DEPARTMENT OF HEALTH & HUMAN SERVICES

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Date: 12/1/00 Total number of pages sent: 2

Comments:

Here's the Q+A on RU486 - I don't think you all should go beyond this →

MSF

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.

HHS *NEWS*

U.S. Department of Health and Human Services

P00-19
September 28, 2000
FOR IMMEDIATE RELEASE

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FDA APPROVES MIFEPRISTONE FOR THE TERMINATION OF EARLY PREGNANCY

The Food and Drug Administration today approved mifepristone (trade name Mifeprex) for the termination of early pregnancy, defined as 49 days or less, counting from the beginning of the last menstrual period.

Under the approved treatment regimen, a woman first takes 600 milligrams of mifepristone (three 200 milligram pills) by mouth. Two days later, she takes 400 micrograms (two 200-microgram pills) of misoprostol, a prostaglandin. Women will return for a follow-up visit approximately 14 days after taking mifepristone to determine whether the pregnancy has been terminated.

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.

"The approval of mifepristone is the result of the FDA's careful evaluation of the scientific evidence related to the safe and effective use of this drug," said Jane E. Henney, M.D., Commissioner of Food and Drugs. "The FDA's review and approval of this drug has adhered strictly to our legal mandate and mission as a science-based public health regulatory agency."

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

The labeling for mifepristone emphasizes that most women using the product will experience some side effects, primarily cramping and bleeding. Bleeding and spotting typically last for between 9 and 16 days. In about one of 100 women, bleeding can be so heavy that a surgical procedure will be required to stop the bleeding.

The drug's labeling also warns that it should not be used in women with the following conditions:

- Confirmed or suspected ectopic ("tubal") pregnancies
- Intrauterine device (IUD) in place
- Chronic failure of the adrenal glands
- Current long-term therapy with corticosteroids
- History of allergy to mifepristone, misoprostol or other prostaglandins
- Bleeding disorders or current anticoagulant (blood-thinning) therapy.

Under the terms of the approval, mifepristone will be distributed to physicians who can accurately determine the duration of a patient'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.

To gather additional data about the use of mifepristone, the Population Council (sponsor of the product) 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.

Mifepristone, which was developed by a French pharmaceutical firm, was first approved for use in France in 1988. Since then, more than 620,000 European women have taken mifepristone in combination with a prostaglandin to terminate pregnancy. The drug has also been approved in the United Kingdom, Sweden, and

other countries.

Mifepristone will be distributed in the U.S. by Danco Laboratories, LLC, New York, N.Y.

More detailed information about this product is available on FDA's website at www.fda.gov/cder/drug/infopage/mifepristone/.

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Office of Public Affairs
Web page created by clb 2000-SEP-28.

DEPARTMENT OF HEALTH & HUMAN SERVICES

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FACSIMILE

DATE: 10.2

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Chief of Staff

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COMMENTS:

_____Pages [including this cover]

Mifepristone Questions and Answers

1. What is MIFEPREX (mifepristone) and how does it work?

Mifepristone is a drug that blocks a hormone called progesterone that is needed for pregnancy to continue. Mifepristone, when used together with another medicine called misoprostol, is used to end an early pregnancy (49 days or less since your last menstrua period began).

2. Is mifepristone approved in any other countries?

Yes, mifepristone has also been approved in the United Kingdom, Sweden and other countries.

3. Who should not take mifepristone?

Some women should not take mifepristone. Do not take mifepristone if it has been more than 49 days since your last menstrual period or if you have:

- a tubal pregnancy
- an intrauterine device (IUD) in place (It must be removed before you take mifepristone)
- problems with your adrenal glands (the glands near your kidneys)
- been treated with certain steroid medications for a long period of time
- bleeding problems or are taking anticoagulant (blood thinning) drug products
- had an allergic reaction to mifepristone, misoprostol or similar drugs

It is important that you understand the need for 2 follow-up visits with your health care provider and that you have access to a medical care facility in case of an emergency.

