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SUPREME COURT
STATE OF OKLAHOMA
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IN THE SUPREME COURT OF THE STATE OF OKLAHOMA

TERRY CLINE, in his official capacity as Oklahoma Commissioner of Health, *et al.*,

Petitioners,

vs.

OKLAHOMA COALITION FOR REPRODUCTIVE JUSTICE, on behalf of itself and its members, *et al.*,

Respondents.

PETITIONERS' BRIEF IN CHIEF

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TERRY CLINE, in his official capacity as Oklahoma Commissioner of Health; *et al.*,	)	
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	)	
vs.	)	**No. 110,765**
	)	
OKLAHOMA COALITION FOR REPRODUCTIVE JUSTICE, on behalf of itself and its members; *et al.*,	)	
	)	
Respondents.	)	

Petitioners' Brief on the Certified Questions

On June 27, 2013, the United States Supreme Court certified to this Court the following questions:

> Whether H. B. No. 1970, Section 1, Chapter 216, O.S.L. 2011[1] prohibits: (1) the use of misoprostol to induce abortions, including the use of misoprostol in conjunction with mifepristone according to a protocol approved by the Food and Drug Administration; and (2) the use of methotrexate to treat ectopic pregnancies.

For the reasons set forth below, the questions should be answered as follows:

1. No, so long as the misoprostol is used as part of a drug protocol approved by the FDA—such as the protocol the FDA approved and included on Mifeprex's drug label—HB 1970 does not prohibit that use of misoprostol.

2. No, HB 1970 does not prohibit the use of methotrexate to treat ectopic pregnancies.

[1] For ease of reference, we will refer to the legislation as "HB 1970."

Introduction

The certified questions were prompted by Respondents' remarkable claim that rather than *requiring* use of the FDA-approved protocol for Mifeprex, HB 1970 actually *bans* the use of that protocol—and even bans the use of medication to treat ectopic pregnancies.[2] Respondents' lawsuit was the first anyone had heard of this interpretation of HB 1970, and for good reason. It (1) ignores the mountain of evidence showing that the Legislature's purpose in enacting HB 1970 was to solve the problem of physicians using potentially dangerous unapproved protocols—not to prevent them from using the FDA-approved protocol, (2) ignores the plain language of the statute, which plainly *requires* use of the FDA-approved Mifeprex protocol, (3) violates basic canons of statutory construction by rendering much of what the Legislature did superfluous and by reading constitutional doubt into the statute when that doubt can easily be avoided, and (4) ignores the very obvious fact that treatment of an ectopic pregnancy is not an abortion and is thus not affected by HB 1970.

The History of HB 1970

I. The FDA approves Mifeprex for use, but significantly restricts its distribution because of safety concerns, including concerns over unapproved use of the drug.

Prior to 2000, no abortion-inducing drug was approved for use in the United States. A handful of abortion providers nonetheless offered medication abortions, most using protocols that involved the use of two drugs that had been approved for other purposes: methotrexate (approved for use in treating arthritis) and misoprostol (approved for use in treating ulcers). Because the safety and efficacy of these off-label protocols was questionable, these providers

[2] Respondents have every reason to claim HB 1970 is as burdensome as possible: doing so supports their claim that the law is "unduly" burdensome.

were the exception to the rule, and the overwhelming majority of abortions performed in the United States were surgical. But in 2000, after a four-year review period, the Food and Drug Administration ("FDA") approved for use in the United States a drug called "Mifeprex,"[3] the first drug specifically designed and intended to cause abortions.[4]

The FDA's review and approval of Mifeprex was highly unusual in several respects. First, the FDA took the surprising step of accelerating its review and approval of the drug pursuant to a regulation that allows for "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses." *See* 21 C.F.R. 314.520 ("Subpart H"). If the application of that regulation to a drug designed to treat a pregnancy seems incongruous, that is because it *was*—the Subpart H approval process had previously been used almost exclusively for new drugs used to treat life-threatening illnesses like cancer or AIDS.[5]

Second, the FDA determined that Mifeprex could be "safely used only if distribution or use is restricted," *see* Subpart H, and thus significantly restricted the distribution of Mifeprex. The FDA specified that it was approving Mifeprex "for the medical termination of intrauterine

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[3] "Mifeprex" is the brand name for the drug mifepristone, which is also sometimes referred to as "RU-486." Unless the context requires otherwise, we will use the term "Mifeprex," to avoid confusion.

[4] Medication abortions now account for only about 25% of the early term abortions performed in the United States each year, and only 17% of the approximately 1.2 million abortions performed in total each year. *Fact Sheet: Facts on Induced Abortions in the United States*, Guttmacher Institute (July 2013), http://www.guttmacher.org/pubs/fb_induced_abortion.html). In other words, American women still overwhelmingly choose surgical abortion over medication abortion despite the costs of the procedures being roughly equivalent.

[5] *See* United States Government Accountability Office, *Food and Drug Administration Approval and Oversight of the Drug Mifeprex*, 11 (Aug. 2008)("As of February 2007, FDA had used this provision to approve 52 drugs, most of which are intended to treat HIV/AIDS or various cancers."), http://www.gao.gov/assets/280/279424.pdf [hereinafter GAO Report].

pregnancy through 49 days' pregnancy"[6] and restricted distribution to only those physicians who met a laundry list of conditions:

> 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 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.[7]

The FDA also required that the "final printed labeling" (the "drug label") for Mifeprex include a "Medication Guide," "Patient Agreement Form," and "Prescriber's Agreement Form," in "identical" form to those that the FDA approved. [8]

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[6] *See* Food and Drug Administration, Mifeprex Letter of Approval 1, App. 1 (Sept. 28, 2000), http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/20687appltr.pdf.

[7] *See id.* at 2.

[8] *See id.* at 1.

In the current Mifeprex drug label that the FDA requires to be used in "identical" form to that it reviewed, the FDA emphasizes that Mifeprex is "For Oral Administration Only."[9] The drug label also repeats what the FDA said in its approval letter: that "Mifepristone is indicated for use in the termination of pregnancy (through 49 days' pregnancy) and has no other approved indication for use during pregnancy."[10] The current Medication Guide warns that a "wom[a]n should not take Mifeprex" if "[i]t has been more than 49 days (7 weeks) since your last menstrual period began."[11] The drug label also describes the approved drug protocol in detail ("the Approved Mifeprex/Misoprostol Protocol"):

> Treatment with Mifeprex and misoprostol for the termination of pregnancy requires three office visits by the patient. Mifeprex should be prescribed 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 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 ug tablets (400 ug) of misoprostol orally. . . .

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[9] *See* Food and Drug Administration, 2009 Approved Label for Mifeprex 1, App. 2 (Apr. 2009), http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020687s015lbl.pdf.

[10] *See id.* at 9.

[11] *See* Food and Drug Administration, 2011 Approved Medication Guide and Prescriber's Agreement for Mifeprex 2, App. 3 (June 2011), http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020687s014lbl.pdf (amending the approved Medication Guide and Prescriber's Agreement for Mifeprex).

