescribers stocking MIFEGYMISO may dispense the medication directly to the woman, where permitted under provincial/territorial law. Alternatively, a prescriber may send a prescription (by fax, verbal prescription or written prescription) to a pharmacy that stocks MIFEGYMISO. The box may then be shipped back to the prescriber office for delivery to the woman.
- Prescribers are encouraged to engage in proactive communication with nearby or local pharmacists/pharmacies to identify pharmacies that stock MIFEGYMISO.

As per the approved Canadian Product Monograph, in addition to completing the MIFEGYMISO education and registration programs, prescribers have to do the

following prior to prescribing MIFEGYMISO:

- Ensure that patients have access to emergency medical care in the 14 days following administration of mifepristone;
- Schedule follow-up 7 to 14 days after patients take mifepristone to confirm complete pregnancy termination;
- Exclude ectopic pregnancy and confirm gestational age by ultrasound;
- Counsel each patient on the risks and benefits of MIFEGYMISO, including bleeding, infection, and incomplete abortion;
- Obtain the patient's written informed consent to take the drug;
- Complete the Patient Information Card that is in the MIFEGYMISO box or ordered directly from Celopharma.

Each patient must be provided with a printed copy of the Mifegymiso Patient Medication Guide.

Follow-up is important to confirm pregnancy termination and complete abortion and to ensure that the patient is not experiencing any of the serious adverse reactions associated with MIFEGYMISO use, such as excessive bleeding or infection/sepsis. MIFEGYMISO treatment failure may require the surgical termination of the pregnancy.

Educational and Information Tools for women
The Patient Medication Guide must be given to women having a medical abortion. It includes information on the drugs to be used, the procedure to be followed before taking the drugs, how to take the drugs, signs and symptoms of the termination, possible side effects, and follow-up.

The Patient Consent Form is provided for signature by the patient and the prescriber. The signed Consent Form should be retained in the patient's file. The Patient Consent Form is not required to be provided to the pharmacist for the filling of the prescription.

The Patient Information Card should be filled in by the prescriber and given to the patient and is signed by both the prescriber and the patient. It includes information on: the date and time of the treatment; the follow-up appointment date and time; and the emergency contact information. The Patient Information Card is located inside MIFEGYMISO box or for order directly from Celopharma.

Revised Patient Medication Information
The box labels and package inserts currently being distributed may not accurately reflect the terms of the revised **Product Monograph**. See above (Background, Revised Patient Medication Information) for additional information.

Pharmacists and Pharmacies
Module 5 of the Medical Abortion Training Program, available on the SOGC Online courses website, is available for pharmacists and, while it is not mandatory, they are encouraged to follow the Training Program prior to setting up an account with Celopharma and ordering and stocking MIFEGYMISO.

Other resources available to healthcare professionals
MIFEGYMISO providers can consider registering with the Canadian Abortion Providers Support, a university-based Canadian online community for health professionals that is managed in collaboration with the SOGC, CFPC and CPhA. Practice guidelines, a map of pharmacies stocking MIFEGYMISO, patient handouts, the latest information on subsidy options for mifepristone, and "Ask-an-Expert" features are available to support professionals.

Report health or safety concerns
Managing marketed health product-related side effects depends on health care professionals and consumers reporting them. Any cases of serious or unexpected side effects in patients receiving MIFEGYMISO should be reported to Celopharma or Health Canada.

Celopharma Inc.
info@celopharma.com

To correct your mailing address or fax number, contact Celopharma Inc.

You can report any suspected adverse reactions associated with the use of health products to Health Canada by:

- Calling toll-free at 1-866-234-2345; or
- Visiting MedEffect Canada's Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax.

For other health product inquiries related to this communication, contact Health Canada at:

Marketed Health Products Directorate
E-mail: mhpd-dpsc@hc-sc.gc.ca
Telephone: 613-954-6522
Fax: 613-952-7738

Original signed by

Paula Tenenbaum
President
Celopharma Inc.