U.S. FOOD & DRUG ADMINISTRATION

August 29, 2023

Meredith Di Liberto, Esq.
Judicial Watch, Inc.
425 Third Street, SW
Suite 800
Washington, DC 20024
Via Email: mdiliberto@judicialwatch.org

RE: FDA FOIA Requests 2022-1620, 2022-1621 and 2022-1622;
Judicial Watch, Inc. v. HHS, Civ. A. No. 22-3152 (APM)

Dear Ms. Di Liberto:

This is a response to the Freedom of Information Act (FOIA) request numbers 2022-1620, 2022-1621, and 2022-1622 that is the subject of the Complaint in *Judicial Watch, Inc. v. HHS*, Civ. A. No. 22-3152 (APM), now pending in the U.S. District Court for the District of Columbia.

FOIA requests 2022-1620, 2022-1621, and 2022-1622 seek, among other things, correspondence regarding Mifeprex (mifepristone) stability and dissolution test results. Please find enclosed 588 pages of responsive records. The pages are Bates-numbered FDACDER000001 to FDACDER000588.

Please direct any questions regarding this response to Christine Coogle of the Department of Justice, at (202) 880-0282 or christine.l.coogle@usdoj.gov.

Sincerely,

Howard R. Philips

Howard Philips
Supervisory Regulatory Counsel
Division of Information Disclosure Policy
Center for Drug Evaluation and Research

cc: Christine Coogle, Esq.
Stephanie Nguyen, Esq.

POPULATION COUNCIL/DANCO LABORATORIES, LLC

ANNUAL REPORT FOR MIFEPRISTONE TABLETS, 200 mg

NDA # 20-687

TIME PERIOD COVERED: SEPTEMBER 28, 2000 –SEPTEMBER 27, 2001

This document constitutes trade secret and confidential commercial information exempt from public disclosure under 21 C.F.R. 20.61. Should FDA tentatively determine that any portion of this document is disclosable in response to a request under the Freedom of Information Act, Danco Laboratories, LLC requests immediate notification and an opportunity for consultation in accordance with 21 C.F.R. 20.45. Contact number is [redacted]

TABLE OF CONTENTS

9(a) SUMMARY OF SIGNIFICANT NEW INFORMATION

The reporting period for the first year since approval included approximately ten and a half months during which Mifeprex was available to health care providers and their patients.

During that time, thirty-two adverse events were reported to Danco and reported by Danco to FDA in periodic reports. Of the 32 reported adverse events, two were 15-day reports (the others were not serious and/or not unexpected). One of the 15-day reports was reported as "hemorrhage due to a ruptured ectopic pregnancy and death." The other was reported as "post abortal parametritis/endometritis, adult respiratory distress syndrome and bilateral pneumonia." This latter 15-day report and one case where fever was reported represent the total reports on the marketed drug suggesting infection. In addition, one infection was reported in the Population Council's 200 mg mifepristone study and one death due to clostridium sordelli infection was reported in the Canadian study. A labeling supplement submitted on November 14, 2001 proposed new text on bacterial infection for inclusion in the prescribing information.

The approval letter for this product waived the pediatric requirement, so nothing on that subject is reported.

9(b) DISTRIBUTION DATA

During the reporting period of September 28, 2000 to September 27, 2001, a total of [redacted] batches were released for distribution.

The NDC number for Mifepristone Tablets, 200 mg is 64875-001-03. A summary of the commercial distribution data for the reporting period is tabulated below.

DISTRIBUTION DATA FOR MIFEPRISTONE TABLETS, 200 mg

NDC 64875-001-03	Number of packages (3 tablets/package)
Number of patient packs shipped	[redacted]
Number of patient packs returned (short dating)	
Net number in commerce	