> Day Fourteen: Post-Treatment Examination Patients will return for a follow-up visit approximately 14 days after the administration of Mifeprex. The visit is very important to confirm by clinical examination or ultrasonographic scan that a complete termination of pregnancy has occurred.[12]

In the "Patient Agreement" that the FDA requires to be used in "identical" form to that it reviewed, the FDA requires each patient to attest that: (1) "I believe I am no more than 49 days (7 weeks) pregnant;" (2) "I will take misoprostol in my provider's office two days after I take Mifeprex (Day 3)"; (3) "I will . . . 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"; and (4) "I will . . . 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."[13] The abortion provider must also sign the Patient Agreement attesting that the patient "signed the Patient Agreement in my presence."[14]

The FDA did not stop there. The "Prescriber's Agreement" that the FDA requires to be used in "identical" form to that it reviewed requires that each abortion provider who wishes to purchase Mifeprex agree to a list of conditions:

> 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

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[12] *See* 2009 Approved Label for Mifeprex, *supra* note 9, at 13–14.

[13] *See* Food and Drug Administration, 2005 Approved Label for Mifeprex 19–20, App. 4 (July 2005), http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/020687s013lbl.pdf (amending, among other things, the Patient Agreement for Mifeprex).

[14] *Id.*

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 identification number in each patient's record.[15]

The FDA expressly conditioned its approval of Mifeprex on the imposition of these postmarketing restrictions—restrictions that reflect that the FDA intends Mifeprex to be used only in the very specific way described on the drug's label.[16] But what these restrictions on the distribution of Mifeprex also reflect is that the FDA lacks the authority to *directly* regulate how Mifeprex is used because the FDA does not, and cannot, regulate the practice of medicine.[17] So once Mifeprex is in the hands of abortion providers, the FDA is powerless to limit how those providers actually use the drug.

II. Abortion providers begin disregarding the FDA's approved protocol in favor of unapproved, off-label protocols.

It soon became apparent that the FDA's postmarketing restrictions were ineffective at preventing unapproved uses of Mifeprex. Almost as soon as the drug hit the market, abortion providers began disregarding the Mifeprex drug label in favor of unapproved, "off-label" protocols that (1) changed the dosage of Mifeprex and misoprostol that was given to the patient, (2) changed how the drug was administered (vaginally or buccally, rather than orally), (3) allowed the patient to self-administer the drugs at home, (4) did not require the patient to return

[15] 2011 Medication Guide and Prescriber's Agreement for Mifeprex, *supra* note 11, at 1–2.

[16] *See* 57 Fed. Reg. 58942, 58949 (1992) (noting that drugs approved with postmarketing restrictions under 21 CFR §314.520 are those that "would not have been approved for use without those restrictions because the risk/benefit balance would not justify such approval.").

[17] *See* 21 U.S.C. § 396 (expressly disclaiming any intent to regulate the practice of medicine within the Food, Drug, and Cosmetics Act).

for a follow-up visit to ensure there were no complications, and (5) extended the period in which medication abortion is available from 49 days to 63 days of gestation.[18]

Today, the majority of medication abortions are being performed according to protocols *other* than the Approved Mifeprex/Misoprostol Protocol.[19] The proliferation of these off-label protocols wasn't sparked by scientific breakthroughs coming after the FDA's approval of the Approved Mifeprex/Misoprostol Protocol. Quite the contrary, various protocols of this sort had existed for *years* prior to the FDA's review of the Approved Mifeprex/Misoprostol Protocol, and some were even proposed to the FDA and disapproved. Abortion providers just *prefer* the unapproved protocols because they allow the medication abortion option to be offered for an additional 14 days and because they are more convenient—instead of administering the medications in their office, and instead of requiring a follow-up visit, the abortion providers can give the patient her pills and send her on her way.

III. Young women begin to die after being given medication abortions pursuant to unapproved Mifeprex/misoprostol protocols.

On September 10, 2003, just a few days after her eighteenth birthday, a healthy young woman named Holly Patterson walked into a Planned Parenthood clinic in California seeking a medication abortion because of an unplanned pregnancy.[20] The clinic utilized an unapproved

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[18] While the most common off-label protocols involve some combination of Mifeprex and misoprostol, other off-label protocols involve the use of methotrexate followed by misoprostol, and others yet involve the use of just misoprostol or just methotrexate. *See generally, e.g.,* National Abortion Federation, *Protocol Recommendations for Use of Methotrexate and Misoprostol in Early Abortions* https://www.prochoice.org/pubs_research/publications/downloads/professional_education/medical_abortion/protocol_recs_meth_miso.pdf; *see also generally* Mehmet Özeren et al., *Methotrexate and misprostol used alone or in combination for early abortion*, 59 Contraception 389 (1999), available at http://www.ncbi.nlm.nih.gov/pubmed/10518234.

[19] Respondents have claimed that the number is as high as 96%. Resp. to Pet. for Certiorari at 4.

[20] *See* Brief of Women and Families Hurt by RU-486 as Amici Curiae in Support of Petitioners 26, (continued...)

Mifeprex/misoprostol protocol, where they administered Mifeprex to Holly at the clinic, but sent her home to self-administer misoprostol, and told her to do so vaginally, rather than orally.[21] Holly soon began to experience extreme cramping and bleeding, and, within a matter of days, she was dead, the victim of an aggressive infection known as Clostridium sordellii toxic shock syndrome.[22]

Holly was the first woman in the United States to die after being given an unapproved protocol, but she was not the last. In fact, by April 2011, seven similar deaths from bacterial infection had followed, each following the use of an unapproved Mifeprex/misoprostol protocol.[23] There have been no such deaths after use of the Approved Mifeprex/Misoprostol Protocol.

IV. The FDA warns about the potential dangers of unapproved Mifeprex/misoprostol protocols, but is powerless to prevent abortion providers from continuing their use.

As word of the deaths began to spread, the FDA issued several warnings highlighting the potential risks of unapproved protocols and stressing that the Approved Mifeprex/Misoprostol Protocol was the *only* protocol that it had confirmed to be safe:

> The Food and Drug Administration (FDA) is aware of four cases of septic deaths in the United States, from September 2003 to June 2005 in women following medical abortion with mifepristone (Mifeprex) and misoprostol. The

[20](...continued)
available at http://www.scotusblog.com/case-files/cases/cline-v-oklahoma-coalition-for-reproductive-justice/ (follow hyperlink to Brief under April 5, 2013).

[21] *Id.*

[22] *Id.*

[23] Food and Drug Administration, *Mifepristone U.S. Postmarketing Adverse Events Summary through 04/30/11*, App. 5, (July 2011), http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrug SafetyInformationforPatientsandProviders/UCM263353.pdf [hereinafter Adverse Events Summary].

> bacteria causing sepsis has been identified in two of the cases as Clostridium sordellii. The other two cases are under ongoing investigation by FDA along with the Centers for Disease Control and Prevention, State and local health departments, and the manufacturer of Mifeprex. All cases involve the off-label dosing protocol consisting of 200 mg of oral Mifeprex followed by 800 mcg of intra-vaginally placed misoprostol. . . .
>
> The approved Mifeprex protocol for a medical abortion through 49 days' 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 protocols, including use of oral misoprostol tablets intravaginally has not been established by the FDA.**[24]

In its latest "Mifepristone U.S. Postmarketing Adverse Events Summary," the FDA noted that as of April 30, 2011, there had been 14 reported deaths in the United States (plus five more overseas), that eight of the domestic deaths resulted from serious infections, and that all eight of those deaths followed the use of an unapproved drug protocol.[25]

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[24] Food and Drug Administration, *Public Health Advisory: Sepsis and Medical Abortion*, App. 6, (July 19, 2005), http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm051734.htm (emphasis added); *see also* Food and Drug Administration, *Public Health Advisory: Sepsis and Medical Abortion*, App. 7 (March 17, 2006), http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm051298.htm (noting two additional deaths and again describing the Approved Mifeprex/Misoprostol Protocol, stressing that it is the only dosing protocol whose safety and efficacy had been established).

