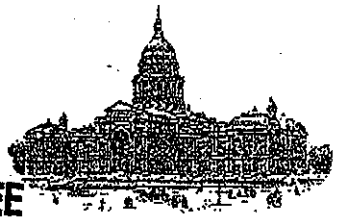
TEXAS HOUSE OF REPRESENTATIVES



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FRANK J. CORTE JR.

January 27, 2010

The Honorable Greg Abbott
Attorney General
State of Texas
P.O. Box 12548
Austin, Texas 78711-2548

FILE # ML-46320-10
I.D. # 46320

RQ-0859-GA

Re: Supplemental request to RQ-0829-GA

Dear General Abbott:

In RQ-0829-GA (October 5, 2009), I asked whether a license is needed for a facility to perform medical abortions. I would ask that, in answering that question, you would also address a closely related issue, to wit, whether drugs that are administered for the purpose of inducing an abortion must be ingested by the patient in the presence of the physician who has prescribed them for her. Based on information that has been brought to my attention, it appears that at least some abortion providers who offer medical abortions allow the prescribed abortifacients to be given (dispensed) to the patient outside the presence of the physician who prescribed them instead of in the presence of the physician. Based upon the statutes, regulations and protocols applicable to medical abortions, as set forth in detail in my request for an opinion (see pp. 3-5 and supporting materials), this practice would appear to be unlawful and unauthorized. In addition to the authorities cited in my original letter, I would briefly mention the following.

The Occupations Code provides, in relevant part:

> General Authority of Physician to Delegate. (a) A physician may delegate to a qualified and properly trained person acting under the physician's supervision any medical act that a reasonable and prudent physician would find within the scope of sound medical judgment to delegate if, in the opinion of the delegating physician:
>
> (1) the act:
>
> (A) can be properly and safely performed by the person to whom the medical act is delegated;
>
> (B) is performed in its customary manner; and

(C) *is not in violation of any other statute*; . . .

OCCUPATIONS CODE § 157.001(a)(1) (emphasis added). Section 245.010(b) of the Health & Safety Code provides that "only a physician as defined by Subtitle B, Title 3, Occupations Code, may perform an abortion." HEALTH & SAFETY CODE § 245.010(b). Accordingly, under the Occupations Code, as limited by the Health & Safety Code, a physician may not delegate the performance of an abortion to another health care professional. Drugs prescribed for the purposed of inducing an abortion must be administered and ingested in the presence of the physician who prescribed them. They may not be administered outside the presence of a physician, nor may they be ingested offsite instead of at the facility where they were dispensed.

Sincerely,

TEXAS HOUSE OF REPRESENTATIVES

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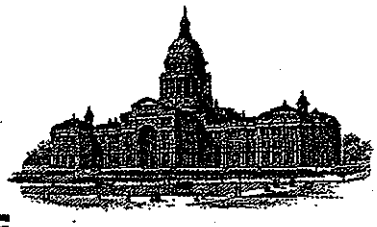

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October 5, 2009

FILE # ML-46195-09
I.D. # 46195

The Honorable Greg Abbott
Attorney General
State of Texas
P.O. Box 12548
Austin, Texas 78711-2548

Dear General Abbott:

As Chairman of the House Committee on Defense & Veterans' Affairs, I am requesting an Opinion from your office on the following question:

> Is a license needed for a facility to perform medical abortions?

Under the Texas Abortion Facility Reporting and Licensing Act, TEX. HEALTH & SAFETY CODE § 245.001 *et seq.*, no person may establish or operate an abortion facility in Texas without being licensed by the Texas Department of Health.[1] The Act defines "abortion facility" as "a place where abortions are performed."[2]

"Abortion," in turn, is defined as:

> an act or procedure performed after pregnancy has been medically verified and with the intent to cause the termination of a pregnancy other than for the purpose of either the birth of a live fetus or removing a dead fetus. The term does not include birth control devices or oral contraceptives.[3]

Only licensed physicians may perform abortions.[4]

Recently, the Texas Department of State Health Services was asked whether a license is needed for a facility to perform medical abortions. Currently, the only drug authorized by the FDA for

[1] TEX. HEALTH & SAFETY CODE § 245.003.
[2] *Id.* § 245.002(2))
[3] *Id.* § 245.002(1)
[4] *Id.* § 245.010(b)

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the express purpose of causing an abortion is Mifeprex (mifepristone), also known as RU-486. (Another FDA approved drug, methotrexate, a cancer treatment drug, is not labeled as an abortifacient, but it has been lawfully administered for that purpose for several years as an "off-label" use.) In a response to this question, Marc Allen Connelly, Deputy General Counsel for the Texas Department of State Health Services, stated as follows:

> As per statute, abortion is defined as an act or procedure performed with the intent to terminate the pregnancy.
>
> If a pregnant woman is given RU-486 at a facility and she ingests it at the facility and subsequently aborts the fetus at the facility, an abortion facility license is required.
>
> If, however, she is prescribed RU-486 or the pill is handed to her, and she leaves the facility, ingests the pill elsewhere, and aborts the fetus elsewhere, no abortion has occurred at the facility and no license is required.

Mr. Connelly then cited the statutory definitions of "abortion" and "abortion facility," TEX. HEALTH & SAFETY CODE §§ 245.002(1), (2), as well as the general licensing requirement, § 245.003. See Appendix 1 for a copy of Mr. Connelly's communication.

Mr. Connelly does not explain whether a license is required if the pregnant woman ingests RU-486 at the facility and subsequently aborts elsewhere, which is how the drug is typically administered and how it usually works. His communication appears to suggest that if a pregnant woman is given RU-486 at a facility, ingests it there, but aborts the fetus elsewhere, no abortion has occurred at the facility and no license is required.

A proper analysis of the applicable statutes and regulations indicates that the administration of RU-486 (or the administration of methotrexate for the same purpose) constitutes an "abortion" within the meaning of § 245.002(1), without regard to the location where the woman ingests the drug or where she subsequently aborts.

Analysis

The starting point for analysis is the language of the statute. An "abortion facility" is defined as "a place where abortions are performed"[5]. "Abortion," in turn, is defined in relevant part as "an act or procedure performed after pregnancy has been medically verified and with the intent to cause the termination of a pregnancy other than for the purpose of either the birth of a live fetus or removing a dead fetus"[6]. Thus, whether a facility should be considered an "abortion facility" depends on whether "abortions" are performed at the facility.

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[5] *Id.* § 245.002(2)
[6] *Id.* § 245.002(1)

Contrary to the implication of Mr. Connelly's communication, "abortion" is *not* defined in terms of where the *pregnancy* is terminated but, rather, where "an act or procedure" is performed "*with the intent to cause* the termination of a pregnancy..." (emphasis added). Two examples involving surgical abortions make this clear. Example one: assume that a physician begins a procedure that is intended to terminate a pregnancy (*e.g.*, a D&E procedure) but, because of an unforeseen complication (excessive bleeding), the patient must be transferred to a hospital where another physician completes the abortion. The physician who began the procedure has performed an "abortion" within the meaning of § 245.002(1). Example two: assume that a physician begins an induction abortion at one facility, by inserting laminaria into the pregnant woman's cervix, then completes the procedure by delivering the fetus at a hospital or an ambulatory surgical center two or three days later. He has performed an "abortion" within the meaning of § 245.002(1) at the first facility.

Just as a *procedure* performed "with the intent to cause the termination of a pregnancy" is an "abortion" without regard to where the abortion is completed, so too is an *act* (administering a drug to a patient) performed with the same intention (causing "the termination of a pregnancy") regardless of where the abortion is completed. In fact, the Texas Administrative Code, in its regulations governing medical abortions, refers to "the abortion *procedure*"[7] (emphasis added).