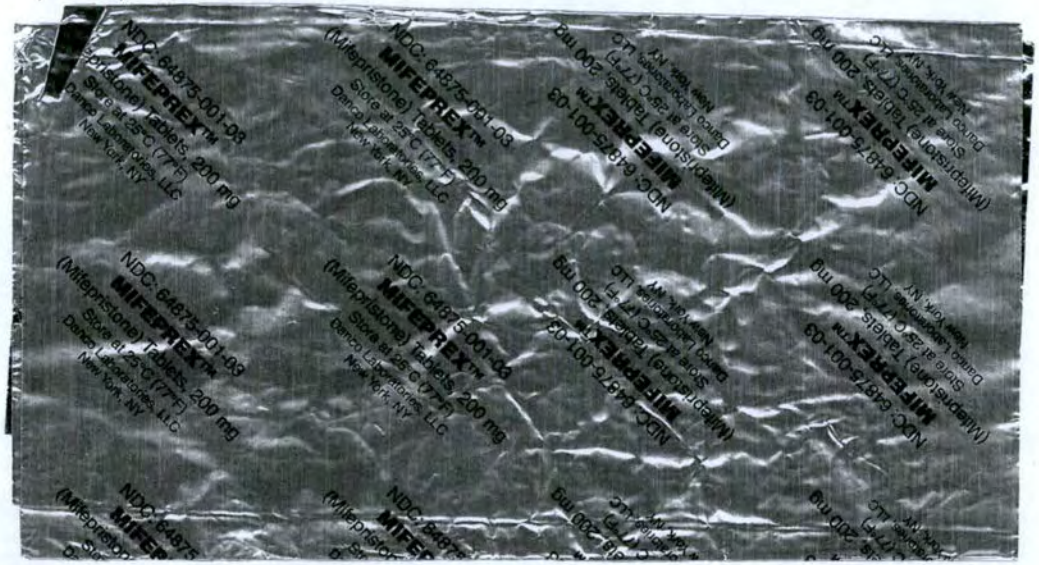
The distribution system agreed with the FDA at approval remains in place.

9(c) LABELING

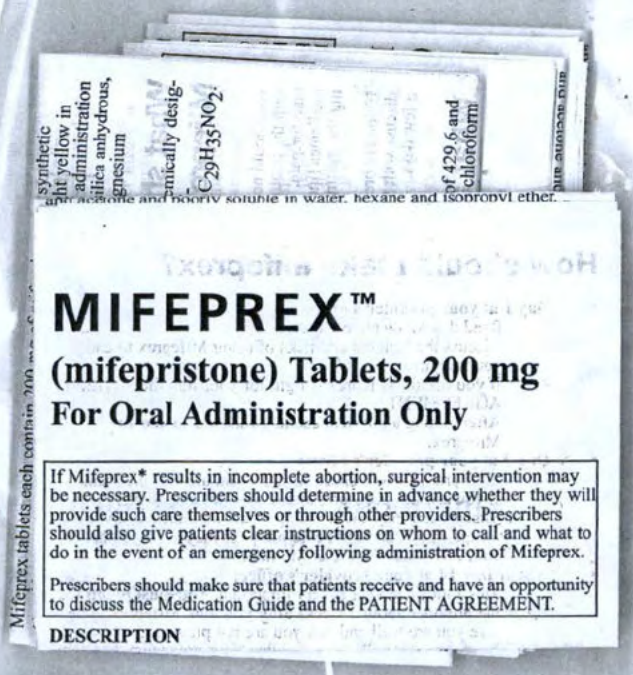
There were no changes in the labeling during the reporting period.

Attached are samples of the printed foil, package insert, package carton, patient brochure and medication guide.

NDA 20-687
Sample of Aluminum Foil
September 2001



NDA 20-687
Sample of Package Insert
September 2001



MIFEPREX™

(mifepristone) Tablets, 200 mg

For Oral Administration Only

If Mifeprex* results in incomplete abortion, surgical intervention may be necessary. Prescribers should determine in advance whether they will provide such care themselves or through other providers. Prescribers should also give patients clear instructions on whom to call and what to do in the event of an emergency following administration of Mifeprex.

Prescribers should make sure that patients receive and have an opportunity to discuss the Medication Guide and the PATIENT AGREEMENT.

DESCRIPTION

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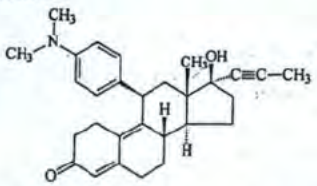
DESCRIPTION

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 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);
- 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
(see CONTRAINDICATIONS)

1. Bleeding

Vaginal bleeding occurs in almost all patients during the treatment procedure. According to data from the U.S. and French trials, women should expect to experience 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.

