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Mifeprex® (mifepristone): FDA Approves Updated Labeling

Danco Laboratories is pleased to announce that on March 29, 2016 the FDA approved new and updated labeling for Mifeprex® (mifepristone). The labeling changes include revisions to the Prescribing Information, Patient Medication Guide, Patient Agreement Form and Prescriber Agreement Form to reflect the most current clinical practices and safety and efficacy data for Mifeprex®.

Mifeprex® is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Mifeprex® is a pill that blocks progesterone, a naturally produced hormone that prepares the lining of the uterus for a fertilized egg and helps maintain pregnancy. Without progesterone the pregnancy cannot continue and the lining of the uterus softens and breaks down and bleeding begins. Mifeprex® is used in a regimen with a prostaglandin, misoprostol, which causes the uterus to contract and helps complete the process.

Mifeprex® was approved for the termination of early pregnancy by FDA on September 28, 2000. In the last 15+ years, it has been used by more than 2.75 million women in the United States. In U.S. clinical studies, Mifeprex® has been shown to be ~97% effective in terminating early pregnancy; approximately 3% of women will require surgical intervention for ongoing pregnancy, heavy bleeding, incomplete expulsion or other reasons.

Some of the key changes to the Mifeprex® labeling include:

NEW LABELING	OLD LABELING
• medical termination of intrauterine pregnancy through 70 days gestation	• medical termination of intrauterine pregnancy through 49 days gestation
• Day 1: Mifeprex® 200 mg (1 tablet) • 24-48 hours after Mifeprex®: Misoprostol 800 mcg (4 tablets) buccally	• Day 1: Mifeprex® 600 mg (3 tablets) • Day 3: Misoprostol 400 mcg (2 tablets) orally
Assessment: • 7-14 days post Mifeprex® • Optional repeat dose of misoprostol	Examination: • Patients return to provider 14 days post Mifeprex®

Mifeprex Important Safety Information

BOXED WARNING:
Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following MIFEPREX use.

Mifeprex®
(Mifepristone) Tablets, 200 mg
THE ORIGINAL EARLY OPTION PILL

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- **Atypical Presentation of Infection. Patients with serious bacterial infections and sepsis can present without fever, bacteremia or significant findings on pelvic examination. A high index of suspicion is needed to rule out serious infection and sepsis.**
- **Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed.**

MIFEPREX is only available through a restricted program called the MIFEPREX REMS Program.

Before prescribing MIFEPREX, inform the patient about these risks. Ensure the patient knows whom to call and what to do if she experiences sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if she experiences abdominal pain or discomfort or general malaise for more than 24 hours after taking misoprostol.

Advise the patient to take the MEDICATION GUIDE with her if she visits an emergency room or another healthcare provider who did not prescribe MIFEPREX, so that provider knows that she is undergoing a medical abortion.

Contraindications

- Administration of MIFEPREX and misoprostol for the termination of pregnancy is contraindicated in patients with any of the following conditions:
  - Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass (the treatment procedure will not be effective to terminate an ectopic pregnancy)
  - Chronic adrenal failure (risk of acute renal insufficiency)
  - Concurrent long-term corticosteroid therapy (risk of acute renal insufficiency)
  - History of allergy to mifepristone, misoprostol, or other prostaglandins (allergic reactions including anaphylaxis, angioedema, rash, hives, and itching have been reported)
  - Hemorrhagic disorders or concurrent anticoagulant therapy (risk of heavy bleeding)
  - Inherited porphyrias (risk of worsening or of precipitation of attacks)
- Use of MIFEPREX and misoprostol for termination of intrauterine pregnancy is contraindicated in patients with an intrauterine device (“IUD”) in place (the IUD might interfere with pregnancy termination). If the IUD is removed, MIFEPREX may be used.

Warnings and Precautions

Infection and Sepsis

As with other types of abortion, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of MIFEPREX. Healthcare providers evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event. A sustained (> 4 hours) fever of 100.4°F or higher, severe abdominal pain, or pelvic tenderness in the days after a medical abortion may be an indication of infection.

A high index of suspicion is needed to rule out sepsis (e.g., from *Clostridium sordellii*) if a patient reports

abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhea) more than 24 hours after taking misoprostol. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. No causal relationship between MIFEPREX and misoprostol use and an increased risk of infection or death has been established. *Clostridium sordellii* infections have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynecologic and non-gynecologic conditions.

Uterine Bleeding

Uterine bleeding occurs in almost all patients during a medical abortion. Prolonged heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours) may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed to prevent the development of hypovolemic shock. Counsel patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding following a medical abortion.

Women should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of all subjects may experience some type of bleeding for 30 days or more. In general, the duration of bleeding and spotting increased as the duration of the pregnancy increased.

Decreases in hemoglobin concentration, hematocrit, and red blood cell count may occur in women who bleed heavily.

Excessive uterine bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, surgical uterine evacuation, administration of saline infusions, and/or blood transfusions. Based on data from several large clinical trials, vasoconstrictor drugs were used in 4.3% of all subjects, there was a decrease in hemoglobin of more than 2 g/dL in 5.5% of subjects, and blood transfusions were administered to ≤ 0.1% of subjects. Because heavy bleeding requiring surgical uterine evacuation occurs in about 1% of patients, special care should be given to patients with hemostatic disorders, hypocoagulability, or severe anemia.

MIFEPREX REMS Program

MIFEPREX is available only through a restricted program under a REMS called the MIFEPREX REMS Program, because of the risks of serious complications

Notable requirements of the MIFEPREX REMS Program include the following:

- Prescribers must be certified with the program by completing the Prescriber Agreement Form.
- Patients must sign a Patient Agreement Form.
- MIFEPREX must be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices and hospitals by or under the supervision of a certified prescriber

Further information is available at 1-877-4 Early Option (1-877-432-7596).

Ectopic Pregnancy

MIFEPREX is contraindicated in patients with a confirmed or suspected ectopic pregnancy because MIFEPREX is not effective for terminating ectopic pregnancies. Healthcare providers should remain alert to the possibility that a patient who is undergoing a medical abortion could have an undiagnosed ectopic pregnancy because some of the expected symptoms experienced with a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. The presence of an ectopic

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pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed MIFEPREX.

Women who became pregnant with an IUD in place should be assessed for ectopic pregnancy.

Rhesus Immunization

The use of MIFEPREX is assumed to require the same preventive measures as those taken prior to and during surgical abortion to prevent rhesus immunization.

Adverse Reactions

Most common adverse reactions (>15%) are nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness. The frequency of adverse reactions varies between studies and may be dependent on many factors including the patient population and gestational age.

Drug Interactions

- CYP3A4 inducers can lower mifepristone concentrations.
- CYP3A4 inhibitors can increase mifepristone concentrations. Use with caution.
- CYP3A4 substrate concentrations can be increased. Caution with coadministration of substrates with narrow therapeutic margin.

Use in Specific Populations

Pregnancy: The risk of fetal malformations in ongoing pregnancy if not terminated is unknown.

To report SUSPECTED ADVERSE REACTIONS, contact Danco Laboratories, LLC at 1-877-432-7596 or medicaldirector@earlyoptionpill.com or www.earlyoptionpill.com or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

For Full Prescribing Information, including **BOXED WARNING and Medication Guide**, or more information about Mifeprex®, please access the Mifeprex® web site, www.earlyoptionpill.com, or call the Mifeprex® hotline at 1-877-4 Early Option (1-877-432-7596).

Danco Laboratories, LLC is a women's health pharmaceutical company that manufactures, markets and distributes Mifeprex® in the United States.