A careful examination of the applicable provisions of the Abortion Facility Reporting and Licensing Act leads to but one conclusion: administering a drug to a pregnant patient with the intention of causing the termination of her pregnancy is an "abortion" without regard to where the patient takes the drug or where she ultimately aborts her unborn child. Any other interpretation of the Act would subvert the purposes for which the Act was adopted: to regulate facilities where abortions are performed. Moreover, Mr. Connelly's interpretation of the Act would allow a physician (and the facility at which he administers an abortifacient) to evade the requirements of Texas law governing parental notice and consent[8] and informed consent[9], which contain similar definitions of abortion[10], as well as the abortion reporting requirement[11]. This would be contrary to both the statutes and the Act. (See also 25 TEX. ADMIN. CODE § 139.60(k)(1)). The Michigan Attorney General has similarly concluded that the administration of mifepristone constitutes an "abortion" under the applicable laws of the State of Michigan (see Appendix 2).

Apart from the foregoing, the hypothetical scenario discussed in Mr. Connelly's communication (the administration of a drug which is intended to cause an abortion and which is ingested offsite) is unlikely to occur. Texas law clearly contemplates that drugs used for abortifacient purposes are to be ingested by the pregnant patient in the presence of her physician. This is evident from the detailed regulations governing medical abortions.[12] Rule 139.53(b)(2) construed together with TEX. HEALTH & SAFETY CODE § 245.010(b) (prohibiting non-physicians

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[7] 25 TEX. ADMIN. CODE § 139.53(b)(2)
[8] TEX. FAMILY CODE § 33.002, TEX. OCCUPATIONS CODE § 164.052(a)(19)
[9] TEX. HEALTH & SAFETY CODE § 171.001, Subchapter B *et seq.*
[10] TEX. FAMILY CODE § 33.001, TEX. HEALTH & SAFETY CODE § 171.002
[11] Abortion Facility Reporting and Licensing Act, TEX. HEALTH & SAFETY CODE § 245.011
[12] 25 TEX. ADMIN. CODE § 139.53(b)

from performing abortions), allows only a physician, and not a person acting under his supervision or a registered nurse, to perform a medical abortion ("[a]ll medical and clinical services of the facility, with the exception of the abortion procedure, shall be provided under the direction of a physician or registered nurse who assumes responsibility for the clinical employees' performance in the facility").[13] That drugs (including those intended to cause abortion) must be ingested at the facility is apparent from the rule governing clinical records of abortion facilities, which provides: "The clinical record shall contain: ...medication administration records. Notations of all pharmaceutical agents shall include *the time and date administered*, the name of the individual administering the agent, and the signature of the person making the notation if different than the individual administering the agent....."[14] (emphasis added).

Moreover, the regimen established by the FDA and the manufacturer of RU-486 (Danco Laboratories) makes it clear that both Mifeprex (mifepristone) and misoprostol, which is taken two days after Mifeprex, are to be ingested *in the presence of the physician who has administered them.* According to the FDA (see Appendix 3):

> The approved Mifeprex regimen for a medical abortion through 49 day's pregnancy is:
>
> - Day One: Mifeprex Administration: 3 tablets of 200 mg of Mifeprex *orally at once*
> - Day Three: Misoprostol Administration: 2 tablets of 200 mcg of misoprostol *orally at once*
> - Day 14: Post-Treatment: the patient must return to confirm that a complete termination has occurred. If not, surgical termination is recommended to manage medical abortion treatment failures.

(emphasis added).

In a question and answer guide regarding Mifeprex (see Appendix 4), the FDA notes, "mifepristone is supplied directly to doctors who meet certain qualifications. It is not available in pharmacies, and it is not legally available over the Internet." Further, physicians who meet those qualifications "must agree to other responsibilities, such as dispensing the Medication Guide...."

The Medication Guide (see Appendix 5), which is provided to the patient, specifies that the tablets of Mifeprex (mifepristone) and misoprostol are to be taken "*at your provider's office*"[15] (emphasis added). This requirement is repeated in the medication label under the directions for Dosage and Administration, which note that "[t]reatment with Mifeprex and misoprostol for the

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[13] *See also* Rule 139.53(b)(3)(A), referring to "the physician(s) providing medical abortion"
[14] 25 TEX. ADMIN. CODE § 139.55(c)(13)
[15] Appendix 5, http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/020687s013lbl.pdf, p. 16

termination of pregnancy requires three office visits by the patient," and specify that "Mifeprex may be administered only in a clinic, medical office, or hospital, by or under the supervision of a physician, able to assess the gestational age of an embryo and to diagnose ectopic pregnancies."[16]

The Patient Agreement[17] (see Appendix 5) expressly states:

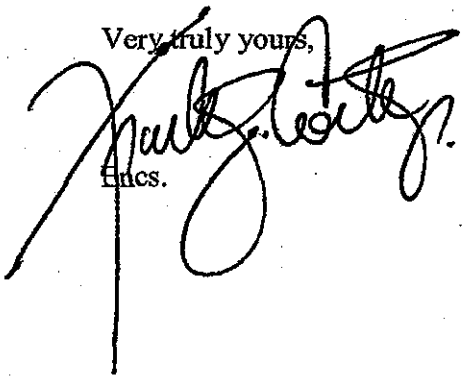
> I understand that I will take Mifeprex *in my provider's office* (Day 1).
>
> I understand that I will take misoprostol *in my provider's office* two days after I take Mifeprex (Day 3)

(emphasis added). The Prescriber's Agreement (Appendix 6) requires the prescribing physician to administer Mifeprex in a manner consistent with the foregoing specifications. It should be noted that the Texas Administrative Code states that "[a] licensed abortion facility shall be in compliance with all state and federal laws pertaining to handling of drugs."[18]

Conclusion

In light of the foregoing, the administration of a drug to a pregnant patient for the purpose of terminating a pregnancy ("other than for the purpose of either the birth of a live fetus or removing a dead fetus") constitutes an "abortion," as that term is defined in the Texas Abortion Facility Reporting and Licensing Act, TEX. HEALTH & SAFETY CODE § 245.002(1), without regard to where the patient ingests the drug or where she ultimately aborts her unborn child. Accordingly, subject to the exemptions set forth in § 245.004 of the Act, any place where such drugs are administered is properly classified as an "abortion facility" under § 245.002(2), and must be licensed under the Act.

Very truly yours,



Encs.

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[16] *Id.* p. 13
[17] *Id* p. 19
[18] 25 TEX. ADMIN. CODE § 139.60(a)

MIFEPREX™
(Mifepristone) Tablets, 200 mg

PRESCRIBER'S AGREEMENT

We are pleased that you wish to become a provider of Mifeprex* (Mifepristone) Tablets, 200 mg, which is indicated for the medical termination of intrauterine pregnancy through 49 days from the first day of the patient's last menstrual period (see full prescribing information). Prescribing Information, Mifeprex Medication Guides and PATIENT AGREEMENT forms will be provided together with your order of Mifeprex.

Prior to establishing your account and receiving your first order, you must sign and return this letter to the distributor, indicating that you have met the qualifications outlined below and will observe the guidelines outlined below. If you oversee more than one office facility, you will need to list each facility on your order form prior to shipping the first order.

By signing the reverse side, you acknowledge receipt of the PRESCRIBER'S AGREEMENT and agree that you meet these qualifications and that you will follow these guidelines for use. You also understand that if you do not follow these guidelines, the distributor may discontinue distribution of the drug to you.

Under Federal law, 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 others, 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. The prescribing information is attached to this letter, and is also available by calling our toll free number, 1-877-4 Early Option (1-877-432-7596), or logging on to our website, www.earlyoptionpill.com.

In addition to these qualifications, you must provide Mifeprex in a manner consistent with the following guidelines.

- Under Federal law, each patient must be provided with a Medication Guide. You 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 them, obtain her signature on the PATIENT AGREEMENT, and sign it yourself.
- The patient's follow-up visit at approximately 14 days is very important to confirm that a complete termination of pregnancy has occurred and that there have been no complications. You must notify Danco Laboratories in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the

event of an on-going pregnancy which is not terminated subsequent to the conclusion of the treatment procedure.