In some cases, excessive bleeding may require treatment by 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. Confirmation of Pregnancy Termination

Patients should be scheduled for and return for a follow-up visit at approximately 14 days after administration of mifepristone to confirm that the pregnancy is completely terminated and to assess the degree of bleeding. Vaginal bleeding is not evidence of the termination of pregnancy. Termination can be confirmed by clinical examination or ultrasonographic scan. Lack of bleeding following treatment, however, usually indicates failure. Medical abortion failures should be managed with surgical termination.

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. 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 or heavy vaginal bleeding is not proof of a complete expulsion;
- 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

Over 620,000 women in Europe have taken mifepristone in combination with a prostaglandin to terminate pregnancy. Among these 620,000 women, about 415,000 have received mifepristone together with misoprostol. As of May 2000 a total of 82 cases have 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

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 anti-progestational 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 1% in the U.S. and French trials are shown in Table 3.

Bleeding and 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, Bleeding for additional information). Women also typically experience abdominal pain, including uterine cramping. Other commonly reported side effects were nausea, vomiting and diarrhea. Pelvic pain, fainting, headache, dizziness, and asthenia occurred rarely. 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
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.

OVERDOSAGE

No serious adverse reactions were reported in tolerance studies in healthy non-pregnant female and healthy male subjects where mifepris- 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 healthcare 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 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 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 the most important information I should know about Mifeprex?

Mifeprex is used to end an early pregnancy. 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. By using Mifeprex, you probably will not need a surgical procedure to end your pregnancy.

When you use Mifeprex, you also need to take another medicine called misoprostol. You take misoprostol 2 days after you take Mifeprex.

You need to sign a statement (PATIENT AGREEMENT). Before you get Mifeprex, you will need to read and understand the information in this Medication Guide. Then you will need to sign a statement that you have decided to end your pregnancy.

You must visit your provider on Day 1, Day 3, and about Day 14. See the section called "How should I take Mifeprex?" for information about what happens at each visit. If you do not follow all the steps in "How should I take Mifeprex?" you will not know if your pregnancy has ended.

What to do if you are still pregnant after Mifeprex or 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.

Symptoms to expect. This treatment causes cramping and bleeding. 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.

If you are not already bleeding after taking Mifeprex, you probably will begin to bleed once you take misoprostol. This is a 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 that come from your uterus. This is an expected part of ending the pregnancy.

Heavy bleeding and the need for surgery. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (curettage) to stop it. This is why you must talk with your provider about what to do if you need emergency care to stop heavy and possibly dangerous bleeding.

Before you take Mifeprex. Your provider will give you a telephone number to call if you have any questions, concerns, or problems. Your provider will also give you the name and phone number of who will handle emergencies.

Talk with your provider. You and your provider should discuss the benefits and risks for you of using Mifeprex.

What is Mifeprex?

Mifeprex blocks a hormone needed for your pregnancy to continue. When used together with another medicine called misoprostol, Mifeprex ends your pregnancy. About 5-8 out of 100 women taking Mifeprex will need a surgical procedure to end the pregnancy or to stop too much bleeding.

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:**
  - Your provider will check to see if you are still pregnant.
  - If you are still pregnant, take 2 misoprostol tablets.
  - Misoprostol may cause cramps, nausea, diarrhea, and other symptoms. Your health care 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 2 weeks after you took 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?

You should not take certain other medicines, because they may interfere with the treatment. Ask your provider about what medicines you can take for pain. 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.

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

What are the possible side effects of using Mifeprex?

See the section "What is the most important information I should know about Mifeprex?" for symptoms to expect.

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

Other side effects of the 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.

If you are worried about any side effects you have, talk with your provider about them. Your provider will give you a telephone number to call if you have any questions, concerns, or problems. Your provider's telephone number is _____.

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 US Food and Drug Administration.

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.
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 the 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:

