. Draft 08/28/00
INTERNAL USE ONLY

Questions and Answers on Mifepristone: INTERNAL USE ONLY

General

Q: What action did FDA take today?

A: Today, FDA approved mifepristone (trade name Mifeprex) for the termination of early pregnancy. The drug is approved to end pregnancies of 49 days or less, counting from the beginning of the last menstrual period.

Q: What treatment regimen did FDA approve?

A: The drug (mifepristone) is administered to a woman by mouth. Two days later, the woman returns to her doctor for oral administration of misoprostol, a prostaglandin that helps cause uterine contractions. Patients will return for a follow-up visit approximately 14 days after taking mifepristone to determine whether the pregnancy has been terminated.

Q: What is the basis for FDA's approval of this regimen?

A: FDA based its approval of mifepristone on data from clinical trials in the United States and in France.

Q: How effective was the regimen in clinical trials?

A: In the U.S. trials, medical termination of pregnancy was complete in 92% of the 827 women in the efficacy study – approximately six percent with mifepristone alone, and the remainder with mifepristone followed by misoprostol. In eight percent of patients, surgical intervention was required. Fewer than 1% of patients had ongoing pregnancies.

In the French trials, more than 95% of the 1,681 women experienced complete termination of pregnancy, 5.3% without misoprostol and the rest after taking both drugs. Surgical intervention was required in 4.5% of women.

Q: Is this the first drug approved in the U.S. for the termination of pregnancy?

A: No. Two other drugs are approved for the termination of pregnancy.

Restrictions

Q: What restrictions did FDA place on the use and distribution of this drug?

A: The drug may only be distributed to physicians who can accurately determine the duration of a woman's pregnancy and detect an ectopic (or tubal) pregnancy. Physicians who prescribe mifepristone must also be able to provide surgical intervention in cases of incomplete abortion or severe bleeding – or they must have made plans in advance to provide such care through others.

FDA approved mifepristone under its "Subpart H" regulations, which specifically allow FDA to establish appropriate controls on the distribution of a drug.

Q: What about distribution?

A: Mifepristone will be distributed directly to qualified physicians. It will not be available through pharmacies or on the Internet.

Q: What decisions has FDA made about labeling this product?

A: FDA is requiring a "black box" warning in the mifepristone labeling for physicians. The "black box" warns that surgical intervention may be necessary and addresses the care patients should receive should such intervention be necessary. In addition, because of the importance of adhering to this treatment regimen, each woman receiving mifepristone will be given a Medication Guide that clearly explains how to take the drug, who should avoid taking it, and what side effects can occur. This Guide is also referenced in the "black box."

Q: Why did FDA impose these restrictions?

A: FDA always seeks to ensure that the products it approves are used appropriately, so that risks are minimized and benefits are maximized. FDA believes that, for this drug, these restrictions are needed to ensure safe use.

In addition, the agency believes that women should have as much accurate information as possible to make an informed decision about this regimen.

Q: According to FDA regulations, Subpart "H" applies to drugs for serious and life-threatening illnesses. Isn't it overkill to invoke this provision for the mifepristone regimen?

A: The sponsor proposed a restricted distribution system for its product, and the FDA advisory committee that discussed this application in July 1996 also recommended such a system. FDA has concluded that the termination of unwanted pregnancy is a serious condition, and that these restrictions are necessary for the safe use of this drug.

Moreover, mifepristone's distribution is typically restricted in other countries where it has been approved. FDA has concluded that establishing certain controls on the distribution of this drug are needed to help ensure that it is used appropriately.

Q: Has distribution of any other drugs been restricted? What are some examples?

A: The distribution of several other drugs has been restricted to assure that they are used safely. For example:

- Clozapine (Clozaril), a drug used to manage severe schizophrenia, is available only through a registry system that ensures monitoring of certain blood test results prior to the delivery of the drug.

- Transmucosal fentanyl (Oralet), a potent analgesic delivered on a lollipop as premedication in pediatric patients before surgery or before painful procedures, is restricted to certain registered hospitals, and is not available retail pharmacy outlets.

- The manufacturer of trovafloxacin/alatrofloxacin mesylate (Trovan/Trovan-IV) agreed to limit distribution only to hospitals and long-term nursing care facilities.

- Thalidomide (Thalomid) is marketed only under a special restricted distribution program. Under that program, only registered prescribers and pharmacists are allowed to prescribe and dispense the product.