- While serious adverse events associated with the use of Mifeprex are rare, you must report any hospitalization, transfusion or other serious event to Danco Laboratories, identifying the patient solely by package serial number to ensure patient confidentiality.
- Each package of Mifeprex has a serial number. As part of maintaining complete records for each patient, you must record this serial number in each patient's record.

Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596)
www.earlyoptionpill.com

Drugs

Mifeprex (mifepristone) Information

Mifeprex is used, together with another medication called misoprostol, to end an early pregnancy (within 49 days of the start of a woman's last menstrual period). Since its approval in September 2000, the Food and Drug Administration has received reports of serious adverse events, including several deaths, in the United States following medical abortion with mifepristone and misoprostol. Each time FDA receives a report of a serious adverse event or death after medical abortion with these drugs, the agency carefully analyzes the available scientific information to determine whether or not the serious adverse event or death is related to the use of the drugs.

As previously reported by the agency, several of the women who died in the United States died from sepsis (severe illness caused by infection of the bloodstream) after medical abortion with mifepristone and misoprostol. Sepsis is a known risk related to any type of abortion. Most of these women were infected with the same type of bacteria, known as *Clostridium sordellii*. The symptoms in these cases of infection were not the usual symptoms of sepsis. We do not know whether using mifepristone and misoprostol caused these deaths.

Patients should contact a healthcare practitioner right away if they have taken these medications for medical abortion and develop stomach pain or discomfort, or have weakness, nausea, vomiting or diarrhea with or without fever, more than 24 hours after taking the misoprostol. These symptoms, even without a fever, may indicate sepsis. Patients should make sure their healthcare practitioner knows they are undergoing a medical abortion.

All providers of medical abortion and emergency room healthcare practitioners should investigate the possibility of sepsis in women who are undergoing medical abortion and present with nausea, vomiting, or diarrhea and weakness with or without abdominal pain. These symptoms even without a fever may indicate a hidden infection. Strong consideration should be given to obtaining a complete blood count in these patients. Significant leukocytosis with a marked left shift and hemoconcentration may be indicative of sepsis.

FDA recommends that healthcare practitioners have a high index of suspicion for serious infection and sepsis in patients with this presentation and consider immediately initiating treatment with antibiotics that includes coverage of anaerobic bacteria such as *Clostridium sordellii*.

FDA does not have sufficient information to recommend the use of prophylactic antibiotics for women having a medical abortion. Reports of fatal sepsis in women undergoing medical abortion are very rare (approximately 1 in 100,000). Prophylactic antibiotic use carries its own risk of serious adverse events such as severe or fatal allergic reactions. Also, prophylactic use of antibiotics can stimulate the growth of "superbugs," bacteria

resistant to everyday antibiotics. Finally, it is not known which antibiotic and regimen (what dose and for how long) will be effective in cases such as the ones that have occurred.

These recommendations are consistent with warnings in the Prescribing Information and information for the patient in the Medication Guide for Mifeprex.

The approved Mifeprex regimen for a medical abortion through 49 day's pregnancy is:

- Day One: Mifeprex Administration: 3 tablets of 200 mg of Mifeprex orally at once
- Day Three: Misoprostol Administration: 2 tablets of 200 mcg of misoprostol orally at once
- Day 14: Post-Treatment: The patient must return to confirm that a complete termination has occurred. If not, surgical termination is recommended to manage medical abortion treatment failures.

The safety and effectiveness of other Mifeprex dosing regimens, including use of oral misoprostol tablets intravaginally, has not been established by the FDA.

On May 11, 2006, FDA, in conjunction with the Centers for Disease Control and Prevention (CDC) and the National Institute of Allergy and Infectious Diseases (NIAID), conducted a public workshop. This workshop, entitled "Emerging Clostridial Disease," discussed the scientific and medical circumstances associated with reports of morbidity and mortality with *Clostridium sordellii* and *Clostridium difficile* infections.

- Questions and Answers (issued 8/29/2007)
- Mifeprex Label [PDF] (approved 7/19/2005)
  - Medication Guide [PDF]
  - Patient Agreement [PDF]

Historical Information

Do Not Buy Mifeprex Over the Internet

- You should not buy Mifeprex over the Internet because you will bypass important safeguards designed to protect your health (and the health of others).
- Mifeprex has special safety restrictions on how it is distributed to the public. Also, drugs purchased from foreign Internet sources are not the FDA-approved versions of the drugs, and they are not subject to FDA-regulated manufacturing controls or FDA inspection of manufacturing facilities.

To learn more about buying drugs safely, please see

- Buying Prescription Medicines Online: A Consumer Safety Guide.

Drugs

Mifeprex Questions and Answers (issued 8/29/2007)

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:

- an ectopic 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 available in pharmacies, and it is not legally available over the Internet.

5. Why are there restrictions for this drug?

FDA's approval of mifepristone is based on studies of mifepristone that were conducted by doctors who had certain qualifications. Both the drug's 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 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. 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.

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

State law determines whether there are any restrictions on minors obtaining surgical or medical abortions.

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

The studies that FDA evaluated when it approved mifepristone included women ages 18-45.

10. 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.

11. What is a Medication Guide?

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

12. Why did FDA develop a Medication Guide for Mifeprex?

FDA determined that a Medication Guide was necessary for women to be able to use Mifeprex effectively and safely. It is important for women to be fully informed about how Mifeprex 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.

13. 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.

14. 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.

15. How much does mifepristone cost?

Manufacturers establish prices for prescription drugs. FDA has no input into or jurisdiction over drug pricing.

16. 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.

17. What serious adverse events have been reported after mifepristone use?

FDA has received reports of ectopic pregnancy (a pregnancylocated outside of the womb, such as in the fallopian tubes), including one case of ectopic pregnancy resulting in death; several cases of severe systemic infection (also called sepsis), including several deaths; and a single case of non-fatal heart attack. At this time, it is unknown whether there is a causal relationship between any of these events and the use of Mifeprex and misoprostol.

In many of these cases, misoprostol was given vaginally, not orally; under the approved regimen, misoprostol is given orally. FDA has not reviewed data on the safety and effectiveness of vaginal administration of misoprostol.

As with all approved drugs, when FDA receives new information regarding adverse events, the agency reviews the new information and, as appropriate, provides updates to doctors and their patients so that they have information on how to use the drug safely.

18. What does FDA know about serious infections reported with Mifeprex use?

Since the approval of Mifeprex in September 2000, FDA has been informed of six deaths in the United States due to serious infections following medical abortion with mifepristone and misoprostol that FDA has concluded may possibly be related to the use of these drugs. These women died from sepsis (serious infection involving the bloodstream). Five cases were found to involve infection with bacteria known as *Clostridium sordellii* and one case involved infection with *Clostridium perfringens*. Sepsis is a known risk related to any type of abortion. The symptoms in all of these cases of serious infection were not the usual symptoms of sepsis. We do not know whether using Mifeprex and misoprostol caused these deaths. In all but one case, the misoprostol was used intravaginally.

19. What are *Clostridium sordellii* and *Clostridium perfringens*?

Clostridium sordellii and *Clostridium perfringens* are bacteria that are anaerobic (they can live without oxygen) and that in very rare cases can produce toxins that are rapidly fatal. Rare infections with *C. sordellii* can occur following childbirth (both by vaginal delivery and by caesarian section), as well as following medical abortions. *C. sordellii* infections can also occur rarely with pelvic, abdominal or bone (orthopedic) surgery, and deep skin infections.

It is unclear exactly what factors cause the bacteria to produce the toxins.

20. Why are serious infections included in the WARNINGS section of the Mifeprex labeling?

All providers of medical abortion and emergency room healthcare practitioners should investigate the possibility of sepsis in women who are undergoing medical abortion and present with nausea, vomiting, or diarrhea and weakness with or without abdominal pain. These symptoms, even without a fever, may indicate a hidden infection. Strong consideration should be given to obtaining a complete blood count in these patients. Significant leukocytosis with a marked left shift and hemoconcentration may be indicative of sepsis.