[25] Adverse Events Summary, *supra* note 24.

The FDA also published "Mifeprex Questions and Answers" in which the FDA again stressed that Mifeprex should not be used after 49 days and that the restrictions it placed on the drug "are necessary for the safe use of the drug."[26] The FDA again noted that deaths have occurred after use of unapproved drug protocols, and that while it "did not know" whether the use of those protocols caused the deaths, the symptoms in each case of serious infection were not the "usual" symptoms of sepsis.[27] The FDA noted that it is aware that some doctors are using unapproved protocols, but again emphasized that it "has not reviewed data on the safety and effectiveness of" unapproved protocols:

> The FDA-approved protocol 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 protocols, 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 protocols have been well described in the literature, the safety and effectiveness of Mifeprex dosing protocols, other than the one approved by FDA, including use of oral misoprostol intravaginally, has not been established by the FDA.[28]

Unfortunately, these warnings proved ineffective—abortion providers simply ignored them and pressed on with their use of unapproved protocols. But again, because of its lack of authority to directly the practice of medicine, all the FDA could do in response to the reported deaths is warn, warn, warn; if there was to be a more robust regulatory response, it was up to the states to provide it.

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[26] Food and Drug Administration, *Mifeprex Questions and Answers*, App. 8 (Feb. 24, 2010), http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111328.htm.

[27] *Id.*

[28] *Id.*

V. The Oklahoma Legislature passes SB 1902, which requires that abortion providers tell their patients when they are using off label protocols.

In 2010, the Oklahoma Legislature took the first step toward filling the regulatory void.[29] Senate Bill 1902 added a new section of law at 63 O.S. § 1-729a.[30] This section of law took several initial steps towards enforcing the restrictions the FDA had placed on Mifeprex. First, SB 1902 essentially codified the FDA's postmarketing restrictions, creating a state law remedy against any physician who failed to comply with the physician requirements imposed by the FDA and codified by SB 1902. SB 1902 also required physicians to tell their patients if they were using an unapproved Mifeprex protocol, required the Mifeprex to be administered in the presence of the physician, imposed certain adverse event reporting requirements, and required physicians to make "reasonable efforts" to ensure that patients return for a follow-up visit within 12 to18 days after the abortion-inducing drug is ingested. These requirements closely followed the Mifeprex Drug Label and Physician's Agreement, which stress to both patient and physician that a 14-day follow up is "very important."

Importantly, SB 1902 did not eliminate the use of unapproved protocols. So long as they informed their patients that they were using an unapproved protocol, abortion providers remained free to use those protocols.

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[29] Doing so is undoubtedly within the State's police power. *Whalen v. Roe*, 429 U.S. 589, 603 n. 30 (1977) ("It is, of course, well settled that the State has broad police powers in regulating the administration of drugs by the health professions."). Indeed, "the State no doubt could prohibit entirely the use of particular . . . drugs." *Id.* at 603; *see also Planned Parenthood Southwest Ohio Region v. DeWine*, 696 F.3d 490, 496 (6th Cir. 2012) ("States . . . may limit off-label use" of FDA-approved drugs). As the Supreme Court has observed, "[t]here can be no question of the authority of the State in the exercise of its police power to regulate the administration, sale, prescription and use of dangerous . . . drugs. The right to exercise this power is so manifest in the interest of the public health and welfare, that it is unnecessary to enter upon a discussion of it beyond saying that it is too firmly established to be successfully called in question." *Whipple v. Martinson*, 256 U.S. 41, 45 (1921).

[30] *See* S.B. No. 1902, Section 1, Chapter 48, O.S.L. 2010, App. 9.

VI. The Oklahoma Legislature passes HB 1970, which requires that abortion providers use only FDA- approved protocols.

In the next legislative session, the Oklahoma Legislature amended 63 O.S. § 1-729a to fill in several significant gaps in the statute. HB 1970 made three primary changes to 63 O.S. § 1-729a. First, it actually *required* the use of the Approved Mifeprex/Misoprostol Protocol and made it clear that the use of unapproved protocols was now unlawful. Second, it required abortion providers to actually examine their patients prior to administering the drugs, a requirement designed to prevent "telemed" abortions, which involve abortion providers videoconferencing with the patient from a remote location. Third, it expanded the statute's scope so that it now applied to "any abortion-inducing drug" rather than just Mifeprex. This was significant because the first version of the statute essentially codified the post-marketing restrictions the FDA had imposed on Mifeprex, but it left a significant loophole where an abortion provider could avoid those restrictions (having to possess the ability to provide surgical intervention if needed, having to personally administer the drugs, having to report adverse reactions to the drug, etc.) by reverting to a drug protocol that did not involve Mifeprex, such as the methotrexate/misoprostol protocol that fell out of favor once Mifeprex was made legal.

VII. At the time it was passed, HB 1970 was heralded for what it was: a regulation of how medication abortions were to be performed, and not a complete ban on those abortions.

The universal reaction to HB 1970 at the time it was passed was that it required use of FDA-approved protocols—not that it banned the approved Mifeprex/misoprostol protocol. The Senate author of HB 1970, Greg Treat, released a statement shortly after the bill was signed into law where he "applauded Gov. Mary Fallin's signing of House Bill 1970 – a measure that will

require physicians to administer abortion inducing drugs in accordance with U.S. Food and Drug Administration (FDA) guidelines."[31]

Representative Randy Grau, the principal author of the bill, added that the law "will also require that patients are scheduled for a follow-appointment and are made aware of the proper usage and effects of the drugs . . .[t]he intent of this legislation is to...better regulate the dangerous drugs that are used in abortions."[32]

The media's reaction was no different. The Tulsa World reported that HB 1970 "would require physicians to administer abortion-inducing drugs, including RU-486, in accordance with U.S. Food and Drug Administration guidelines,"[33] while the Daily Oklahoman reported that HB 1970 "requires physicians to administer abortion-inducing drugs in accordance with U.S. Food and Drug Administration guidelines."[34]

Even the strongly anti-abortion group Americans United for Life described the legislation as simply requiring "that abortion providers dispense abortion-inducing drugs only in the way tested and approved by the Food and Drug Administration (FDA) and outlined in the drug's label."[35]

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[31] *See* Press Release, Senator Greg Treat, *Treat applauds signing of measure regulating abortion-inducing drugs*, App. 10 (May 12, 2011), http://www.oksenate.gov/news/press_releases/press_releases_2011/pr20110512a.html.

[32] *Id.*

[33] Barbara Hoberock, *Measure Would Restrict Abortion-Inducing Drugs*, Tulsa World, Apr. 27, 2011, App. 11.

[34] Michael McNutt, *Legislation Updates at the State Capitol*, Daily Oklahoman, May 12, 2011, App. 12..

[35] Press Release, Americans United for Life, *AUL Says Oklahoma HB 1970 Protects Women from Dangerous Off-Label Use of Abortion-Inducing Drugs*, App. 13 (May 12, 2011), http://www.aul.org/2011/05/aul-says-oklahoma-hb-1970-protects-women-from-dangerous-off-label-use-of-abortion-inducing-drugs.

In other words, the contemporaneous understanding of HB 1970 was that it was aimed at solving the problem of unapproved use of Mifeprex and did so by requiring use of the FDA's Approved Mifeprex/Misoprostol Protocol. Neither the authors of the law, the media, nor pro-life groups understood the law to effectuate a complete ban on medication abortions.