- 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: _____

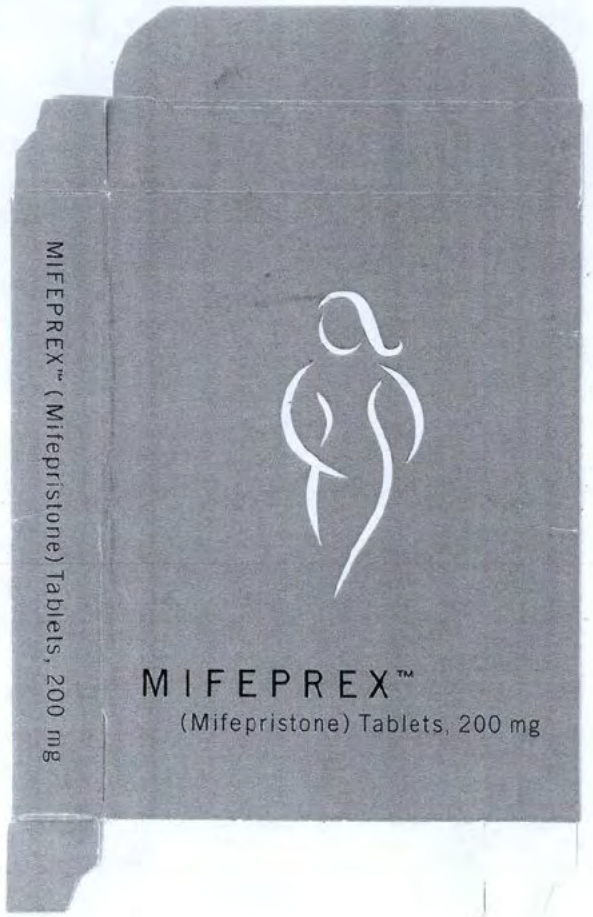
Name of Provider print: _____

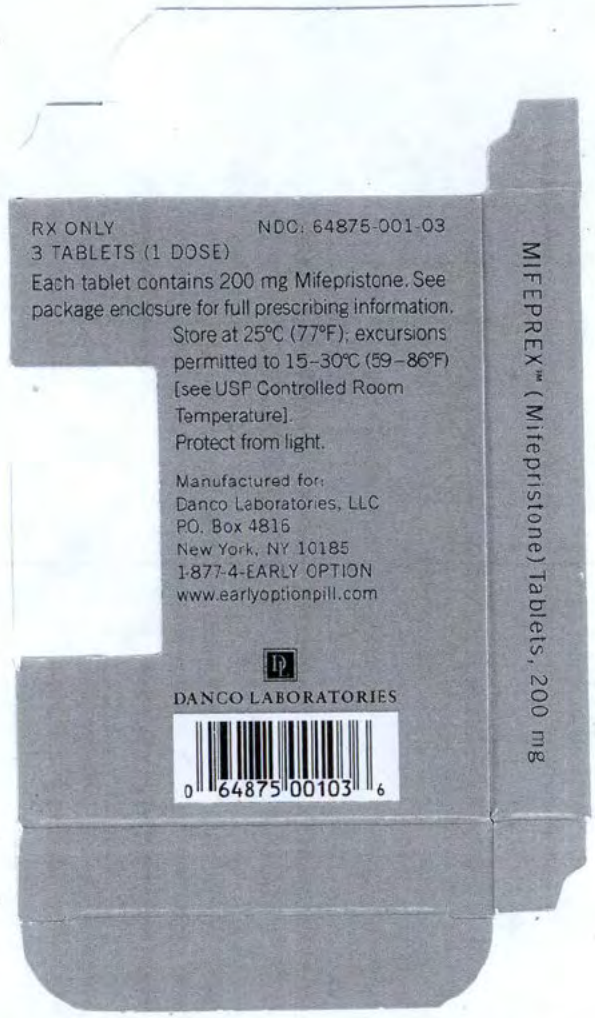
Date: _____

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.