21. Why are women using misoprostol vaginally?

The FDA-approved regimen for medical abortion consists of taking 600 mg (three 200 mg tablets) of oral mifepristone on Day One and 400 mcg (two 200

mcg tablets) of oral misoprostol on Day Three. FDA is aware that medical practitioners may be using modified regimens, including prescribing different doses of mifepristone and misoprostol, dosing misoprostol on a different day, and advising the woman that the oral misoprostol tablets may be inserted into the vagina. While some of the modified regimens have been well described in the literature, the safety and effectiveness of Mifeprex dosing regimens, other than the one approved by FDA, including use of oral misoprostol intravaginally, has not been established by the FDA.

22. Does the vaginal use of oral misoprostol tablets in medical abortion cause infection?

FDA has no evidence that vaginal use of misoprostol causes infection. The companies making misoprostol tablets have performed and met the usual quality control tests for marketing misoprostol oral tablets.

For four of the fatal cases of *C. sordellii* sepsis, FDA has tested batches of mifepristone and misoprostol and has not found any contamination with the type of bacteria involved.

23. Should women undergoing medical abortion be getting antibiotics to prevent fatal infections?

At this time, FDA does not have sufficient information to recommend the use of preventive antibiotics for all women undergoing medical abortion. Reports of fatal sepsis in women undergoing medical abortion are very rare (1 in 100,000). Preventive antibiotic use carries its own risk of serious adverse events such as severe or fatal allergic reactions. Also, preventive use of antibiotics can stimulate the growth of "superbugs," bacteria resistant to everyday antibiotics. While FDA cannot recommend preventive antibiotics, we advise healthcare practitioners to be vigilant so that patients suspected of having an infection are immediately given antibiotics that would treat infections with bacteria such as *C. sordellii*.

24. What steps are being taken to investigate new cases of serious infection?

FDA works with the Centers for Disease Control and the manufacturer of Mifeprex to investigate all cases of serious infection that are reported following the use of Mifeprex and misoprostol.

25. What is a ruptured ectopic pregnancy and how often does this happen?

An ectopic pregnancy is any pregnancy that develops outside of the womb. It occurs in 2% of all pregnancies. The ectopic pregnancy is usually located in one of the fallopian tubes. As the fetus grows, it damages the tube, causing it to rupture (burst) and bleed. Unless they are discovered and treated early, almost 40% of ectopic pregnancies rupture suddenly, causing pain and dangerous bleeding in the abdominal cavity. The other 60% usually cause slow bleeding in the abdomen. Ruptured ectopic pregnancies can be fatal. According to data

gathered by the Centers for Disease Control from death certificates in the U.S., 237 women were reported to have died of ectopic pregnancies between 1991 and 1999.

The Mifeprex labeling states that the use of Mifeprex and misoprostol for the termination of pregnancy is contraindicated in patients with confirmed or suspected ectopic pregnancy. Mifeprex is not an effective treatment for an ectopic pregnancy.

26. Are there any reports of heart attacks following use of mifepristone with drugs other than misoprostol?

In other countries, in the early 1990's, three prostaglandins, misoprostol, sulprostone, and gemeprost, were used with mifepristone to terminate pregnancy. Heart attacks due to coronary spasm, one of them fatal, were reported in three of the more than 60,000 women given sulprostone (an injected prostaglandin) with mifepristone in other countries. As a result, sulprostone is no longer used in combination with mifepristone for medical abortion. Two cases of coronary spasm, one resulting in a heart attack, were reported for gemeprost when used in combination with mifepristone for medical abortion. Neither sulprostone nor gemeprost are approved for use in the U.S.

27. Is FDA considering withdrawing Mifeprex from the market?

At this time, FDA believes that the benefits of Mifeprex outweigh the risks. As it does with all prescription drugs, FDA continues to monitor the safety and effectiveness of mifepristone.

MIFEPREX® (mifepristone) Tablets, 200 mg
For Oral Administration Only

Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following Mifeprex* use. No causal relationship between the use of Mifeprex and misoprostol and these events has been established. Before prescribing Mifeprex, inform the patient about the risk of these serious events and discuss the MEDICATION GUIDE and the PATIENT AGREEMENT. Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, if she experiences sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if she experiences abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhea) more than 24 hours after taking misoprostol.

- Atypical Presentation of Infection. Patients with serious bacterial infections (e.g. *Clostridium sordellii*) and sepsis can present without fever, bacteremia or significant findings on pelvic examination following an abortion. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. A high index of suspicion is needed to rule out serious infection and sepsis (see WARNINGS).

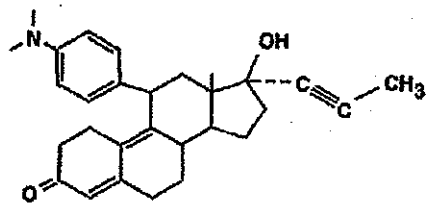
- Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. Advise patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding (see WARNINGS).

Patients should be advised to take their MEDICATION GUIDE with them if they visit an emergency room or another health care provider who did not prescribe Mifeprex, so that provider will be aware that the patient is undergoing a medical abortion.

DESCRIPTION

Mifeprex tablets each contain 200 mg of mifepristone, a synthetic steroid with antiprogestational effects. The tablets are light yellow in color, cylindrical and biconvex, and are intended for oral administration only. The tablets include the inactive ingredients colloidal silica anhydrous, corn starch, povidone, microcrystalline cellulose, and magnesium stearate.

Mifepristone is a substituted 19-nor steroid compound chemically designated as 11ß-[*p*-(Dimethylamino)phenyl]-17ß-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one. Its empirical formula is $C_{29}H_{35}NO_2$. Its structural formula is:



The compound is a yellow powder with a molecular weight of 429.6 and a melting point of 192-196°C. It is very soluble in methanol, chloroform and acetone and poorly soluble in water, hexane and isopropyl ether.

* Mifeprex is a registered trademark of Danco Laboratories, LLC.

CLINICAL PHARMACOLOGY

Pharmacodynamic Activity

The anti-progestational activity of mifepristone results from competitive interaction with progesterone at progesterone-receptor sites. Based on studies with various oral doses in several animal species (mouse, rat, rabbit and monkey), the compound inhibits the activity of endogenous or exogenous progesterone. The termination of pregnancy results.

Doses of 1 mg/kg or greater of mifepristone have been shown to antagonize the endometrial and myometrial effects of progesterone in women. During pregnancy, the compound sensitizes the myometrium to the contraction-inducing activity of prostaglandins.

Mifepristone also exhibits antiglucocorticoid and weak antiandrogenic activity. The activity of the glucocorticoid dexamethasone in rats was inhibited following doses of 10 to 25 mg/kg of mifepristone. Doses of 4.5 mg/kg or greater in human beings resulted in a compensatory elevation of adrenocorticotropic hormone (ACTH) and cortisol. Antiandrogenic activity was observed in rats following repeated administration of doses from 10 to 100 mg/kg.

Pharmacokinetics and Metabolism

Absorption

Following oral administration of a single dose of 600 mg, mifepristone is rapidly absorbed, with a peak plasma concentration of 1.98 mg/l occurring approximately 90 minutes after ingestion. The absolute bioavailability of a 20 mg oral dose is 69%.

Distribution

Mifepristone is 98% bound to plasma proteins, albumin and α_1-acid glycoprotein. Binding to the latter protein is saturable, and the drug displays nonlinear kinetics with respect to plasma concentration and clearance. Following a distribution phase, elimination of mifepristone is slow at first (50% eliminated between 12 and 72 hours) and then becomes more rapid with a terminal elimination half-life of 18 hours.

Metabolism

Metabolism of mifepristone is primarily via pathways involving N-demethylation and terminal hydroxylation of the 17-propynyl chain. *In vitro* studies have shown that CYP450 3A4 is primarily responsible for the metabolism. The three major metabolites identified in humans are: (1) RU 42 633, the most widely found in plasma, is the N-monodemethylated metabolite; (2) RU 42 848, which results from the loss of two methyl groups from the 4-dimethylaminophenyl in position 11ß; and (3) RU 42 698, which results from terminal hydroxylation of the 17-propynyl chain.