Summary of the Argument

I. Question #1: Whether HB 1970 prohibits the use of misoprostol to induce abortions, including the use of misoprostol in conjunction with mifepristone according to a protocol approved by the Food and Drug Administration.

The plain language of HB 1970 allows the use of the Approved Mifeprex/Misoprostol Protocol. Because that protocol requires the use of misoprostol, HB 1970 does not prevent the use of misoprostol as part of that—or any other—FDA-approved protocol. Additionally, even if HB 1970 were ambiguous on this point (it is not), the law cannot be read as completely preventing the use of misoprostol, because such a reading would mean the law completely bans medication abortions, and that makes no sense in light of the numerous provisions in the law that clearly contemplate that medication abortions will continue after the law is effective. And lastly, reading the law as a complete ban on medication abortions violates the canon of constitutional avoidance by creating a potential constitutional infirmity where none need exist.

II. Question #2: Whether HB 1970 prohibits the use of methotrexate to treat ectopic pregnancies.

HB 1970 does not prohibit the use of methotrexate to treat ectopic pregnancies because treatment of an ectopic pregnancy is not an "abortion," and HB 1970 only applies to drugs that are used to induce abortions.

Argument and Authorities

I. HB 1970 allows misoprostol to be used as part of the Approved Mifeprex/Misoprostol Protocol.

As Petitioners explained in the underlying case, there are multiple reasons why Respondents' interpretation of the Oklahoma law—that it bans the use of misoprostol and thus bans even use of the Approved Mifeprex/Misoprostol Protocol—is wrong. First, the plain language of HB 1970 allows use of the Approved Mifeprex/Misoprostol Protocol; that is what the law unambiguously says, and that is how it was undisputedly intended.

A. The text of HB 1970 unambiguously allow use of the Approved Mifeprex/Misoprostol Protocol.

The relevant provision in HB 1970 is subpart C, which provides that:

> No physician who provides RU-486 (mifepristone) or any abortion-inducing drug shall knowingly or recklessly fail to provide or prescribe the RU-486 (mifepristone) or any abortion-inducing drug according to the protocol tested and authorized by the U.S. Food and Drug Administration and as authorized in the drug label for the RU-486 (mifepristone) or any abortion-inducing drug.

H.B. No. 1970, Section 1, Chapter 216, O.S.L. 2011. As subpart (A)(1) makes clear, when used "with the intent of causing an abortion," misoprostol is an "abortion-inducing drug." *Id.* So subpart C can be read as follows:

> No physician who provides [Mifeprex] or [misoprostol] shall knowingly or recklessly fail to provide or prescribe the [Mifeprex] or [misoprostol] according to the protocol tested and authorized by the U.S. Food and Drug Administration and as authorized in the drug label for the [Mifeprex] or [misoprostol].

The plain text of the law thus allows misoprostol to be used to induce an abortion so long as it is "provided or prescribed...according to the protocol tested and authorized by the U.S. Food and Drug Administration and as authorized in the drug label for the Mifeprex ***or*** misoprostol."[36]

[36] Respondents seemingly want to transform "as authorized in the drug label for the Mifeprex ***or*** (continued...)

Because the use of misoprostol is undisputedly authorized in the drug label for Mifeprex, HB 1970 unambiguously allows the use of misoprostol as part of the Approved Mifeprex/Misoprostol Protocol.

B. HB 1970's title confirms that the statute does not ban medication abortions.

Additionally, the title of HB 1970 gives no indication that the law is a ban on medication abortions. *Kratz v. Kratz*, 1995 OK 63 ¶ 15, 905 P.2d 753, 756 ("The title to an Act is a valuable aid in its construction and may be considered in determining legislative intent.") To the contrary, the title describes legislation that *requires* the use of FDA-approved protocols, and which imposes a host of requirements that only make sense if medication abortions are still allowed post-enactment:

> An Act relating to public health and safety; amending Section 1, Chapter 48, O.S.L. 2010 (63 O.S. Supp. 2010, Section 1-729a), which relates to RU-486 for the purpose of inducing abortions; adding definitions; **requiring that physicians prescribe certain drugs according to certain protocol**; modifying duties of certain physicians; requiring physician to examine woman and document gestational age prior to administering certain drugs; requiring follow-up appointment to be scheduled for certain patient; providing for severability; and providing an effective date.

H.B. No. 1970, Section 1, Chapter 216, O.S.L. 2011 (emphasis added).

By contrast, when the Legislature intends to ban a particular type of abortion, that intent is clearly expressed in the title. For example, in the title to 2011's HB 1888, the "Pain-Capable Unborn Child Protection Act", which was co-sponsored by Senator Treat and Representative

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[36](...continued)
misoprostol" into "as authorized in the drug label for the Mifeprex ***and*** misoprostol," in order to read the law as banning the use or misoprostol to induce an abortion in all circumstances because that use is not authorized in the misoprostol drug label. In other words, they read in a requirement that the use of misprostol to induce an abortion must be authorized in both the drug label for Mifeprex ***and*** the drug label for misoprostol. This is plainly not what the law requires.

Grau (the authors of HB 1970), the Legislature clearly expressed an intent to ban abortions performed after a certain gestational age:

> An Act relating to public health and safety; creating the Pain-Capable Unborn Child Protection Act; providing short title; defining terms; making legislative findings; establishing purpose; prohibiting the performance of an abortion without certain determination; **prohibiting the performance of an abortion upon determination of certain age of unborn child**; providing for exceptions; requiring that the manner in which physicians terminate certain pregnancies provides the best opportunity for unborn child's survival; requiring certain report by physician; including certain information; requiring State Department of Health to issue certain report; stating certain penalties for physicians; requiring the State Board of Health to promulgate rules; providing date on which certain provisions shall become effective; providing penalty; permitting certain individuals to maintain action including injunctive relief; providing for attorney fees; requiring court to rule regarding anonymity; requiring written findings under certain circumstance; providing for severability; providing for certain interpretation; providing for codification; and providing an effective date.

H.B. 1888, Chapter 89, O.S.L. 2011 (emphasis added); *see also* H.B. 1595, Chapter 227, O.S.L. 2006 ("prohibiting the performance of an abortion solely on account of the sex of the unborn child.").

The permissive language contained in the title to HB 1970, when contrasted with the prohibitory language the Legislature uses when it intends to ban a type of abortion, illustrates that the Legislature intended HB 1970 to impose requirements on *how* medication abortion are to be performed, not to ban them. This is confirmed by the fact that the title describes the new requirements that plainly contemplate that medication abortions will continue after the legislation takes effect (e.g., "requiring follow-up appointment to be scheduled").

C. Reading HB 1970 as effectuating a complete ban on medication abortions renders most of the statute it amended superfluous.

Reading HB 1970 as prohibiting the use of misoprostol, and thus effectuating a complete ban on medication abortions, violates a basic tenet of statutory interpretation by rendering a

large portion of the Oklahoma law superfluous. *Bryant v. Com'r of Dept. of Public Safety*, 1996 OK 134 ¶ 11, 937 P.2d 496 ("Statutes must be read to render every part operative and to avoid rendering it superfluous or useless."). Indeed, if HB 1970 were interpreted as banning all medication abortions, numerous provisions of the law make little sense. For instance, as amended by the new Oklahoma law, 63 O.S .§ 1-729a: (1) sets forth detailed qualifications for physicians who perform medication abortions, § 1-729a(B)1-5; (2) describes disclosures that physicians who perform medication abortions must make to their patients,§ 1-729a(D)1-5; (3) describes many specific things a physician must do before, during, and after the medication abortion,§ 1-729a(E)-(F); (4) requires physicians to schedule follow-up visits after the medication abortion is performed, § 1-729a(E)-(F); and (5) describes post-procedure reporting requirements with which physicians who perform medication abortions must comply,§ 1-729a(G)1-2.