Patients must also be registered and participate in mandatory pregnancy testing prior to receiving the drug.

Q: Why is FDA requiring a physician to be able to provide surgical intervention or to provide a plan for obtaining those services for each woman using mifepristone?

A: Clinical trials and experience in countries where mifepristone is approved have shown that this regimen fails in five to eight of 100 women. Therefore, if the regimen fails and a woman still wants to terminate the pregnancy, a follow-up surgical procedure will be necessary and must be available.

Also, in about one of 100 women, bleeding can be so heavy that a surgical procedure will be required to stop the bleeding.

Q: Will FDA or the manufacturer establish a registry of physicians who have access to mifepristone?

A: Neither FDA nor the manufacturer has any plans to establish a registry of physicians.

Q: How can cancer patients obtain mifepristone?

A: Mifepristone is available for certain cancer patients through a single patient IND. Patients must be treated according to a specified treatment plan. The drug is provided by the Feminist Majority Foundation.

Pressure on FDA:

Q: There have been press reports that the politics of abortion have delayed FDA's action. How does the agency respond to those reports?

A: FDA is a scientific regulatory agency that makes decisions on the basis of science. The agency's review and approval of mifepristone adhered strictly to its legal mandate and mission as a science-based public health regulatory agency.

Q: The average review time for priority drugs is now six months. The sponsor sent FDA its application in March, 1996. Why did this review take so much longer?

A: FDA sent the sponsor an "approvable" letter in September 1996, six months after receiving the application. The letter identified outstanding issues that needed to be resolved before FDA could approve mifepristone. The sponsor responded to those issues in September 1999. FDA issued another "approvable" letter in February, 2000, asking additional questions. The sponsor has now answered those questions.

Q: Some members of Congress have expressed their opposition to mifepristone. Could Congress overturn FDA's decision?

A: It would be unprecedented for Congress to overrule an FDA decision to approve a medical product.

Q: FDA is a regulatory agency in the executive branch of the Federal government. Could a new administration overrule FDA's approval of mifepristone?

A: As an executive branch agency in the Department of Health and Human Services, FDA has bases its judgments concerning medical and public health matters on sound science. FDA based its approval of mifepristone on data from clinical trials in the U.S. and in France. It would be unprecedented for a new administration to overrule an FDA decision to approve a medical product.

Q: Who manufactures and distributes mifepristone?

A: Danco Laboratories, LLC, based in New York City, distributes mifepristone. Neither the Population Council, the sponsor of this product, nor Danco Laboratories has disclosed the identity of the manufacturer.

Q: Why won't FDA disclose the identity and location of the manufacturing site?

A: Because many threats and acts of violence have been directed at persons associated with reproductive rights issues similar to those raised by mifepristone, FDA will not disclose the identity of the manufacturer or the manufacturing site.

Under these circumstances, this manufacturing information is considered confidential commercial information.

Q: Why is FDA withholding the names of its employees who reviewed the new drug application for mifepristone?

A: Because many threats and actions of violence have been directed at persons associated with reproductive rights issues similar to those raised by mifepristone, FDA will not disclose these employees' names. Under these circumstances, this employee information is considered personal privacy information.

The regimen:

Q: How can mifepristone be safely used?

A: Basically, a woman should follow all the instructions for taking the product. First, a woman must read the Medication Guide and sign the Patient Agreement Form.

Day 1: a patient will be given three 200 milligram tablets of mifepristone.

Day 3: a patient must return to determine if expulsion has occurred. (Expulsion is infrequent with mifepristone alone, happening only in five or six percent of cases.) If expulsion has not occurred, the patient will be given two 200 microgram tablets of misoprostol that she will take orally.

Day 14: the patient will return for a follow-up visit. This visit is very important to confirm that a complete termination of pregnancy has occurred.

Q: How did FDA conclude that mifepristone is safe when its use results in the termination of a pregnancy?

A: The sponsor submitted a new drug application to the FDA, seeking the agency's approval to market mifepristone for the termination of early pregnancy. FDA concluded that the results from the clinical trials established that mifepristone is safe and effective for its intended use. In its review and approval of this application, FDA adhered strictly to its legal mandate and mission as a science-based regulatory agency.

Q: Why did FDA require a second visit on Day 3, when the product is being studied and used in a U.S. clinical trial without a return visit on Day 3?