Excretion

By 11 days after a 600 mg dose of tritiated compound, 83% of the drug has been accounted for by the feces and 9% by the urine. Serum levels are undetectable by 11 days.

Special Populations

The effects of age, hepatic disease and renal disease on the safety, efficacy and pharmacokinetics of mifepristone have not been investigated.

Clinical Studies

Safety and efficacy data from the U.S. clinical trials and from two French trials of mifepristone are reported below. The U.S. trials provide safety data on 859 women and efficacy data on 827 women with gestation durations of 49 days or less (dated from the first day of the last menstrual period). In the two French clinical trials, safety evaluable data are available for 1800 women, while efficacy information is available for 1681 of these women. Success was defined as the complete expulsion of the products of conception without the need for surgical intervention. The overall rates of success and failure, shown by reason for failure, for the U.S. and French studies appear in Table 1.

In the U.S. trials, 92.1% of the 827 subjects had a complete medical abortion, as shown in Table 1. In 52 women (6.3%) expulsion occurred within two days, and resulted from the action of mifepristone (600 mg) alone, unaided by misoprostol, an analog of prostaglandin E_1. All other women without an apparent expulsion took a 400 µg dose of misoprostol two days after taking mifepristone. Many women (44.1%) in the U.S. trials expelled the products of conception within four hours after taking misoprostol and 62.8% experienced expulsion within 24 hours after the misoprostol administration. There were 65 women (7.9%) who received surgical interventions: 13 (1.6%) were medically indicated interventions during the study period, mostly for excessive bleeding; five (0.6%) interventions occurred at the patient's request; 39 women (4.7%) had incomplete abortions at the end of the study protocol; and eight (1.0%) had ongoing pregnancies at the end of the study protocol.

Women who participated in the U.S. trials reflect the racial and ethnic composition of American women. The majority of women (71.4%) were Caucasian, while 11.3% were African American, 10.9% were East Asian, and 4.7% were Hispanic. A small percentage (1.7%) belonged to other racial or ethnic groups. Women aged 18 to 45 were enrolled in the trials. Nearly two-thirds (66.0%) of the women were under 30 years old with a mean age of 27 years.

In the French trials, complete medical abortion occurred in 95.5% of the 1681 subjects, as shown in Table 1. In 89 women (5.3%), complete abortion occurred within two days of taking mifepristone (600 mg). About half of the women (50.3%) in the French trials expelled the products of conception during the first four hours immediately following administration of misoprostol and 72.3% experienced expulsion within 24 hours after taking misoprostol. In total, 4.5% of women in the French trials ultimately received surgical intervention for excessive bleeding, incomplete abortions, or ongoing pregnancies at the end of the protocol.

Table 1

Outcome Following
Treatment with Mifepristone and Misoprostol in the U.S. and French Trials

	U.S. Trials		French Trials	
	N	%	N	%
Complete medical abortion	**762**	**92.1**	**1605**	**95.5**
Timing of expulsion				
Before second visit	52	(6.3)	89	(5.3)
During second visit				
– less than 4 hrs after misoprostol	365	(44.1)	846	(50.3)
After second visit				
– greater than 4 hrs but less than 24 hrs after misoprostol	155	(18.7)	370	(22.0)
– greater than 24 hrs after misoprostol	68	(8.2)	145	(8.6)
Time of expulsion unknown	122	(14.8)	155	(9.2)
Surgical intervention	**65**	**7.9**	**76**	**4.5**
Reason for surgery				
Medically necessary interventions during the study period	13	(1.6)	NA	(NA)
Patient request	5	(0.6)	NA	(NA)
Treatment of bleeding during study	NA	(NA)	6	(0.3)
Incomplete expulsion at study end	39	(4.7)	48	(2.9)
Ongoing pregnancy at study end	8	(1.0)	22	(1.3)
Total	**827**	**100**	**1681**	**100**

Note: Mifepristone 600 mg oral was administered on Day 1, misoprostol 400 µg oral was given on Day 3 (second visit).

INDICATION AND USAGE

Mifeprex is indicated for the medical termination of intrauterine pregnancy through 49 days' pregnancy. For purposes of this treatment, pregnancy is dated from the first day of the last menstrual period in a presumed 28 day cycle with ovulation occurring at mid-cycle. The duration of pregnancy may be determined from menstrual history and by clinical examination. Ultrasonographic scan should be used if the duration of pregnancy is uncertain, or if ectopic pregnancy is suspected.

Any intrauterine device ("IUD") should be removed before treatment with Mifeprex begins.

Patients taking Mifeprex must take 400 µg of misoprostol two days after taking mifepristone unless a complete abortion has already been confirmed before that time (see DOSAGE AND ADMINISTRATION).

Pregnancy termination by surgery is recommended in cases when Mifeprex and misoprostol fail to cause termination of intrauterine pregnancy (see PRECAUTIONS).

CONTRAINDICATIONS

Administration of Mifeprex and misoprostol for the termination of pregnancy (the "treatment procedure") is contraindicated in patients with any one of the following conditions:

- Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass (the treatment procedure will not be effective to terminate an ectopic pregnancy) (see WARNINGS);
- IUD in place (see INDICATION AND USAGE);
- Chronic adrenal failure;
- Concurrent long-term corticosteroid therapy;
- History of allergy to mifepristone, misoprostol or other prostaglandin;
- Hemorrhagic disorders or concurrent anticoagulant therapy;
- Inherited porphyrias.

Because it is important to have access to appropriate medical care if an emergency develops, the treatment procedure is contraindicated if a patient does not have adequate access to medical facilities equipped to provide emergency treatment of incomplete abortion, blood transfusions, and emergency resuscitation during the period from the first visit until discharged by the administering physician.

Mifeprex also should not be used by any patient who may be unable to understand the effects of the treatment procedure or to comply with its regimen. Patients should be instructed to review the MEDICATION GUIDE and the PATIENT AGREEMENT provided with Mifeprex carefully and should be given a copy of the product label for their review. Patients should discuss their understanding of these materials with their health care providers, and retain the MEDICATION GUIDE for later reference (see PRECAUTIONS).

WARNINGS

Patients must be monitored and undergo appropriate medical evaluation and intervention should any of the following serious adverse events occur following a spontaneous, surgical, or medical abortion, including following Mifeprex use:

1. Vaginal Bleeding

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

According to data from the U.S. and French trials, women should expect to experience vaginal bleeding or spotting for an average of nine to 16 days, while up to 8% of all subjects may experience some type of bleeding for 30 days or more. Bleeding was reported to last for 69 days in one patient in the French trials. In general, the duration of bleeding and spotting increased as the duration of the pregnancy increased.

Excessive vaginal bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, curettage, administration of saline infusions, and/or blood transfusions. In the U.S. trials, 4.8% of subjects received administration of uterotonic medications and nine women (1.0%) received intravenous fluids. Vasoconstrictor drugs were used in 4.3% of all subjects in the French trials, and in 5.5% of women there was a decrease in hemoglobin of more than 2 g/dL. Blood transfusions were administered in one of 859 subjects in the U.S. trials and in two of 1800 subjects in the French trials. Since heavy bleeding requiring curettage occurs in about 1% of patients, special care should be given to patients with hemostatic disorders, hypocoagulability, or severe anemia.

2. Infection and Sepsis

As with other types of abortion, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of Mifeprex (see BOXED WARNINGS). No causal relationship between these events and the use of Mifeprex and misoprostol has been established. Physicians evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event. In particular, a sustained fever of 100.4°F or higher, severe abdominal pain, or pelvic tenderness in the days after a medical abortion may be an indication of infection.

A high index of suspicion is needed to rule out sepsis (from e.g. *Clostridium sordellii*) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhea) more than 24 hours after taking misoprostol. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. These deaths occurred in women who used vaginally administered misoprostol, but no causal relationship between vaginal misoprostol use and an increased risk of infection or death has been established. *Clostridium sordellii* infections have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynecologic and non-gynecologic conditions.