If the Oklahoma Legislature intended to effectuate a complete ban of medication abortions, it certainly made some odd drafting choices in doing so because each of these provisions plainly assumes that medication abortions can and will be performed after HB 1970 is in effect.

D. Respondents' interpretation of HB 1970 is one designed to cast doubt on the constitutionality of the law; therefore, it is an interpretation that must be avoided.

And lastly, even if Respondents' interpretation of HB 1970 wasn't inconsistent with the plain text of the law, that interpretation violates the canon of constitutional avoidance by creating a potential constitutional infirmity where none need exist. *State ex rel. Dept. of Transp. v. Pile*, 1979 OK 152 ¶ 16, 603 P.2d 337 ("This court is bound to accept an interpretation that avoids constitutional doubt as to the validity of the provision."); *see Clark v. Martinez*, 543 U.S.

371, 381 (2005) (the canon is a "tool for choosing between competing plausible interpretations of a statutory text, resting on the reasonable presumption that [the legislature] did not intend the alternative which raises serious constitutional doubts."). Indeed, the very reason Respondents argue that the law prevents the use of misoprostol is so that they can argue that the law effectuates a complete ban on medication abortion and should thus be considered "unduly" burdensome. And while the United State Supreme Court has upheld even complete bans of certain abortion procedures, *see Gonzales v. Carhart*, 550 U.S. 124 (2007) (upholding the federal ban on partial-birth abortions based in part on the medical uncertainty over the safety of the procedure), any constitutional doubt over the validity of HB 1970 is eliminated if it is read as a regulation that simply requires that medication abortions be performed only in the manner that the FDA has confirmed to be safe.

II. HB 1970 has no effect on Oklahoma physicians' ability to treat ectopic pregnancies.

HB 1970 only regulates "abortion-inducing drugs," and treatment of an ectopic pregnancy is *not* an abortion. In fact, the Legislature explicitly excluded treatment of an ectopic pregnancy when it defined "abortion" for purposes of Article 7 of Title 63:

> **As used in this article..."Abortion" means the use or prescription of any instrument, medicine, drug, or any other substance or device intentionally to terminate the pregnancy of a female known to be pregnant with an intention other than** to increase the probability of a live birth, to preserve the life or health of the child after live birth, **to remove an ectopic pregnancy**, or to remove a dead unborn child who died as the result of a spontaneous miscarriage, accidental trauma, or a criminal assault on the pregnant female or her unborn child.

63 O.S. § 1-730(A)(1).[37] So while HB 1970 specifies that its coverage includes methotrexate only when "prescribed specifically with the intent of causing an abortion,"[38] use of methotrexate to treat an ectopic pregnancy would never be covered because that use would not be "specifically with the intent of causing an abortion." *See* H.B. 1970, Section 1(A)(1), Chapter 216, O.S.L. 2011(amending 63 O.S. § 1-729a).

What Respondents ask the Court to do is ignore both the controlling statutory definition of "abortion" and the very specific limiting language the Legislature used to describe the circumstances under which methotrexate should be considered an "abortion-inducing drug" (i.e., when "prescribed specifically with the intent of causing an abortion"). But even if the Court accepted Respondents' invitation to do so, the use of methotrexate to treat an ectopic pregnancy cannot otherwise be read to fall within HB 1970's coverage because an "ectopic pregnancy" is not a true "pregnancy" as that term is understood in the medical community. Indeed, "[a]ccording to both the scientific community and long-standing federal policy, a woman is considered pregnant only when a fertilized egg has implanted in the wall of her uterus,"[39] whereas an "ectopic pregnancy" by definition occurs somewhere other than the uterus.[40] So when HB 1970 generally defines abortion-inducing drugs as those "prescribed or dispensed with

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[37] HB 1970 amends 63 O.S. § 1-729, which is part of the same article as 63 O.S. § 1-730.

[38] For example, methotrexate would be covered when used as part of one of the unapproved abortion protocols that uses methotrexate and misoprostol.

[39] Rachel Benson Gold, *The Implications of Defining When a Woman Is* Pregnant, The Guttmacher Report on Public Policy (Guttmacher Institute), May 2005, http://www.guttmacher.org/pubs/tgr/08/2/gr080207.html.

[40] *See, e.g., Stedman's Medical Dictionary* 451 (5th ed. William Wood and Co.)(defining "ectopic pregnancy" as "the development of an impregnated ovum outside of the cavity of the uterus").

the intent of terminating the clinically diagnosable pregnancy of a woman," that definition again categorically excludes any drug prescribed or dispensed to treat an ectopic pregnancy.

Conclusion

Petitioners' interpretation of the law is the only interpretation of the law that is consistent with what the law plainly says and with the Legislature's intent.[41] Thus, the Court should answer the certified questions as follows:

1. No, so long as the misoprostol is used as part of a drug protocol approved by the FDA—such as the protocol the FDA approved and included on Mifeprex's drug label—HB 1970 does not prohibit that use of misoprostol.

2. No, HB 1970 does not prohibit the use of methotrexate to treat ectopic pregnancies.

Respectfully submitted,

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[41] And it should not be overlooked that this interpretation comes from the Attorney General, whose opinion "is binding upon the state officials whom it affects." *State ex rel. Fent v. State ex rel. Okla. Water Res. Bd.*, 2003 OK 29 ¶ 16, 66 P.3d 432, 441. Thus, this interpretation of the law is not Petitioners' "best guess" as to how the law will be interpreted and enforced; it is in fact how it *will* be enforced.

Certificate of Service

I hereby certify that on the 14th day of August, 2013, a true and correct copy of the foregoing instrument was sent to the following by email:

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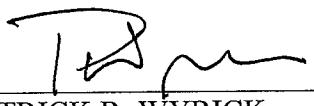


PATRICK R. WYRICK

APPENDIX 1

SEP 28 2000

NDA 20-687

Population Council
Attention: Sandra P. Arnold
Vice President, Corporate Affairs
1230 York Avenue
New York, NY 10021

Dear Ms. Arnold:

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, April 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]

Sincerely,

/S/

Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APPENDIX 2

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).

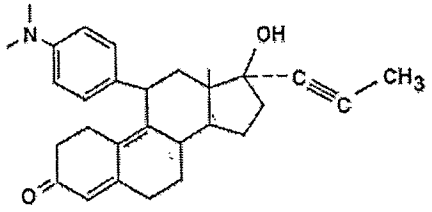
- Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. Advise patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding (see WARNINGS).

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. Most of these deaths occurred in women who used vaginally administered misoprostol. No causal relationship between Mifeprex and misoprostol use and an increased risk of infection or death has been established. *Clostridium sordellii* infections have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynecologic and non-gynecologic conditions.

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, pelvic infection), ruptured ectopic pregnancy, shortness of breath, tachycardia (including racing pulse, heart palpitations, heart pounding), and hematometra.

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

APPENDIX 3

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 most of these cases misoprostol was used in the vagina. There is no information that use of Mifeprex and 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.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

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 3: 4/22/09
*Mifeprex is a registered trademark of Danco Laboratories, LLC.

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 identification 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
*MIFEPREX is a registered trademark of Danco Laboratories, LLC.