Mifepristone has not been studied in women who are heavy smokers. Please tell your doctor if you smoke more than 10 cigarettes a day.

4. Is mifepristone distribution restricted?

Yes, mifepristone is supplied directly to doctors who meet certain qualifications. It is not and will not be available in pharmacies, and it is not legally available over the Internet.

5. Why are there restrictions for this drug?

Studies of mifepristone were conducted by doctors who had certain qualifications. Both the drug sponsor and the 1996 Reproductive Drug Products Advisory Committee also recommended that FDA restrict distribution of mifepristone to qualified doctors. FDA has concluded that these restrictions are necessary for the safe use of the drug.

6. What qualifications must doctors have to obtain mifepristone?

Doctors must have the ability to date pregnancies accurately and to diagnose tubal pregnancies. Doctors must also be qualified to provide any necessary surgery, or have made arrangements for any necessary surgery. Doctors must ensure that women have access to medical facilities for emergency care, and must agree to other responsibilities such as dispensing the Medication Guide and reporting any adverse events to the sponsor.

7. What authority does FDA have to restrict distribution of a drug?

The law authorizes FDA to approve new drugs only if they have been demonstrated to be safe and effective for use under the conditions of use recommended in the label. FDA has broad authority to require restrictions on distribution to ensure safe and effective use. FDA's full legal authority to restrict distribution of a drug is described in more detail in the preamble to agency drug regulations. Federal Register Notice.

8. Can health care providers other than doctors dispense mifepristone?

Some states allow physicians to supervise other health care practitioners, such as certified registered nurse practitioners and nurse midwives, and these states may allow supervised health care provider to dispense mifepristone. Health care providers should check their state law provisions.

9. Is there an age restriction for termination of pregnancy?

State law determines whether there are any restriction on minors obtaining surgical or medical abortions. FDA has not set any separate age restriction on the provision of Mifepristone states may set age restrictions on termination of pregnancy if they believe such restrictions are appropriate..

10. Are there studies with mifepristone in women under the age of 18?

Studies to evaluate mifepristone included women ages 18-45.

11. What are the possible side effects of using mifepristone?

Mifepristone treatment will cause vaginal bleeding. In some cases vaginal bleeding can be very heavy. In a few cases, this bleeding will need to be stopped by a surgical procedure.

Other possible side effects of the treatment include diarrhea, nausea, vomiting, headache, dizziness, back pain, and tiredness.

The possible side effects are described in the Medication Guide. Please read the

Medication Guide.

12. What is a Medication Guide?

A Medication Guide is a leaflet that contains certain FDA-approved information, written especially for patients.

13. Why did FDA develop a Medication Guide for mifepristone?

FDA determined that a Medication Guide was necessary for women to be able to use mifepristone effectively and safely. It is important for women to be fully informed about how mifepristone works and about its risks, as well as the need for follow-up visits with their health care provider, especially on the 14th day after mifepristone is administered. The Medication Guide will help ensure that women follow the directions for use and that they return to their health care provider for follow-up visits.

Before you receive mifepristone, your doctor will provide you with the Medication Guide and ask you to sign a statement (Patient Agreement) that you have decided to en your pregnancy.

14. Can I become pregnant again if I take mifepristone?

You can become pregnant again right after your pregnancy ends. If you do not want to get become pregnant again, start using a birth control method of your choice as soon as your pregnancy ends.

15. Does FDA endorse the use of this drug?

FDA does not endorse or promote any drug product. The agency evaluates all drug applications submitted by sponsors to determine whether a drug is safe and effective fo its proposed indication under the conditions of use in the labeling. This means that the benefits of the drug outweigh its risks. The same standards were applied to the new drug application for mifepristone as are applied to all applications.

16. How much will mifepristone cost?

Manufacturers establish prices for prescription drugs. FDA has no input into or jurisdiction over drug pricing. FDA does not know what mifepristone will cost when it becomes available.