3. Confirmation of Pregnancy Termination

Patients should be scheduled for and return for a follow-up visit at approximately 14 days after administration of Mifeprex to confirm that the pregnancy is completely terminated and to assess the

degree of bleeding. Termination can be confirmed by clinical examination or ultrasonographic scan. Lack of bleeding following treatment usually indicates failure; however, prolonged or heavy bleeding is not proof of a complete abortion. Medical abortion failures should be managed with surgical termination. Advise the patient whether you will provide such care or will refer her to another provider as part of counseling prior to prescribing Mifeprex.

4. Ectopic Pregnancy
Mifeprex is contraindicated in patients with a confirmed or suspected ectopic pregnancy since Mifeprex is not effective for terminating these pregnancies (see CONTRAINDICATIONS). Physicians should remain alert to the possibility that a patient who is undergoing a medical abortion could have an undiagnosed ectopic pregnancy since some of the expected symptoms of a medical abortion may be similar to those of a ruptured ectopic pregnancy. The presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed Mifeprex.

PRECAUTIONS

General

Mifeprex is available only in single dose packaging. Administration must be under the supervision of a qualified physician (see DOSAGE AND ADMINISTRATION).

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

There are no data on the safety and efficacy of mifepristone in women with chronic medical conditions such as cardiovascular, hypertensive, hepatic, respiratory or renal disease; insulin-dependent diabetes mellitus; severe anemia or heavy smoking. Women who are more than 35 years of age and who also smoke 10 or more cigarettes per day should be treated with caution because such patients were generally excluded from clinical trials of mifepristone.

Although there is no clinical evidence, the effectiveness of Mifeprex may be lower if misoprostol is administered more than two days after mifepristone administration.

Information for Patients

Patients should be fully advised of the treatment procedure and its effects. Patients should be given a copy of the MEDICATION GUIDE and the PATIENT AGREEMENT. (Additional copies of the MEDICATION GUIDE and the PATIENT AGREEMENT are available by contacting Danco Laboratories at 1-877-4 Early Option) (1-877-432-7596). Patients should be advised to review both the MEDICATION GUIDE and the PATIENT AGREEMENT, and should be given the opportunity to discuss them and obtain answers to any questions they may have prior to receiving Mifeprex. Patients should be advised to take their MEDICATION GUIDE with them if they visit an emergency room or another health care provider who did not prescribe Mifeprex, so that provider will be aware that the patient is undergoing a medical abortion.

Each patient must understand:

- the necessity of completing the treatment schedule, including a follow-up visit approximately 14 days after taking Mifeprex;
- that vaginal bleeding and uterine cramping probably will occur;
- that prolonged heavy vaginal bleeding is not proof of a complete abortion;

- that if the treatment fails, there is a risk of fetal malformation;
- that medical abortion treatment failures are managed by surgical termination; and
- the steps to take in an emergency situation, including precise instructions and a telephone number that she can call if she has any problems or concerns.

Another pregnancy can occur following termination of pregnancy and before resumption of normal menses. Contraception can be initiated as soon as the termination of the pregnancy has been confirmed, or before the woman resumes sexual intercourse.

Patient information is included with each package of Mifeprex (see MEDICATION GUIDE).

Laboratory Tests

Clinical examination is necessary to confirm the complete termination of pregnancy after the treatment procedure. Changes in quantitative human Chorionic Gonadotropin (hCG) levels will not be decisive until at least 10 days after the administration of Mifeprex. A continuing pregnancy can be confirmed by ultrasonographic scan.

The existence of debris in the uterus following the treatment procedure will not necessarily require surgery for its removal.

Decreases in hemoglobin concentration, hematocrit and red blood cell count occur in some women who bleed heavily. Hemoglobin decreases of more than 2 g/dL occurred in 5.5% of subjects during the French clinical trials of mifepristone and misoprostol.

Clinically significant changes in serum enzyme (serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase, gamma-glutamyltransferase (GT)) activities were rarely reported.

Drug Interactions

Although specific drug or food interactions with mifepristone have not been studied, on the basis of this drug's metabolism by CYP 3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum levels of mifepristone). Furthermore, rifampin, dexamethasone, St. John's Wort, and certain anticonvulsants (phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum levels of mifepristone).

Based on *in vitro* inhibition information, coadministration of mifepristone may lead to an increase in serum levels of drugs that are CYP 3A4 substrates. Due to the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP 3A4 substrates and have narrow therapeutic range, including some agents used during general anesthesia.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies to evaluate the carcinogenic potential of mifepristone have been performed. Results from studies conducted *in vitro* and in animals have revealed no genotoxic potential for mifepristone. Among the tests carried out were: Ames test with and without metabolic activation; gene conversion test in *Saccharomyces cerevisiae* D4 cells; forward mutation in *Schizosaccharomyces pompe* P1 cells; induction of unscheduled DNA synthesis in cultured HeLa cells; induction of chromosome aberrations in CHO cells; *in vitro* test for gene mutation in V79 Chinese hamster lung cells; and micronucleus test in mice.

The pharmacological activity of mifepristone disrupts the estrus cycle of animals, precluding studies designed to assess effects on fertility during drug administration. Three studies have been performed in rats to determine whether there were residual effects on reproductive function after termination of the drug exposure.

In rats, administration of the lowest oral dose of 0.3 mg/kg/day caused severe disruption of the estrus cycles for the three weeks of the treatment period. Following resumption of the estrus cycle, animals were mated and no effect on reproductive performance was observed. In a neonatal exposure study in rats, the administration of a subcutaneous dose of mifepristone up to 100 mg/kg on the first day after birth had no adverse effect on future reproductive function in males or females. The onset of puberty was observed to be slightly premature in female rats neonatally exposed to mifepristone. In a separate study in rats, oviduct and ovary malformations in female rats, delayed male puberty, deficient male sexual behavior, reduced testicular size, and lowered ejaculation frequency were noted after exposure to mifepristone (1 mg every other day) as neonates.

Pregnancy

Mifepristone is indicated for use in the termination of pregnancy (through 49 days' pregnancy) and has no other approved indication for use during pregnancy.

Teratogenic Effects

Human Data

As of September 2000, over 620,000 women in Europe had taken mifepristone in combination with a prostaglandin to terminate pregnancy. Among these 620,000 women, about 415,000 received mifepristone together with misoprostol. As of May 2000 a total of 82 cases had been reported in which women with on-going pregnancies after using mifepristone alone or mifepristone followed by misoprostol declined to have a surgical procedure at that time. These cases are summarized in Table 2.

Table 2

Reported Cases (as of May 2000) of On-going Pregnancies Not Terminated by Surgical Abortion at the End of Treatment with Mifepristone Alone or with Mifepristone-Misoprostol

	Mifepristone Alone	Mifepristone-Misoprostol	Total
Subsequently had surgical abortion	**3**	**7**	**10**
No abnormalities detected	*2*	*7*	*9*
Abnormalities detected (sirenomelia, cleft palate)	*1*	*0*	*1*
Subsequently resulted in live birth	**13**	**13**	**26**
No abnormalities detected at birth	*13*	*13*	*26*
Abnormalities detected at birth	*0*	*0*	*0*
Other/Unknown	**26**	**20**	**46**
Total	**42**	**40**	**82**

Several reports in the literature indicate that prostaglandins, including misoprostol, may have teratogenic effects in human beings. Skull defects, cranial nerve palsies, delayed growth and psychomotor development, facial malformation and limb defects have all been reported after exposure during the first trimester.

Animal Data

Teratology studies in mice, rats and rabbits at doses of 0.25 to 4.0 mg/kg (less than 1/100 to approximately 1/3 the human exposure level based on body surface area) were carried out. Because of the antiprogestational activity of mifepristone, fetal losses were much higher than in control animals. Skull deformities were detected in rabbit studies at approximately 1/6 the human exposure, although no teratogenic effects of mifepristone have been observed to date in rats or mice. These deformities were most likely due to the mechanical effects of uterine contractions resulting from decreased progesterone levels.