A: Mifepristone was approved on the basis of data from clinical trials, designed by the sponsor, in which every woman in the study was required to return to her physician for a second visit. Unless pregnancy termination through the use of mifepristone alone has been confirmed by clinical examination or an ultrasonographic scan, the woman will take misoprostol during this second visit.

A third visit, to confirm that a complete termination of pregnancy has occurred, is also required.

Q: Why can't all physicians prescribe mifepristone?

A: FDA is restricting the distribution of mifepristone to physicians with specific qualifications, such as the ability to diagnose a tubal pregnancy. These restrictions are designed to ensure safe and appropriate use of the product.

Q: Can nurse-practitioners, midwives, or others prescribe mifepristone? Why?

A: Some states allow physicians to supervise other health care practitioners such as certified registered nurse practitioners and nurse midwives, and these states may allow a supervised health care provider to dispense mifepristone.

Q: What about misoprostol? Is the use of misoprostol an unlabeled use?

A: Under the approved treatment regimen, misoprostol is administered on day three to help stimulate uterine contractions. This use of misoprostol is contained in the approved labeling of mifepristone. It is based on the clinical trials for the regimen of the two drugs, which FDA found to be safe and effective for the termination of early pregnancy.

Q: The manufacturer of misoprostol just issued a warning to physicians not to use the drug in pregnant women, and there have been press reports that the manufacturer worked with FDA on this warning. How can FDA reconcile this warning with the approval of mifepristone when used with misoprostol?

A: Misoprostol (used alone) is currently approved for use in protecting patients from gastric ulcers induced by certain pain relievers. A women who is or may be pregnant – and who does NOT wish to terminate her pregnancy -- should know that she should not take misoprostol for prevention of gastric ulcers or any other reason.

The "Dear Doctor" letter issued by Searle on August 23, 2000, warns prescribers that misoprostol may cause abortion. It therefore emphasizes that misoprostol is contraindicated for use by any pregnant woman who does not wish to terminate her pregnancy.

As part of the mifepristone-misoprostol regimen, misoprostol is appropriate for use to terminate early pregnancy.

Q: Searle just distributed new labeling for its misoprostol product (Cytotec) that says the product is not approved for abortion. What is FDA's position on this labeling?

A: Now that FDA has approved the treatment plan for the use of mifepristone followed by the administration of misoprostol for the medical termination of intrauterine pregnancy through 49 days of pregnancy, the statement in the Searle label is inappropriate. FDA has asked that it be removed.

<u>Patient Safety and Side Effects</u>:

Q: What are the major side effects of mifepristone?

A: The Medication Guide provides information that women should be aware of concerning the incidence of side effects from administration of Mifeprex. These include cramping and, sometimes, heavy bleeding. After misoprostol administration on Day 3, there may be nausea, vomiting, and diarrhea. Before taking this medication, a woman must be fully aware of what to expect and will have to sign the Patient Agreement form.

The problems or side effects that women should be warned about include bleeding or spotting that is likely to occur from 9 to 16 days and that has been reported to last as long as 69 days. Up to eight percent of women may experience some kind of bleeding for 30 days or more. Surgical intervention may be needed to control the bleeding.

Q: What steps has FDA taken to ensure that women are adequately informed about how to use this regimen safely?

A: FDA is requiring that each woman who takes mifepristone receive a Medication Guide that clearly explains how to take the drug, who should avoid taking it, and what side effects can occur.

Each woman taking this drug must also read the Medication Guide and sign the patient agreement form before the drug will be administered.

Q: What if a woman changes her mind?

A: Among the many safeguards FDA has established for this treatment regimen are the requirements that each woman read the Medication Guide for mifepristone and that she also sign the Patient Agreement Form. These safeguards are designed to ensure that every woman knows and understands that this regimen is for the termination of early pregnancy and is committed to that course of action.

FDA and the sponsor have established a program to inform women about this regimen, including the risk of birth defects if the regimen does not end the pregnancy. Women are instructed that surgical termination may be needed, and the Patient Agreement Form certifies that they understand this possibility.

Q: Critics of this drug say it is dangerous to women and fetuses. How does FDA respond?

A: FDA and the sponsor have established a program to inform women about this regimen, including the risk of birth defects if the regimen does not end the pregnancy. Although the data on this risk are very limited, there are several reports in the medical literature of defects after first trimester exposure to prostaglandins, including misoprostol.