Reference ID: 2957855

APPENDIX 4

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).

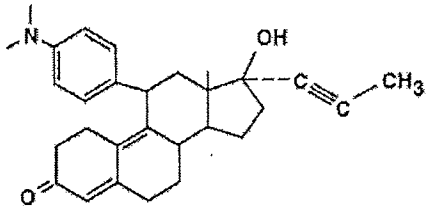
- Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. Advise patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding (see WARNINGS).

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

APPENDIX 5

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 approva 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 witl 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 abortio 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 foi 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 fo 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 terminatior 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.

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[1].

Related Information

- Mifeprex Adverse Events Report as of April, 2011 (PDF - 22KB)[2]
  7/19/2011
- Mifeprex Questions and Answers[3]
  Updated 2/24/2010
- Historical Information on Mifepristone (marketed as Mifeprex)[4]

Labeling and Regulatory History from Drugs@FDA

- Mifepristone (marketed as Mifeprex) Prescribing and Label Information[5]
- Mifeprex (mifepristone) Prescribing Information July 2005[6]
- Mifeprex Medication Guide (PDF - 62KB)[7]
- Mifeprex (mifepristone) Tablets - Patient Agreement (PDF - 56KB)[8]

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APPENDIX 6

Drugs

Public Health Advisory: Sepsis and Medical Abortion

November 4, 2005 Update: All four cases of fatal infection tested positive for Clostridium sordellii. In addition, FDA tested drug from manufacturing lots of mifepristone and misoprostol and found no contamination with Clostridium sordellii

July 19, 2005: The Food and Drug Administration (FDA) is aware of four cases of septic deaths in the United States, from September 2003 to June 2005 in women following medical abortion with mifepristone (Mifeprex) and misoprostol. The bacteria causing sepsis has been identified in two of the cases as *Clostridium sordellii*. The other two cases are under ongoing investigation by FDA along with the Centers for Disease Control and Prevention, State and local health departments, and the manufacturer of Mifeprex. All cases involve the off-label dosing regimen consisting of 200 mg of oral Mifeprex followed by 800 mcg of intra-vaginally placed misoprostol. The two confirmed cases of *Clostridium sordellii* did not have the usual signs and symptoms of an infection. Although these deaths are reported from California, all providers of medical abortion and their patients need to be aware of the risks of sepsis. As more information becomes available, FDA will alert the public.

In the meantime, FDA recommends that healthcare professionals and patients be aware of the following:

- All providers of medical abortion and emergency room health care providers should investigate the possibility of sepsis in patients who are undergoing medical abortion and present with nausea, vomiting, or diarrhea and weakness with or without abdominal pain, and without fever or other signs of infection more than 24 hours after taking misoprostol. To help identify those patients with hidden infection, strong consideration should be given to obtaining a complete blood count.
- FDA recommends that physicians suspect infection in patients with this presentation anc consider immediately initiating treatment with antibiotics that includes coverage of anaerobic bacteria such as *Clostridium sordellii*.
- At this time FDA does not have sufficient information to recommend the use of prophylactic antibiotics. Reports of fatal sepsis in women undergoing medical abortion is very rare (approximately 1 in 100,000). Prophylactic antibiotic use carries its own risk c 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.
- The approved Mifeprex regimen for a medical abortion through 49 days' 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 al 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.

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

FDA is also working with the manufacturers of Mifeprex and misoprostol tablets to conduct special tests to ensure that there was no contamination of either product with *Clostridium sordellii*.

Information pertaining to Mifeprex can be found at Mifeprex (mifepristone) Information[1].

FDA will update this advisory as more definitive information becomes available.

Related Information

- Mifeprex (mifepristone) Information[2]

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APPENDIX 7

Public Health Advisory: Sepsis and medical abortion with mifepristone (Mifeprex)

3/17/2006

The Food and Drug Administration has been informed of two additional deaths following medical abortion with mifepristone (Mifeprex). The Agency received verbal notification of the deaths in the United States from the manufacturer, Danco Laboratories. At this time we are investigating all circumstances associated with these cases and are not able to confirm the causes of death. However, all providers of medical abortion and their patients need to be aware of the specific circumstances and directions for use of this drug and all risks including sepsis when considering treatment. In particular, physicians and their patients should fully discuss early potential signs and symptoms that may warrant immediate medical evaluation.

The approved Mifeprex regimen for a medical abortion through 49 days' 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.

These recommendations are consistent with warnings in the Prescribing Information and information for the patient in the Medication Guide. FDA also emphasizes that healthcare professionals and patients should be aware of the following:

- All providers of medical abortion and emergency room health care providers should investigate the possibility of sepsis in patients who are undergoing medical abortion and present with nausea, vomiting, or diarrhea and weakness with or without abdominal pain, and without fever or other signs of infection more than 24 hours after taking misoprostol. To help identify those patients with hidden infection, strong consideration should be given to obtaining a complete blood count.

- FDA recommends that physicians suspect infection 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. 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.

As previously provided in our July 19, 2005 Public Health Advisory, updated on November 4, 2005, the Agency is aware of four previous confirmed deaths from sepsis in the United States, from September 2003 to June 2005, in women following medical abortion with

mifepristone (Mifeprex) and misoprostol. All four cases of fatal infection tested positive for *Clostridium sordellii*. All four cases involved the off-label dosing regimen consisting of 200 mg of oral Mifeprex followed by 800 mcg of intra-vaginally placed misoprostol. In addition, FDA tested drug from manufacturing lots of mifepristone and misoprostol and found no contamination with *Clostridium sordellii*.

We do not know whether these new deaths were caused by sepsis or, if they were, if they were caused by infection with *Clostridium sordellii*. However, FDA, in conjunction with the Centers for Disease Control and Prevention (CDC) and the National Institute of Allergy and Infectious Diseases (NIAID), is conducting a public workshop on May 11, 2006. This scientific workshop entitled, "Emerging Clostridial Disease," at the CDC Conference Center, Atlanta, Georgia, is being conducted to discuss the scientific and medical circumstances associated with reports of morbidity and mortality associated with *C. sordellii* and *C difficile* infections. These reports include cases and clusters of *C. sordellii* toxic shock syndrome following treatment with mifepristone, *C. sordellii* sepsis associated with skin grafts, and rapidly fatal toxin-mediated cases of community-associated *C. difficile* infection. The primary goal of the workshop is to bring together scientific and public health experts to develop a draft research agenda leading to a better understanding of the virulence, pathogenesis, host factors, and non-antimicrobial risk factors contributing to those reports.

Information pertaining to Mifeprex can be found at Mifeprex (mifepristone) Information[1]

Information pertaining to Emerging Clostridial Diseases Public Workshop can be found at Public Workshop on Emerging Clostridial Disease May 11, 2006, Atlanta, Georgia [2]

Related Information

- Mifeprex (mifepristone) Information[3]
- Public Workshop on Emerging Clostridial Disease, May 11, 2006, Atlanta, Georgia[4]
- Public Health Advisory: Sepsis and Medical Abortion[5]
  7/19/2005 Updated 11/4/2005

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APPENDIX 8

Mifeprex Questions and Answers

(Issued 8/29/2007 Updated 2/24/2010)

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[1].

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, suc as in the fallopian tubes), including one case of ectopic pregnancy resulting in death; severa 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 eight 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). Seven 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.