Nonteratogenic Effects

The indication for use of Mifeprex in conjunction with misoprostol is for the termination of pregnancy through 49 days' duration of pregnancy (as dated from the first day of the last menstrual period). These drugs together disrupt pregnancy by causing decidual necrosis, myometrial contractions and cervical softening, leading to the expulsion of the products of conception.

Nursing Mothers

It is not known whether mifepristone is excreted in human milk. Many hormones with a similar chemical structure, however, are excreted in breast milk. Since the effects of mifepristone on infants are unknown, breast-feeding women should consult with their health care provider to decide if they should discard their breast milk for a few days following administration of the medications.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The treatment procedure is designed to induce the vaginal bleeding and uterine cramping necessary to produce an abortion. Nearly all of the women who receive Mifeprex and misoprostol will report adverse reactions, and many can be expected to report more than one such reaction. About 90% of patients report adverse reactions following administration of misoprostol on day three of the treatment procedure. Those adverse events that occurred with a frequency greater than or equal to 1% in the U.S. and French trials are shown in Table 3.

Vaginal bleeding and uterine cramping are expected consequences of the action of Mifeprex as used in the treatment procedure. Following administration of mifepristone and misoprostol in the French clinical studies, 80 to 90% of women reported bleeding more heavily than they do during a heavy menstrual period (see WARNINGS, Vaginal Bleeding). Women also typically experience abdominal pain, including uterine cramping. Other commonly reported side effects were nausea, vomiting and diarrhea. Some adverse reactions reported during the four hours following administration of misoprostol were judged by women as being more severe than others: the percentage of women who considered any particular adverse event as severe ranged from 2 to 35% in the U.S. and French trials. After the third day of the treatment procedure, the number of reports of adverse reactions declined progressively in the French trials, so that by day 14, reports were rare except for reports of bleeding and spotting.

Table 3

Type of Reported Adverse Events Following Administration of Mifepristone and Misoprostol in the U.S. and French Trials* (percentages)

	U.S. Trials	French Trials
Abdominal Pain (cramping)	96	NA
Uterine cramping	NA	83
Nausea	61	43
Headache	31	2
Vomiting	26	18
Diarrhea	20	12
Dizziness	12	1
Fatigue	10	NA
Back pain	9	NA
Uterine hemorrhage	5	NA
Fever	4	NA
Viral infections	4	NA
Vaginitis	3	NA
Rigors (chills/shaking)	3	NA
Dyspepsia	3	NA
Insomnia	3	NA
Asthenia	2	1
Leg pain	2	NA
Anxiety	2	NA
Anemia	2	NA
Leukorrhea	2	NA
Sinusitis	2	NA
Syncope	1	NA
Endometritis/Salpingitis/Pelvic Inflammatory Disease	1	NA
Decrease in hemoglobin greater than 2 g/dL	NA	6
Pelvic pain	NA	2
Fainting	NA	2

* Only adverse reactions with incidence ≥1% are included.

Postmarketing Experience

The following adverse reactions have also been reported during post-approval use of Mifeprex and misoprostol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. No causal relationship between these events and Mifeprex and misoprostol has been established:

Allergic reaction (including rash, hives, itching), hypotension (including orthostatic), light-headedness, loss of consciousness, post-abortal infection (including endomyometritis, parametritis), ruptured ectopic pregnancy, shortness of breath, and tachycardia (including racing pulse, heart palpitations, heart pounding).

OVERDOSAGE

No serious adverse reactions were reported in tolerance studies in healthy non-pregnant female and healthy male subjects where mifepristone was administered in single doses greater than threefold that recommended for termination of pregnancy. If a patient ingests a massive overdose, she should be observed closely for signs of adrenal failure.

The oral acute lethal dose of mifepristone in the mouse, rat and dog is greater than 1000 mg/kg (about 100 times the human dose recommended for termination of pregnancy).

DOSAGE AND ADMINISTRATION

Treatment with Mifeprex and misoprostol for the termination of pregnancy requires three office visits by the patient. Mifeprex should be prescribed only by physicians who have read and understood the prescribing information. Mifeprex may be administered only in a clinic, medical office, or hospital, by or under the supervision of a physician, able to assess the gestational age of an embryo and to diagnose ectopic pregnancies. Physicians must also be able to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.

Day One: Mifeprex Administration

Patients must read the MEDICATION GUIDE and read and sign the PATIENT AGREEMENT before Mifeprex is administered.

Three 200 mg tablets (600 mg) of Mifeprex are taken in a single oral dose.

Day Three: Misoprostol Administration

The patient returns to the health care provider two days after ingesting Mifeprex. Unless abortion has occurred and has been confirmed by clinical examination or ultrasonographic scan, the patient takes two 200 µg tablets (400 µg) of misoprostol orally.

During the period immediately following the administration of misoprostol, the patient may need medication for cramps or gastrointestinal symptoms (see ADVERSE REACTIONS). The patient should be given instructions on what to do if significant discomfort, excessive vaginal bleeding or other adverse reactions occur and should be given a phone number to call if she has questions following the administration of the misoprostol. In addition, the name and phone number of the physician who will be handling emergencies should be provided to the patient.

Day 14: Post-Treatment Examination

Patients will return for a follow-up visit approximately 14 days after the administration of Mifeprex. This visit is very important to confirm by clinical examination or ultrasonographic scan that a complete termination of pregnancy has occurred.

According to data from the U.S. and French studies, women should expect to experience vaginal bleeding or spotting for an average of nine to 16 days. Up to 8% of women may experience some type of bleeding for more than 30 days. Persistence of heavy or moderate vaginal bleeding at this visit, however, could indicate an incomplete abortion.

Patients who have an ongoing pregnancy at this visit have a risk of fetal malformation resulting from the treatment. Surgical termination is recommended to manage medical abortion treatment failures (see PRECAUTIONS, Pregnancy).

Adverse events, such as hospitalization, blood transfusion, ongoing pregnancy, or other major complications following the use of Mifeprex and misoprostol must be reported to Danco Laboratories. Please provide a brief clinical and administrative synopsis of any such adverse events in writing to:

Medical Director
Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4-Early Option (1-877-432-7596)

For immediate consultation 24 hours a day, 7 days a week with an expert in mifepristone, call Danco Laboratories at 1-877-4 Early Option (1-877-432-7596).

HOW SUPPLIED

Mifeprex will be supplied only to licensed physicians who sign and return a Prescriber's Agreement. Distribution of Mifeprex will be subject to specific requirements imposed by the distributor, including procedures for storage, dosage tracking, damaged product returns and other matters. Mifeprex is a prescription drug, although it will not be available to the public through licensed pharmacies.

Mifeprex is supplied as light yellow, cylindrical, bi-convex tablets imprinted on one side with "MF." Each tablet contains 200 mg of mifepristone. Tablets are packaged in single dose blister packets containing three tablets and are supplied in individual cartons (National Drug Code 6487500103).

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Manufactured for:
Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596)
www.earlyoptionpill.com

MEDICATION GUIDE

Mifeprex (MIF-eh-prex)
(mifepristone)

Read this information carefully before taking Mifeprex and misoprostol. It will help you understand how the treatment works. This MEDICATION GUIDE does not take the place of talking with your health care provider (provider).

What is Mifeprex?

Mifeprex is used to end an early pregnancy. It blocks a hormone needed for your pregnancy to continue. It is not approved for ending later pregnancies. Early pregnancy means it is 49 days (7 weeks) or less since your last menstrual period began. When you use Mifeprex (Day 1), you also need to take another medicine misoprostol, 2 days after you take Mifeprex (Day 3), to end your pregnancy. But, about 5-8 out of 100 women taking Mifeprex will need a surgical procedure to end the pregnancy or to stop too much bleeding.

What is the most important information I should know about Mifeprex?

What symptoms should I be concerned with? Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth. Prompt medical attention is needed in these circumstances. Serious infection has resulted in death in a very small number of cases in which misoprostol was used in the vagina. There is no information that vaginal use of misoprostol caused these deaths. If you have any questions, concerns, or problems, or if you are worried about any side effects or symptoms, you should contact your provider. Your provider's telephone number is _____.