As of May 2000, 82 cases had been reported in which women with ongoing pregnancies after using mifepristone, alone or followed by misoprostol, declined to have a surgical procedure. Of those, follow-up information is available for 36. Twenty-six of those women experienced live births, and none of the infants had any abnormalities detected at birth. Ten of the women later decided to have a surgical termination, and of those, there was one case of fetal malformation.

Q: Has the sponsor agreed to carry out postmarketing studies of mifepristone?

A: To gather additional data about the use of mifepristone, the Population Council has made a commitment to conduct postmarketing studies. These include a study comparing patient outcomes among physicians who refer their patients needing surgical intervention, compared to those who perform surgical procedures themselves; an audit of prescribers that will examine whether patients and their physicians are signing the patient agreement and placing it in the patient's medical record, as required; and a system for surveillance, reporting and tracking rare ongoing pregnancies after treatment with mifepristone in the U.S.

Q: The sponsor of mifepristone has agreed to conduct postmarketing studies involving this drug. Doesn't that mean FDA really thinks the regimen is unsafe?

A: No. It is not at all unusual for sponsors to conduct postmarketing studies on their approved products.

Access:

Q: Who may prescribe mifepristone?

A: The drug will be distributed only to physicians who can accurately determine the duration of a woman's pregnancy and detect an ectopic (or tubal) pregnancy. Physicians who prescribe mifepristone must also be able to provide surgical intervention in cases of incomplete abortion or severe bleeding – or they must have made plans in advance for patients to obtain such care through others.

Q: Will it be available in pharmacies?

A: No. Mifepristone will be available only through qualified physicians.

Q: What health professionals will have access to mifepristone?

A: Some states allow physicians to supervise other health care practitioners such as certified registered nurse practitioners and nurse midwives, and these states may allow a supervised health care provider to dispense mifepristone.

Q: Will mifepristone be available over the Internet?

A: No. FDA and the sponsor have established a treatment regimen with many safeguards, including the direct distribution of the drug only to qualified physicians.

Q: In 1990 FDA issued an Import Alert that banned the importation of mifepristone into the United States. The drug was listed under several other names. Is that Import Alert still valid?

A: FDA issued this Import Alert because of safety concerns for people taking the unapproved drug without adequate supervision from a health care professional. Now that FDA has approved Mifeprex, the Import Alert has been revised to exempt this specific product from the alert. Formulations of mifepristone not covered by the NDA or by an IND in effect would still be denied entry into the U.S., however.

Q: Has mifepristone been studied for other uses? If so, will those studies continue?

A: Mifepristone is being studied for a variety of uses, because it can block steroid receptors. In particular, it is being investigated as a potential treatment for cancers whose tumors have progesterone receptors.

ADDITIONAL QUESTIONS AND ANSWERS—INERNAL USE ONLY

Q: Did the White House or Secretary Shalala intervene in FDA's review of mifepristone?

A: No. Neither the White House nor the Secretary were involved in FDA's decision. FDA based its decision on the science.

Q: Earlier this year there were reports that FDA was going to impose severe restrictions on the availability of mifepristone. What changed FDA's thinking?

A: Some early press reports on this issue were inaccurate. When FDA is nearing the end of a product review, give and take between the agency and the sponsor is normal.

Q: President Clinton in 1993 asked Secretary Shalala to see what could be done to expedite the availability of mifepristone. The Secretary in 1994 said that "FDA will do all it can to quickly evaluate mifepristone." What happened? Why did FDA not tell the sponsor until 1996 that mifepristone was "approvable?"

A: Many things had to occur before the FDA could take any action. The sponsor had to obtain patent rights to the drug, and this happened in May, 1994. The sponsor then had to identify a manufacturer for the drug, file an IND with the FDA, and design and conduct clinical studies of the product. Finally, the sponsor had to analyze the data and submit a marketing application to the FDA.

FDA received the new drug application in March 1996. It began reviewing the application immediately, held an advisory committee meeting in July, and issued an "approvable" letter in September 1996.

Q: Who made the decision to approve mifepristone?

A: Many FDA employees contribute to the review and approval of a new product. The "approval" letter FDA sends to the sponsor is typically signed by a senior official.

In the case of mifepristone, FDA is not disclosing the identity of the reviewers and others who reviewed this application.

Q: What about reports that FDA has hired armed guards and heightened security?

A: FDA does not comment on security matters.