Mifepristone Questions and Answers

1. What is FDA announcing?

FDA is announcing that the prescribing information and Medication Guide for Mifeprex has been updated to include a revised Black Box warning for Mifeprex and Danco Laboratories has issued a new Dear Doctor Letter for Mifeprex.

2. Why have the prescribing information and Medication Guide for Mifeprex been updated and why has Danco issued a new Dear Doctor Letter for Mifeprex?

FDA has been informed of additional postmarketing adverse events in the United States involving cases of bacterial infection in women following the use of Mifeprex and misoprostol for medical abortion. Overwhelming bacterial infection (septic shock) has led to death

Although serious infection and death following medical abortion is rare health care professionals and patients should be aware of the possibility that it may occur.

The label and Medication Guide are the primary sources of information for physicians and patients. The revised labeling and Medication Guide present new information about bacterial infection and its possible presenting signs and symptoms. When FDA receives and reviews new information, the agency provides appropriate updates to doctors and their patients so that they have essential information on how to use a drug safely. A Dear Health Care Practitioner letter and a Dear Emergency Room Director letter will assist in disseminating the updated information as quickly as possible to those physicians who use Mifeprex and misoprostol as well as emergency room physicians who may care for women seeking medical attention after using the treatment. Finally, these letters will enclose a chapter from Obstetric and Gynecologic Emergencies Diagnosis and Management (NY: McGraw-Hill, 2004) about complications of induced surgical and medical abortions so that emergency rooms will have a reference available.

3. What are the changes to the Prescribing Information and Medication Guide?

To communicate new safety information about Mifeprex, Danco Laboratories has updated the BOXED WARNING and WARNINGS sections of the Prescribing Information as well as the Medication Guide and the Patient Agreement.

Infection and Sepsis
New information on infection and sepsis has been included in the BOXED WARNING and WARNINGS sections of the Prescribing Information:

> In postmarketing experience following the use of Mifeprex and misoprostol, FDA has received reports of cases of serious bacterial infection, including very rare cases of fatal septic shock. No causal relationship between these events and the use of Mifeprex has been established. Although infection following medical abortion is rare, prescribers should be alert to the possibility of infection in their patients. In particular, a sustained fever of 100.4 degrees Fahrenheit or higher, severe abdominal pain, or pelvic tenderness in the days after taking Mifeprex and misoprostol may be an indication of infection. Atypical presentations of serious infection and sepsis, without fever, severe abdominal pain, or pelvic tenderness, but with significant leukocytosis, tachycardia, or hemoconcentration can occur.

Vaginal Bleeding

Information on vaginal bleeding has been added to the BOXED WARNING to highlight the serious nature of this event if not promptly treated. The WARNINGS section already stated that vaginal bleeding occurs in almost all patients during the treatment procedure.

> "According to data from the U.S. and French trials, women should expect to experience vaginal bleeding or spotting for an average of nine to 16 days, while up to 8% of all subjects may experience some type of bleeding for 30 days or more." "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." "Excessive vaginal bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, curettage, and/or blood transfusions."

Prescribers should counsel their patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding following a medical abortion.

Ectopic Pregnancy

Information on ectopic pregnancy has been added to the WARNINGS section to alert physicians to the possibility that a patient who is undergoing a medical abortion could have an undiagnosed ectopic pregnancy since some of the expected symptoms of a medical abortion may be similar to those of a ruptured ectopic pregnancy.

> No causal relationship between these events and Mifeprex and misoprostol has been established. Mifeprex is already contraindicated in patients with a confirmed or suspected ectopic pregnancy since Mifeprex is not effective for terminating these pregnancies. The presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed Mifeprex.

The Patient Agreement has been updated to reflect the new safety information on serious bacterial infection and vaginal bleeding as well as the Medication Guide in the section titled "What is the most important information I should know about Mifeprex?"

4. **What is a serious bacterial infection and how often does this occur following medical abortion?**

   Serious and sometimes fatal infections occur very rarely following spontaneous, surgical, and medical abortions, including following Mifeprex use. A serious bacterial infection is one that spreads throughout the body, having the potential to pose a life-threatening situation. Very rarely, serious bacterial infections may lead to septic shock and death.

5. **What is septic shock?**

   Septic shock is the result of an overwhelming systemic bacterial infection when there is both decreased blood pressure and blood flow in the body. This is a medical emergency because vital organs, such as the brain, heart, kidneys, lungs, and liver, may not function properly or may fail.