17. Will insurance companies pay for mifepristone?

The FDA has no input into or legal control over whether an insurance company does or does not cover the cost of a drug. Insurance coverage is a decision made by your insurance provider. Please call your insurance company if you have questions, about whether your particular insurance provider will cover the cost of mifepristone.

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FDA/Center for Drug Evaluation and Research
Last Updated: September 28, 2000
Originator: OTCOM/DLIS

HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

P00-19
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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

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effects can occur.

"The approval of mifepristone is the result of the FDA's careful evaluation of the scientific evidence related to the safe and effective use of this drug," said Jane E. Henney, M.D., Commissioner of Food and Drugs. "The FDA's review and approval of this drug has adhered strictly to our legal mandate and mission as a science-based public health regulatory agency."

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medical record, as required; and a system for surveillance, reporting and tracking rare ongoing pregnancies after treatment with mifepristone in the U.S.

Mifepristone, which was developed by a French pharmaceutical firm, was first approved for use in France in 1988. Since then, more than 620,000 European women have taken mifepristone in combination with a prostaglandin to terminate pregnancy. The drug has also been approved in the United Kingdom, Sweden, and other countries.

Mifepristone will be distributed in the U.S. by Danco Laboratories, LLC, New York, N.Y.

More detailed information about this product is available on FDA's website at http://www.fda.gov/cder/drug/infopage/mifepristone/

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Draft 09/28/00
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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?

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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.

<u>Pressure on FDA</u>:

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.

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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.

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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.

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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.

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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.

Patient Safety and Side Effects:

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.

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As of May 2000, 82 cases have 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.

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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—INTERNAL 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 patents for 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 then 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.

External Q[illegible] for FDA's Web Site

1. What is MIFEPREX (mifepristone) and how does it work?
Mifepristone is a drug that blocks a hormone called progesterone that is needed for pregnancy to continue. Mifepristone, when used together with another medicine called misoprostol, is used to end an early pregnancy (49 days or less since your last menstrual period began).

2. Is mifepristone approved in any other countries?
Yes, mifepristone is approved in many other countries including France, the United Kingdom, and Sweden.

3. Who should not take mifepristone?
Some women should not take mifepristone. Do not take mifepristone if it has been more than 49 days since your last menstrual period or if you have:

- a tubal pregnancy
- an intrauterine device (IUD) in place (must be removed before you take mifepristone)
- problems with your adrenal glands (glands near your kidneys)
- been treated with certain steroid medicines for a long period of time
- bleeding problems or are taking anticoagulant (blood-thinning) drug products
- had an allergic reaction to mifepristone, misoprostol or similar drugs

It is important that you understand the [illegible] follow-up visits with your health care provider and that you have access to a [illegible] facility in case of an emergency.

Mifepristone has not been studied in women who are heavy smokers. Please tell your doctor if you smoke more than 10 cigarettes a day.

4. Is mifepristone distribution restricted?
Yes, mifepristone is supplied directly to doctors who meet certain qualifications. It is not and will not be available in pharmacies. It is not legally available over the Internet.

5. Why are there restrictions for this drug?
Studies of mifepristone were conducted by doctors who had certain qualifications. Both the drug sponsor and the 1996 Reproductive Health Drugs Advisory Committee also recommended that FDA restrict distribution of mifepristone to qualified doctors. FDA has concluded that these restrictions are necessary for the safe use of the drug.

6. What qualifications must doctors have to prescribe mifepristone?
Doctors must have the ability to date pregnancies accurately and to diagnose tubal pregnancies. Doctors must also be able to provide any necessary surgery, or have

made arrangements for any necessary [illegible] providers must ensure that women have access to medical facilities for emergency [illegible] must agree to other responsibilities, such as dispensing the Medication Guide [illegible] any adverse events to the sponsor.