Page Last Updated: 02/24/2010
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

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U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Ph. 1-888-INFO-FDA (1-888-463-6332)
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U.S. Department of Health & Human Services

Links on this page:

1. /downloads/Drugs/DrugSafety/UCM088643.pdf

APPENDIX 9

ENROLLED SENATE
BILL NO. 1902

By: Jolley, Lamb and Marlatt of the Senate

and

McNiel, Reynolds, Cooksey, Derby, Faught, Wesselhoft, Kern, Wright (John), Billy and Tibbs of the House

An Act relating to public health and safety; defining certain terms; prohibiting the provision of RU-486 under certain circumstances; requiring certain physicians to perform certain actions in specified circumstances; requiring the administration of a certain drug to be performed under specified conditions; requiring certain follow-up; requiring certain information to be contained in a patient's medical records; requiring certain written report under specified circumstances; requiring copy of certain report to be sent to specified entities; mandating certain reports be compiled and maintained; making certain information public record; prohibiting the release of certain information in specified circumstances; providing for certain penalties; permitting certain persons to maintain an action; authorizing the provision of attorney fees in certain circumstances; prohibiting certain persons to be the subject of specified actions; repealing Section 7, Chapter 36, O.S.L. 2008 (63 O.S. Supp. 2009, Section 1-729), which relates to regulation of RU-846; providing for codification; and declaring an emergency.

BE IT ENACTED BY THE PEOPLE OF THE STATE OF OKLAHOMA:

SECTION 1. NEW LAW A new section of law to be codified in the Oklahoma Statutes as Section 1-729a of Title 63, unless there is created a duplication in numbering, reads as follows:

A. As used in this section:

1. "Federal law" means any law, rule, or regulation of the United States or any drug approval letter of the U.S. Food and Drug Administration that governs or regulates the use of RU-486 (mifepristone) for the purpose of inducing abortions;

2. "Personal identifying information" means any information designed to identify a person and any information commonly used or capable of being used alone or in conjunction with any other information to identify a person; and

3. "Physician" means a doctor of medicine or osteopathy legally authorized to practice medicine in the state.

B. No person shall knowingly or recklessly give, sell, dispense, administer, prescribe, or otherwise provide RU-486, also known as mifepristone, for the purpose of inducing an abortion in a pregnant female, unless the person who gives, sells, dispenses, administers, prescribes, or otherwise provides the RU-486 (mifepristone) is a physician who:

1. Has the ability to assess the duration of the pregnancy accurately;

2. Has the ability to diagnose ectopic pregnancies;

3. Has the ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or has made and documented in the patient's medical record plans to provide such care through other qualified physicians;

4. Is able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary; and

5. Has read and understood the prescribing information for the use of RU-486 (mifepristone) as provided by the drug manufacturer in accordance with the requirements of the U.S. Food and Drug Administration.

C. No physician who provides RU-486 (mifepristone) for the purpose of inducing an abortion shall knowingly or recklessly fail to:

1. Provide each patient with a copy of the drug manufacturer's medication guide for RU-486 (mifepristone);

2. Fully explain the procedure to the patient, including, but not limited to, explaining whether the physician is using the drug in accordance with the U.S. Food and Drug Administration regimen or an evidence-based regimen, and, if using an evidence-based regimen, specifying that the regimen differs from the U.S. Food and Drug Administration regimen and providing detailed information on the evidence-based regimen being used;

3. Provide the female with a copy of the drug manufacturer's patient agreement and obtain the patient's signature on the patient agreement;

4. Sign the patient agreement; and

5. Record the drug manufacturer's package serial number in the patient's medical record.

D. When RU-486 (mifepristone) is used for the purpose of inducing an abortion, the drug must be administered by or in the same room and in the physical presence of the physician who prescribed, dispensed, or otherwise provided the drug to the patient. The physician inducing the abortion, or a person acting on behalf of the physician inducing the abortion, shall make all reasonable efforts to ensure that the patient returns twelve (12) to eighteen (18) days after the administration or use of RU-486 (mifepristone) for a follow-up visit so that the physician can confirm that the pregnancy has been terminated and assess the patient's medical condition. A brief description of the efforts made to comply with this subsection, including the date, time, and

identification by name of the person making such efforts, shall be included in the patient's medical record.

E. 1. If a physician provides RU-486 (mifepristone) for the purpose of inducing an abortion and if the physician knows that the female who uses the RU-486 (mifepristone) for the purpose of inducing an abortion experiences within one (1) year after the use of RU-486 (mifepristone) an incomplete abortion, severe bleeding, or an adverse reaction to the RU-486 (mifepristone) or is hospitalized, receives a transfusion, or experiences any other serious event, the physician shall, as soon as is practicable, but in no case more than sixty (60) days after the physician learns of the adverse reaction or serious event, provide a written report of the incomplete abortion, severe bleeding, adverse reaction, hospitalization, transfusion, or serious event to the drug manufacturer. If the physician is a doctor of medicine, the physician shall simultaneously provide a copy of the report to the State Board of Medical Licensure and Supervision. If the physician is a doctor of osteopathy, the physician shall simultaneously provide a copy of the report to the State Board of Osteopathic Examiners. The relevant Board shall compile and retain all reports it receives pursuant to this subsection. All reports the relevant Board receives under this subsection are public records open to inspection pursuant to the Oklahoma Open Records Act; however, absent an order by a court of competent jurisdiction, neither the drug manufacturer nor the relevant Board shall release the name or any other personal identifying information regarding a person who uses or provides RU-486 (mifepristone) for the purpose of inducing an abortion and who is the subject of a report the drug manufacturer or the relevant Board receives under this subsection.

2. No physician who provides RU-486 (mifepristone) to a pregnant female for the purpose of inducing an abortion shall knowingly or recklessly fail to file a report required under paragraph 1 of this subsection. Knowing or reckless failure to comply with this subsection shall subject the physician to sanctioning by the licensing board having administrative authority over such physician.

F. Any female upon whom an abortion has been performed, the father of the unborn child who was the subject of the abortion if the father was married to the woman who received the abortion at the

time the abortion was performed, or a maternal grandparent of the unborn child, may maintain an action against the person who performed the abortion in knowing or reckless violation of this section for actual and punitive damages. Any female upon whom an abortion has been attempted in knowing or reckless violation of this section may maintain an action against the person who attempted to perform the abortion for actual and punitive damages.

G. If a judgment is rendered in favor of the plaintiff in any action described in this section, the court shall also render judgment for a reasonable attorney fee in favor of the plaintiff against the defendant. If a judgment is rendered in favor of the defendant and the court finds that the plaintiff's suit was frivolous and brought in bad faith, the court shall also render judgment for a reasonable attorney fee in favor of the defendant against the plaintiff.

H. No pregnant female who obtains or possesses RU-486 (mifepristone) for the purpose of inducing an abortion to terminate her own pregnancy shall be subject to any action brought under subsection F of this section.

SECTION 2. REPEALER Section 7, Chapter 36, O.S.L. 2008 (63 O.S. Supp. 2009, Section 1-729), is hereby repealed.

SECTION 3. It being immediately necessary for the preservation of the public peace, health and safety, an emergency is hereby declared to exist, by reason whereof this act shall take effect and be in full force from and after its passage and approval.

Passed the Senate the 10th day of March, 2010.

Presiding Officer of the Senate

Passed the House of Representatives the 29th day of March, 2010.

Presiding Officer of the House
of Representatives

APPENDIX 10

Oklahoma State Senate

Communications Division
State Capitol

Oklahoma City, Oklahoma 73105

For Immediate Release: May 12, 2011

Treat applauds signing of measure regulating abortion-inducing drugs

Sen. Greg Treat today applauded Gov. Mary Fallin's signing of House Bill 1970 – a measure that will require physicians to administer abortion inducing drugs in accordance with U.S. Food and Drug Administration (FDA) guidelines.