6. **What are the recognizable signs and symptoms of infection?**

   In the days after treatment with Mifeprex and misoprostol, having a fever of 100.4 degrees Fahrenheit or higher that lasts for more than 4 hours and/or lower abdominal pain or pelvic tenderness may be signs of an infection. It is important that the patient contact her health care provider right away if she develops any of these signs or symptoms or has any questions. Patients should have an emergency contact to call if there are problems, especially if they experience severe pain, heavy bleeding or fever.

7. **Can Mifeprex and misoprostol actually cause serious bacterial infections?**

   No. A causal relationship between use of the drugs and serious bacterial infection has not been established. There is a risk of infection with any termination of pregnancy, either spontaneous or through medical or surgical abortion. It is important for health care providers to explain the treatment regimen's risks and benefits to patients, answer their questions and provide them with information about potentially serious signs and symptoms that would signal the need to seek medical attention right away.

8. **Why is prolonged or heavy bleeding now part of the Black Box warnings?**

   In Europe, there was a death from severe prolonged bleeding in a woman who did not seek follow-up medical care. Bleeding during medical abortion is a known side effect and has been in the WARNINGS section of the labeling since the drug was approved. FDA and Danco agree that prolonged or heavy bleeding severe enough to cause a death can be avoided if patients and health care providers monitor bleeding carefully. To prevent complications of severe blood loss, the Warning has been elevated to call everyone's attention to the need to carefully monitor bleeding and that prompt medical or surgical care may be needed.

9. **What other actions have been taken since Mifeprex was approved to assure the safety of the drug?**

Mifeprex was approved in 2000 for the termination of early pregnancy, defined as 49 days or less. In April 2002, a Dear Health Care Practitioner Letter was sent to prescribers to warn about the risks of serious infection and sepsis following abortion as well as to remind prescribers to rule out ectopic pregnancies prior to use.

10. Has FDA responded to the citizen's petition on this product?

No. FDA is still reviewing and considering the pending citizens petition.

11. What information has FDA received pertaining to adverse events for mifepristone?

Through November 5, 2004, FDA has received information from United States post-marketing reports (i.e., not from clinical trials) of 676 adverse events that occurred among patients who had taken mifepristone for medical termination of pregnancy. These adverse events ranged from minor symptoms such as nausea and dizziness to more serious adverse events, including hospitalization and death. These events cannot with certainty be causally attributed to mifepristone because of information gaps about patient health status, clinical management of the patient, concurrent drug use and other possible medical or surgical treatments. Because FDA has eliminated duplicate reports that we have identified and, in some cases, reclassified the adverse event terms for individual cases after reviewing the narrative details, the numbers provided here may differ from the numbers of the reports that may be obtained through Freedom of Information Act requests.

Approximately 350,000 women have been treated with mifepristone in the US, from its approval in 2000 through the end of October, 2004.

Post-Marketing Adverse Events in US Women Who Used Mifepristone for Termination of Pregnancy	
Died	3
Ectopic pregnancies[1]	17
Experienced blood loss requiring transfusions[2]	72
Serious bacterial infections, including sepsis	7

[1] Administration of mifepristone and misoprostol is contraindicated in patients with confirmed or suspected ectopic pregnancy (a pregnancy outside the uterus).

[2] As stated in the mifepristone labeling, bleeding or spotting can be expected for an average of 9-16 days, and may last for up to 30 days.

12. The table in the previous question shows that there have been three deaths in the United States. Has FDA investigated the deaths of the women who had a medical abortion? What does FDA know about these deaths?

Yes, and the FDA has completed its investigation of these deaths. One death in September, 2001 was associated with a ruptured ectopic (tubal) pregnancy. The other two deaths (one in September, 2003, and the other in January, 2004) were associated with septic shock. The MedWatch reports for the three deaths were reported to FDA in October, 2001, September, 2003, and August, 2004, respectively. The coroner's report for the January, 2004 death indicated that the patient terminated her pregnancy with methotrexate. However, information subsequently submitted by the healthcare provider indicated that the patient had in fact received mifepristone and misoprostol, not methotrexate. Danco Laboratories was not notified by the healthcare provider about this death until August, 2004, after which they notified FDA.

13. What further action will FDA take regarding Mifeprex?

The revised labeling will provide physicians and patients with important information so that they can respond and possibly prevent rare but serious complications that may occur with any abortion. FDA monitors postmarketing reports and will continue to closely monitor safety reports associated with the use of Mifeprex and misoprostol and may take further action.