7. What authority does FDA have to r[illegible] distribution of a drug?
The law authorizes FDA to approve new [illegible] if they have been demonstrated to be safe and effective for use under the conditions [illegible] recommended in the label. FDA has broad authority to require restrictions [illegible] to ensure safe and effective use. FDA's full legal authority to restrict [illegible] drug is described in more detail in the preamble to agency drug regulations [illegible] (PDF or scanned copy)

8. Can health care providers other [illegible] dispense mifepristone?
Some states allow physicians to supervise [illegible] care practitioners, such as certified registered nurse practitioners and nurse [illegible] these states may allow a supervised health care provider to dispense [illegible] Health care providers should check their state law provisions.

9. Is there an age restriction for ter[illegible] pregnancy?
States may set age restrictions on termination [illegible] if they believe such restrictions are appropriate.

10. Are there studies with mifepristone [illegible] under the age of 18?
Studies to evaluate mifepristone include [illegible] ages 18-45.

11. What are the possible side effects [illegible] mifepristone?
Mifepristone treatment will cause vaginal [illegible] In some cases vaginal bleeding can be very heavy. In a few cases, this bleeding will need to be stopped by a surgical procedure.

Other possible side effects of the treatment include diarrhea, nausea, vomiting, headache, dizziness, back pain, and tiredness.

The possible side effects are described in the Medication Guide. Please read the **Medication Guide (LINK).**

12. What is a Medication Guide?
A Medication Guide contains FDA-approved information, written especially for patients.

13. Why did FDA develop a Medication Guide for mifepristone?
FDA determined that a Medication Guide is necessary for women to be able to use mifepristone effectively and safely. It is important for women to be fully informed about how mifepristone works and about risks, including the need for follow-up visits with their health care provider, especially [illegible] after mifepristone is administered. The Medication Guide will help ensure [illegible] follow the directions for use and that they return to their health care provider [illegible] visits.

Before you receive mifepristone, [redacted] you with the Medication Guide and ask you to sign a statement (Pa[redacted] you have decided to end your pregnancy.

14. Can I become pregnant again [redacted]?
You can becoms pregnant again [redacted] pregnancy ends. If you do not want to become pregnant again, start using a [redacted] method of your choice as soon as your pregnancy ends.

15. Does FDA endorse the use of [redacted]?
FDA does not endorse or promote [redacted]. The agency evaluates all drug applications submitted by sponsors [redacted] whether a drug is safe and effective for its proposed indication under the [redacted] the labeling. This means that the benefits of the drug outweigh its [redacted] dards were applied to the new drug application for mifepristone as are [redacted] all applications.

16. How much will mifepristone [redacted]?
Manufacturers establish prices for [redacted]. FDA has no jurisdiction over drug pricing.

17. Will insurance companies pay [redacted]?
Insurance coverage is a decision [redacted] provider. Please call your insurance company if you have qu[redacted]

HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

P00-19
September 28, 2000
FOR IMMEDIATE RELEASE

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FDA APPROVES MIFEPRISTONE FOR THE TERMINATION OF EARLY PREGNANCY

The Food and Drug Administration today approved mifepristone (trade name Mifeprex) for the termination of early pregnancy, defined as 49 days or less, counting from the beginning of the last menstrual period.

Under the approved treatment regimen, a woman first takes 600 milligrams of mifepristone (three 200 milligram pills) by mouth. Two days later, she takes 400 micrograms (two 200-microgram pills) of misoprostol, a prostaglandin. Women will return for a follow-up visit approximately 14 days after taking mifepristone to determine whether the pregnancy has been terminated.

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

-More-

effects can occur.

"The approval of mifepristone is the result of the FDA's careful evaluation of the scientific evidence related to the safe and effective use of this drug," said Jane E. Henney, M.D., Commissioner of Food and Drugs. "The FDA's review and approval of this drug has adhered strictly to our legal mandate and mission as a science-based public health regulatory agency."

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

The labeling for mifepristone emphasizes that most women using the product will experience some side effects, primarily cramping and bleeding. Bleeding and spotting typically last for between 9 and 16 days. In about one of 100 women, bleeding can be so heavy that a surgical procedure will be required to stop the bleeding.