Be sure to contact your provider promptly if you have any of the following:

Heavy Bleeding. Contact your provider right away if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours or if you are concerned about heavy bleeding. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical abortion/D&C) to stop it.

Abdominal Pain or "Feeling Sick". If you have abdominal pain or discomfort, or you are "feeling sick", including weakness, nausea, vomiting or diarrhea, with or without fever, more than 24 hours after taking misoprostol, you should contact your provider without delay. These symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).

Fever. In the days after treatment, if you have a fever of 100.4°F or higher that lasts for more than 4 hours, you should contact your provider right away. Fever may be a symptom of a serious infection or another problem (including an ectopic pregnancy).

Take this MEDICATION GUIDE with you. When you visit an emergency room or a provider who did not give you your Mifeprex, you should give them your MEDICATION GUIDE so that they understand that you are having a medical abortion with Mifeprex.

What to do if you are still pregnant after Mifeprex with misoprostol treatment. If you are still pregnant, your provider will talk with you about the other choices you have, including a surgical

procedure to end your pregnancy. There is a chance that there may be birth defects if the pregnancy is not ended.

Talk with your provider. Before you take Mifeprex, you should read this MEDICATION GUIDE and sign a statement (PATIENT AGREEMENT). You and your provider should discuss the benefits and risks of your using Mifeprex.

Who should not take Mifeprex?

Some women should not take Mifeprex. Do not take it if:

- It has been more than 49 days (7 weeks) since your last menstrual period began.
- You have an IUD. It must be taken out before you take Mifeprex.
- Your provider has told you that you have a pregnancy outside the uterus (ectopic pregnancy).
- You have problems with your adrenal glands (chronic adrenal failure).
- You take a medicine to thin your blood.
- You have a bleeding problem.
- You take certain steroid medicines.
- You cannot return for the next 2 visits.
- You cannot easily get emergency medical help in the 2 weeks after you take Mifeprex.
- You are allergic to mifepristone, misoprostol, or medicines that contain misoprostol, such as Cytotec or Arthrotec.

Tell your provider about all your medical conditions to find out if you can take Mifeprex. Also, tell your provider if you smoke at least 10 cigarettes a day.

How should I take Mifeprex?

- **Day 1 at your provider's office:**
  - Read this MEDICATION GUIDE.
  - Discuss the benefits and risks of using Mifeprex to end your pregnancy.
  - If you decide Mifeprex is right for you, sign the PATIENT AGREEMENT.
  - After getting a physical exam, swallow 3 tablets of Mifeprex.
- **Day 3 at your provider's office:**
  - If you are still pregnant, take 2 misoprostol tablets.
  - Misoprostol may cause cramps, nausea, diarrhea, and other symptoms. Your provider may send you home with medicines for these symptoms.
- **About Day 14 at your provider's office:**
  - This follow-up visit is very important. You must return to the provider about 14 days after you have taken Mifeprex to be sure you are well and that you are not pregnant.
  - Your provider will check whether your pregnancy has completely ended. If it has not ended, there is a chance that there may be birth defects. If you are still pregnant, your provider will talk with you about the other choices you have, including a surgical procedure to end your pregnancy.

What should I avoid while taking Mifeprex and misoprostol?

Do not take any other prescription or non-prescription medicines (including herbal medicines or supplements) at any time during the treatment period without first asking your provider about them because they may interfere with the treatment. Ask your provider about what medicines you can

take for pain.

If you are breastfeeding at the time you take Mifeprex and misoprostol, discuss with your provider if you should stop breastfeeding for a few days.

What are the possible and reasonably likely side effects of Mifeprex?

Cramping and bleeding are expected with this treatment. Usually, these symptoms mean that the treatment is working. But sometimes you can get cramping and bleeding and still be pregnant. This is why you must return to your provider on Day 3 and about Day 14. See "How should I take Mifeprex?" for more information on when to return to your provider. If you are not already bleeding after taking Mifeprex, you probably will begin to bleed once you take misoprostol, the medicine you take on Day 3. Bleeding or spotting can be expected for an average of 9–16 days and may last for up to 30 days. Your bleeding may be similar to, or greater than, a normal heavy period. You may see blood clots and tissue. This is an expected part of ending the pregnancy.

Other common symptoms of treatment include diarrhea, nausea, vomiting, headache, dizziness, back pain, and tiredness. These side effects lessen after Day 3 and are usually gone by Day 14. Your provider will tell you how to manage any pain or other side effects.

When should I begin birth control?

You can become pregnant again right after your pregnancy ends. If you do not want to become pregnant again, start using birth control as soon as your pregnancy ends or before you start having sexual intercourse again.

* * *

Medicines are sometimes prescribed for purposes other than those listed in a MEDICATION GUIDE. For more information, ask your provider for the information about Mifeprex that is written for health care professionals. Ask your provider if you have any questions.

This MEDICATION GUIDE has been approved by the U.S. Food and Drug Administration.

Rev 2: 7/19/05

PATIENT AGREEMENT

Mifeprex (mifepristone) Tablets

1. I have read the attached MEDICATION GUIDE for using Mifeprex and misoprostol to end my pregnancy.
2. I discussed the information with my health care provider (provider).
3. My provider answered all my questions and told me about the risks and benefits of using Mifeprex and misoprostol to end my pregnancy.
4. I believe I am no more than 49 days (7 weeks) pregnant.
5. I understand that I will take Mifeprex in my provider's office (Day 1).
6. I understand that I will take misoprostol in my provider's office two days after I take Mifeprex (Day 3).
7. My provider gave me advice on what to do if I develop heavy bleeding or need emergency care due to the treatment.
8. Bleeding and cramping do not mean that my pregnancy has ended. Therefore, I must return to my provider's office in about 2 weeks (about Day 14) after I take Mifeprex to be sure that my pregnancy has ended and that I am well.
9. I know that, in some cases, the treatment will not work. This happens in about 5 to 8 women out of 100 who use this treatment.
10. I understand that if my pregnancy continues after any part of the treatment, there is a chance that there may be birth defects. If my pregnancy continues after treatment with Mifeprex and misoprostol, I will talk with my provider about my choices, which may include a surgical procedure to end my pregnancy.
11. I understand that if the medicines I take do not end my pregnancy and I decide to have a surgical procedure to end my pregnancy, or if I need a surgical procedure to stop bleeding, my provider will do the procedure or refer me to another provider who will. I have that provider's name, address and phone number.
12. I have my provider's name, address and phone number and know that I can call if I have any questions or concerns.
13. I have decided to take Mifeprex and misoprostol to end my pregnancy and will follow my provider's advice about when to take each drug and what to do in an emergency.
14. I will do the following:
    - contact my provider right away if in the days after treatment I have a fever of 100.4°F or higher that lasts for more than 4 hours or severe abdominal pain.
    - contact my provider right away if I have heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours).
    - contact my provider right away if I have abdominal pain or discomfort, or I am "feeling sick", including weakness, nausea, vomiting or diarrhea, more than 24 hours after taking misoprostol.
    - take the MEDICATION GUIDE with me when I visit an emergency room or a provider who did not give me Mifeprex, so that they will understand that I am having a medical abortion with Mifeprex.
    - return to my provider's office in 2 days (Day 3) to check if my pregnancy has ended. My provider will give me misoprostol if I am still pregnant.
    - return to my provider's office about 14 days after beginning treatment to be sure that my pregnancy has ended and that I am well.

Patient Signature: _____

Patient Name (print): _____

Date: _____

The patient signed the PATIENT AGREEMENT in my presence after I counseled her and answered all her questions. I have given her the MEDICATION GUIDE for mifepristone.

Provider's Signature: _____

Name of Provider (print): _____

Date: _____

After the patient and the provider sign this PATIENT AGREEMENT, give 1 copy to the patient before she leaves the office and put 1 copy in her medical record. Give a copy of the MEDICATION GUIDE to the patient.

Rev 2: 7/19/05