"Governor Fallin has been a consistent champion for the sanctity of life, and I'm very pleased she has signed this bill into law," said Treat, R-Oklahoma City. "Oklahoma is blessed to now have a governor who recognizes and defends the value of human life. This legislation protects women and the unborn from potentially deadly medicine."

Co-authored by Treat, the measure will require that physicians examine their patients before prescribing an abortion-inducing drug.

"I'm very grateful to Rep. Grau and Sen. Treat for their efforts to protect the unborn and their mothers," Fallin said. "This legislation provides important safeguards for pregnant women, and is a critical part of our effort to promote the cause of life."

Rep. Randy Grau, principal author of HB 1970, said the bill will also require physicians to schedule a follow-up appointment and provide the patient with the drug's label to ensure the patient is fully aware of the risks associated with the drug.

"I believe abortion-inducing drugs must be better regulated in order to ensure the safety of pregnant women," said Grau, R-Edmond. "Every patient is different and doctors will now be required to perform an exam and schedule follow-up care before prescribing an abortion-inducing drug. This ensures that the drugs are prescribed only after careful review and that the doctor addresses any adverse effects in a follow-up appointment. I thank Governor Fallin for signing the

legislation."

For more information, contact:
Sen. Treat: (405) 521-5632

APPENDIX 11

Measure would restrict abortion-inducing drugs

By BARBARA HOBEROCK World Capitol Bureau on Apr 27, 2011

OKLAHOMA CITY - The Senate on Tuesday passed a measure that would put restrictions on the use of abortion drugs.

House Bill 1970 by Sen. Greg Treat, R-Oklahoma City, and Rep. Randy Grau, R-Edmond, returns to the House for consideration of Senate amendments.

The measure would require physicians to administer abortion-inducing drugs, including RU-486, in accordance with U.S. Food and Drug Administration guidelines.

Treat said the measure is designed to reduce the number of abortions and protect women's health.

The measure would prevent administration of the abortion drugs vaginally and reduce the amount of time the drugs could be administered from 8.4 weeks to seven weeks, requiring more medication, said Kate Neary-Pounds, director of Reproductive Services of Tulsa.

"Barring women from having a medical abortion after seven weeks' gestation forces women to undergo a surgery procedure when they otherwise would have the option of a safe procedure using the medications alone," Neary-Pounds said. "Our experience shows that making the process more difficult doesn't change a woman's mind, it just creates more of a burden on the patient and the provider. This is obviously the intent of the legislation."

Because additional medication would be required, it would potentially result in more side effects, she said.

Current protocol for administering the drugs is based on recommendations by the American College of Obstetricians and Gynecologists and the National Abortion Federation, Neary-Pounds said.

"This legislation makes it a crime to provide a medical abortion under a protocol that is based on scientific, medical evidence, denying women in Oklahoma access to what is standard medical practice," she said.

In other action:

The Senate passed a measure that would allow holders of concealed-carry permits to leave guns in locked cars on CareerTech campuses. CareerTech superintendents have voiced opposition to the measure. Kara Gae Neal, Tulsa Technology Center's superintendent and CEO, is among them.

HB 1652 heads to a conference committee, said Sen. Steve Russell, R-Oklahoma City, the Senate author. It must be heard again by both chambers if it comes out of the committee, he said.

The Senate sent Gov. Mary Fallin a bill that would raise fees associated with disposal of tires. HB 1939 would increase the fee on most passenger vehicles to $2.50 a tire from $1, said Sen. Rob Johnson, R-Kingfisher, the Senate author.

Johnson said the measure is needed because the fund that pays for the disposal of tires doesn't have enough money to cover costs.

The Senate passed HB 1010, which would increase the age of judicial retirement to 67 from 65. It would allow some judges to retire at 62 but receive fewer benefits. The measure heads to the House, said Sen. Brian Crain, R-Tulsa.

APPENDIX 12

Legislation updates at the State Capitol

• Published: May 12, 2011

BILL UPDATES

PUBLIC ART

At stake: House Bill 1665 suspends the Art in Public Places Act, which requires that a percentage of certain state construction projects be spent on public art. The program is suspended for the next three fiscal years.

What happened: Signed by the governor.

What's next: Takes effect in late August.

Anti-abortion

At stake: House Bill 1970 requires physicians to administer abortion-inducing drugs in accordance with U.S. Food and Drug Administration guidelines.

What happened: Signed by the governor.

What's next: Takes effect Nov. 1.

License fees

At stake: Senate Bill 953 increases the fee for reinstatement of a suspended driver's license from $25 to $50. The increase is to go to a trooper academy to train Oklahoma Highway Patrol recruits.

What's happened: Signed by the governor.

What's next: Takes effect in late August.

Report fees

At stake: Senate Bill 954 increases the cost for Oklahoma Highway Patrol collision reports from $7 to $15. The increase is to go to a trooper academy to train patrol recruits.

What happened: Signed by the governor.

What's next: Takes effect July 1.

COURTS

At stake: House Bill 1234 would authorize district courts to expand the use of videoconferencing in various court proceedings.

What happened: Passed House 92-0.

What's next: Goes to the governor.

MICHAEL MCNUTT, CAPITOL BUREAU

APPENDIX 13

AMERICANS UNITED FOR LIFE

AUL Says Oklahoma HB 1970 Protects Women from Dangerous Off-Label Use of Abortion-Inducing Drugs

May 12, 2011

"The enactment of HB 1970 puts an end to the dangerous, off-label use of abortion-inducing drugs – a predatory practice promoted by an abortion industry more concerned with profits than women's health and safety," said Daniel McConchie, AUL Vice President of Government Affairs.

Oklahoma City, OK – (May 12, 2011) – Americans United for Life praised Oklahoma Governor Mary Fallin for signing HB 1970, a law that will ensure abortion providers are not dispensing already-dangerous abortion-inducing drugs in an unapproved and medically-inappropriate manner.

HB 1970 requires that abortion providers dispense abortion-inducing drugs only in the way tested and approved by the Food and Drug Administration (FDA) and outlined in the drug's label. These requirements will prevent the dangerous "off-label" use of abortion-inducing drugs that has killed at least seven women in the United States alone—an "off-label" use that Planned Parenthood readily admits, on its website and in court documents, to using. Rep. Randy Grau and Sen. Greg Treat introduced the bill for the purpose of protecting women from the proven dangers inherent in abortion-inducing drugs. The new law will require that physicians examine a woman before dispensing an abortion-inducing drug to assess the stage of the pregnancy and to ensure that she does not have any hidden conditions making the drug even more dangerous for her.

Daniel McConchie, Vice President of Government Affairs for Americans United for Life, commended the Governor and state legislators who acted on the bill: "For too long, abortion providers have been dispensing abortion-inducing drugs in an unsafe manner that serves only to boost their profit margins. With this legislation, this practice will stop and women in Oklahoma will be better protected from such predatory practices in the state."

To see a copy of the law, visit:
http://www.oklegislature.gov/BillInfo.aspx?Bill=hb1970 [1]

For more information on the Abortion-Inducing Drug Safety Act, go to:
http://www.aul.org/legislative-resources/order-model-legislation [2].

http://www.aul.org/2011/05/aul-says-oklahoma-hb-1970-protects-women-from-dangerous-off-label-use-of-abortion-inducing-drugs/

Paid for by Americans United for Life