The drug's labeling also warns that it should not be used in women with the following conditions:

- Confirmed or suspected ectopic ("tubal") pregnancies
- Intrauterine device (IUD) in place
- Chronic failure of the adrenal glands

- Current long-term therapy with corticosteroids
- History of allergy to mifepristone, misoprostol or other prostaglandins
- Bleeding disorders or current anticoagulant (blood-thinning) therapy.

Under the terms of the approval, mifepristone will be distributed to physicians who can accurately determine the duration of a patient'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.

To gather additional data about the use of mifepristone, the Population Council (sponsor of the product) 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.

Mifepristone, which was developed by a French pharmaceutical firm, was first approved for use in France in 1988. Since then, more than 620,000 European women have taken mifepristone in combination with a prostaglandin to terminate pregnancy. The drug has also been approved in the United Kingdom, Sweden, and other countries.

Mifepristone will be distributed in the U.S. by Danco Laboratories, LLC, New York, N.Y.

More detailed information about this product is available on FDA's website at http://www.fda.gov/cder/drug/infopage/mifepristone/

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Draft 09/28/00
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.

<u>Pressure on FDA</u>:

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.

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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.

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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.

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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.

Patient Safety and Side Effects:

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.

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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.

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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.

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

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

A: FDA does not comment on security matters.

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- been treated with certain steroid medications for a long period of time
- bleeding problems or are taking anticoagulant (blood-thinning) drug products
- had an allergic reaction to mifepristone, misoprostol or similar drugs

It is important that you understand the need for 2 follow-up visits with your health care provider and that you have access to a medical facility in case of an emergency.

Mifepristone has not been studied in women who are heavy smokers. Please tell your doctor if you smoke more than 10 cigarettes a day.

4. Is mifepristone distribution restricted?
Yes, mifepristone is supplied directly to doctors who meet certain qualifications. It is not and will not be available in pharmacies. It is not legally available over the Internet.

5. Why are there restrictions for this drug?
Studies of mifepristone were conducted by doctors who had certain qualifications. Both the drug sponsor and the 1996 Reproductive Drug Products Advisory Committee also recommended that FDA restrict distribution of mifepristone to qualified doctors. FDA has concluded that these restrictions are necessary for the safe use of the drug.

6. What qualifications must doctors have to prescribe mifepristone?
Doctors must have the ability to date pregnancies accurately and to diagnose tubal pregnancies. Doctors must also be able to provide any necessary surgery, or have

made arrangements for any necessary [illegible] providers must ensure that women have access to medical facilities for emergency [illegible] must agree to other responsibilities, such as dispensing the Medication Guide [illegible] reporting any adverse events to the sponsor.

7. What authority does FDA have to re[illegible] prescription of a drug?
The law authorizes FDA to approve new [illegible] if they have been demonstrated to be safe and effective for use under the conditions [illegible] recommended in the label. FDA has broad authority to require restrictions [illegible] distribution to ensure safe and effective use. FDA's full legal authority to restrict [illegible] drug is described in more detail in the preamble to agency drug regulations. [illegible] (CFR or scanned copy)

8. Can health care providers other [illegible] dispense mifepristone?
Some states allow physicians to supervise [illegible] care practitioners, such as certified registered nurse practitioners and nurse [illegible] these states may allow a supervised health care provider to dispense mifepristone. Health care providers should check their state law provisions.

9. Is there an age restriction for terminating a pregnancy?
States may set age restrictions on terminating a pregnancy if they believe such restrictions are appropriate.

10. Are there studies with mifepristone [illegible] under the age of 18?
Studies to evaluate mifepristone included women ages 18-45.

11. What are the possible side effects [illegible] mifepristone?
Mifepristone treatment will cause vaginal bleeding. In some cases vaginal bleeding can be very heavy. In a few cases, this bleeding will need to be stopped by a surgical procedure.

Other possible side effects of the treatment [illegible] diarrhea, nausea, vomiting, headache, dizziness, back pain, and tiredness.

The possible side effects are described in the Medication Guide. Please read the **Medication Guide (LINK).**

12. What is a Medication Guide?
A Medication Guide contains FDA-approved [illegible] information, written especially for patients.

13. Why did FDA develop a Medication Guide for mifepristone?
FDA determined that a Medication Guide is necessary for women to be able to use mifepristone effectively and safely. It is important for women to be fully informed about how mifepristone works and about serious risks, the need for follow-up visits with their health care provider, especially [illegible] after mifepristone is administered. The Medication Guide will help ensure [illegible] to follow the directions for use and that they return to their health care provider [illegible] visits.

Before you receive mifepristone, [redacted] provide you with the Medication Guide and ask you to sign a statement (Patient [redacted]) that you have decided to end your pregnancy.

14. Can I become pregnant again [redacted] mifepristone?
You can become pregnant again right [redacted] pregnancy ends. If you do not want to become pregnant again, start using a [redacted] method of your choice as soon as your pregnancy ends.

15. Does FDA endorse the use of [redacted]?
FDA does not endorse or promote any [redacted]. The agency evaluates all drug applications submitted by sponsors to determine whether a drug is safe and effective for its proposed indication under the conditions specified in the labeling. This means that the benefits of the drug outweigh its risks. The same standards were applied to the new drug application for mifepristone as are applied to all applications.

16. How much will mifepristone cost?
Manufacturers establish prices for their products. FDA has no jurisdiction over drug pricing.

17. Will insurance companies pay for [redacted]?
Insurance coverage is a decision made by each insurance provider. Please call your insurance company if you have questions.

Jenni ffnf
66x23

DEPARTMENT OF HEALTH & HUMAN SERVICES

Chief of Staff

Washington, D.C. 20201

FACSIMILE

DATE: _____

TO: H. Howard

FAX#: 7878

FROM: Mary Beth Donahue
Chief of Staff

Phone: 202/690-7431 Fax: 202/401-5783

COMMENTS:

11 **Pages [including this cover]**

U.S. Food and Drug Administration • Center for Drug Evaluation and Research

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Mifepristone Information

The Food and Drug Administration has approved mifepristone (trade name Mifeprex) for t termination of early pregnancy, defined as 49 days or less, counting from the beginning of last menstrual period.

Press Release on Mifepristone Approval (9/28/2000)

Mifepristone Approval Letter 9/28/00. Optional Format: PDF. (9/28/2000)

Mifepristone Label. Optional Format: PDF (9/28/2000)

Mifepristone MedGuide. Optional Format: PDF. (9/28/2000)

Questions and Answers about Mifepristone (9/28/2000)

Patient Agreement Form (9/28/2000)

Prescriber's Agreement Form (9/28/2000)

Mifepristone Review (9/28/2000)

Federal Register Final Rule, Restrictions on Use After Marketing (12/2/1992)

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FDA/Center for Drug Evaluation and Research
Last Updated: September 28, 2000
Originator: OTCOM/DLIS

fyi - re: website

NDA 20-687

Population Council
Attention: **[Redacted]**
Vice President, Corporate Affairs
1230 York Avenue: **[Redacted]**
New York, NY 10021

Dear **[Redacted]**:

Please refer to your new drug application (NDA) dated March 14, 1996, received March 18, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MIFEPREX™ (mifepristone) Tablets, 200 mg.

We acknowledge receipt of your submissions dated April 19, June 20, July 25, August 15 and September 16 and 26, 1996; January 30, March 31, July 28, August 5, September 24, November 26, 1997; January 30 (2), February 19, Aril 27, June 25, October 26, December 8, 1998; February 8 and 22, March 31, April 28, May 10 and 20, June 3 (2), 15, 23, 25, and 30, July 14 (2) and 22, August 3, 13, 18 and 30, September 3, 8, 13 and 30, October 5, 26 and 28, November 16 and 29 (2), December 6, 7 and 23, 1999; and January 11, 21 and 28 (2), February 16 and 24, March 3, 6, 9, 10, 30 and 31 (2), April 20, May 3, 11 and 17, June 22 and 23, July 11, 13, 25 and 27, August 18, 21 and 24, September 8, 12, 15 (2), 19 (2), 20, 21, 22, 26 (2), and 27 (2), 2000. Your submission of March 30, 2000 constituted a complete response to our February 18, 2000 action letter.

This new drug application provides for the use of Mifeprex™ for the medical termination of intrauterine pregnancy through 49 days' pregnancy.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to approve Mifeprex™ (mifepristone) Tablets, 200 mg, for use as recommended in the agreed upon labeling text. The application is approved under 21 CFR 314 Subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced regulations.

The final printed labeling (FPL) [including the professional labeling (Package Insert), the Medication Guide required for this product under 21 CFR Part 208, the Patient Agreement Form, and the Prescriber's Agreement Form] must be identical to the submitted draft labeling (Package Insert, Medication Guide, Patient Agreement Form, and the Prescriber's Agreement Form submitted September 27, 2000; and the immediate container and carton labels submitted July 25, 2000). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 20-687." Approval of this submission by FDA is not required before the labeling is used.

Under 21 CFR 314.520, distribution of the drug is restricted as follows:

Mifeprex™ must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex™.
- Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, give her an opportunity to read

and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well.

- Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an ongoing pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure.
- Must report any hospitalization, transfusion or other serious events to the sponsor or its designate.
- Must record the Mifeprex™ package serial number in each patient's record.

With respect to the aspects of distribution other than physician qualifications described above, the following applies:

- Distribution will be in accordance with the system described in the March 30, 2000 submission.

  This plan assures the physical security of the drug product and provides specific requirements imposed by and on the distributor including procedures for storage, dosage tracking, damaged product returns, and other matters.

We also note the following Phase 4 commitments, specified in your submission dated September 15, 2000. These commitments replace all previous commitments cited in the September 18, 1996 and the February 18, 2000 approvable letters. These Phase 4 commitments are:

1. A cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention. Previous study questions related to age, smoking, and follow-up on day 14 (compliance with return visit) will be incorporated into this cohort study, as well as an audit of signed Patient Agreement forms.
2. A surveillance study on outcomes of ongoing pregnancies.

You have agreed to provide the final Phase 4 protocols for these studies within six months.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call **[Redacted]** Regulatory Project Manager, at **[Redacted]**.

Sincerely,

[Redacted]

Director

Office of Drug
Evaluation III
Center for Drug
Evaluation and
Research

Mifepristone Questions and Answers

1. What is MIFEPREX (mifepristone) and how does it work?

Mifepristone is a drug that blocks a hormone called progesterone that is needed for pregnancy to continue. Mifepristone, when used together with another medicine called misoprostol, is used to end an early pregnancy (49 days or less since your last menstrual period began).

2. Is mifepristone approved in any other countries?

Yes, mifepristone has also been approved in the United Kingdom, Sweden and other countries.

3. Who should not take mifepristone?

Some women should not take mifepristone. Do not take mifepristone if it has been more than 49 days since your last menstrual period or if you have:

- a tubal pregnancy
- an intrauterine device (IUD) in place (It must be removed before you take mifepristone)
- problems with your adrenal glands (the glands near your kidneys)
- been treated with certain steroid medications for a long period of time
- bleeding problems or are taking anticoagulant (blood thinning) drug products
- had an allergic reaction to mifepristone, misoprostol or similar drugs

It is important that you understand the need for 2 follow-up visits with your health care provider and that you have access to a medical care facility in case of an emergency.

Mifepristone has not been studied in women who are heavy smokers. Please tell your doctor if you smoke more than 10 cigarettes a day.

4. Is mifepristone distribution restricted?

Yes, mifepristone is supplied directly to doctors who meet certain qualifications. It is not and will not be available in pharmacies, and it is not legally available over the Internet.

5. Why are there restrictions for this drug?

Studies of mifepristone were conducted by doctors who had certain qualifications. Both the drug sponsor and the 1996 Reproductive Drug Products Advisory Committee also recommended that FDA restrict distribution of mifepristone to qualified doctors. FDA has concluded that these restrictions are necessary for the safe use of the drug.

6. What qualifications must doctors have to obtain mifepristone?

Doctors must have the ability to date pregnancies accurately and to diagnose tubal pregnancies. Doctors must also be qualified to provide any necessary surgery, or have made arrangements for any necessary surgery. Doctors must ensure that women have access to medical facilities for emergency care, and must agree to other responsibilities, such as dispensing the Medication Guide and reporting any adverse events to the sponsor.

7. What authority does FDA have to restrict distribution of a drug?

The law authorizes FDA to approve new drugs only if they have been demonstrated to be safe and effective for use under the conditions of use recommended in the label. FDA has broad authority to require restrictions on distribution to ensure safe and effective use. FDA's full legal authority to restrict distribution of a drug is described in more detail in the preamble to agency drug regulations. Federal Register Notice.

8. Can health care providers other than doctors dispense mifepristone?

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. Health care providers should check their state law provisions.

9. Is there an age restriction for termination of pregnancy?

State law determines whether there are any restriction on minors obtaining surgical or medical abortions. FDA has not set any separate age restriction on the provision of Mifepristone states may set age restrictions on termination of pregnancy if they believe such restrictions are appropriate..

10. Are there studies with mifepristone in women under the age of

18?

Studies to evaluate mifepristone included women ages 18-45.

11. What are the possible side effects of using mifepristone?

Mifepristone treatment will cause vaginal bleeding. In some cases vaginal bleeding can be very heavy. In a few cases, this bleeding will need to be stopped by a surgical procedure.

Other possible side effects of the treatment include diarrhea, nausea, vomiting, headache, dizziness, back pain, and tiredness.

The possible side effects are described in the Medication Guide. Please read the **Medication Guide**.

12. What is a Medication Guide?

A Medication Guide is a leaflet that contains certain FDA-approved information, written especially for patients.

13. Why did FDA develop a Medication Guide for mifepristone?

FDA determined that a Medication Guide was necessary for women to be able to use mifepristone effectively and safely. It is important for women to be fully informed about how mifepristone works and about its risks, as well as the need for follow-up visits with their health care provider, especially on the 14th day after mifepristone is administered. The Medication Guide will help ensure that women follow the directions for use and that they return to their health care provider for follow-up visits.

Before you receive mifepristone, your doctor will provide you with the Medication Guide and ask you to sign a statement (Patient Agreement) that you have decided to end your pregnancy.

14. Can I become pregnant again if I take mifepristone?

You can become pregnant again right after your pregnancy ends. If you do not want to get become pregnant again, start using a birth control method of your choice as soon as your pregnancy ends.

15. Does FDA endorse the use of this drug?

FDA does not endorse or promote any drug product. The agency evaluates all drug applications submitted by sponsors to determine whether a drug is safe and effective for its proposed indication under the conditions of use in the labeling. This means that the benefits of the drug outweigh its risks. The same

standards were applied to the new drug application for mifepristone as are applied to all applications.

16. How much will mifepristone cost?

Manufacturers establish prices for prescription drugs. FDA has no input into or jurisdiction over drug pricing. FDA does not know what mifepristone will cost when it becomes available.

17. Will insurance companies pay for mifepristone?

The FDA has no input into or legal control over whether an insurance company does or does not cover the cost of a drug. Insurance coverage is a decision made by your insurance provider. Please call your insurance company if you have questions, about whether your particular insurance provider will cover the cost of mifepristone.

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FDA/Center for Drug Evaluation and Research
Last Updated: September 28, 2000
Originator: OTCOM/DLIS