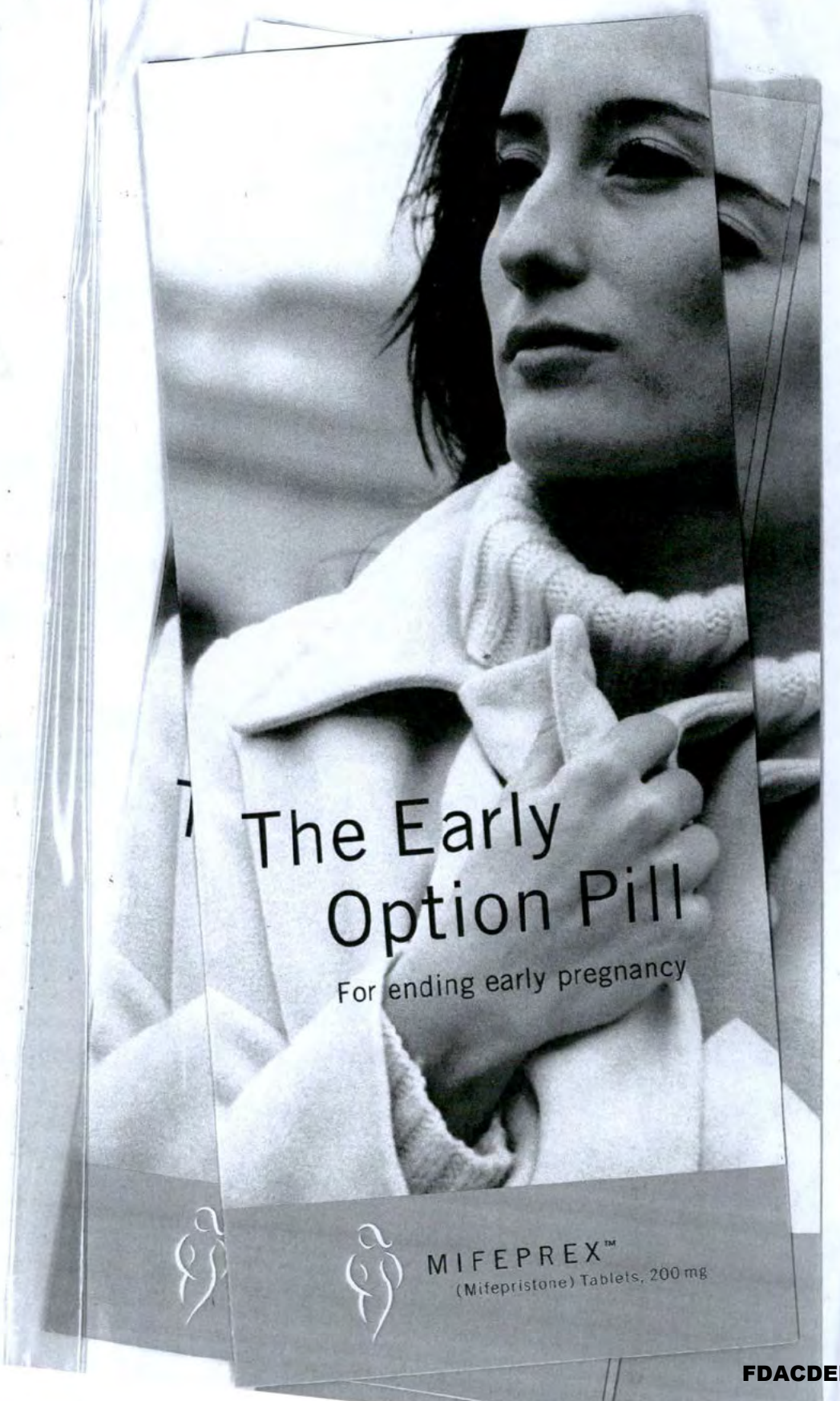
9/28/00

NDA 20-687
Sample of Package Carton
September 2001





NDA 20-687
Sample of Patient Brochure
September 2001



PRIVATE OPTION

How is Mifeprex provided?

Mifeprex is provided through a doctor's office or clinic. The early option pill can be taken only during the first seven weeks of pregnancy. You make three visits over a two-week period. At the first visit, you receive the Medication Guide (to help you understand how the early option works), counseling and sign a statement that you have decided to end your pregnancy. You then take three tablets, each containing 200 milligrams of Mifeprex.

Two days later, you return and take two tablets each containing 200 micrograms of misoprostol. A follow-up visit approximately 12 days later is very important to check that the pregnancy has ended because if it has not ended, there is a chance that there may be birth defects. A few women who take Mifeprex will need a surgical procedure to end the pregnancy or to stop heavy bleeding. Your health care provider will communicate to you how s/he has planned to handle this possibility.

Mifeprex offers you a more private option, with support and counseling readily available throughout the process. Your provider will give you a name and number to call if you have any questions and, if different, a name and number to call in an emergency.

Where do I get more information?

For more information on Mifeprex*, please contact the Mifeprex hotline by phone at: 1-877-4 Early Option (1-877-432-7596)

Or find us on the Internet at: www.earlyoptionpill.com

The Early Option Pill

For ending early pregnancy

* Mifeprex is a trademark of Danco Laboratories, LLC.

DANCO LABORATORIES

MIFEPREX™
(Mifepristone) Tablets, 200 mg

The Early Option Pill

What is Mifeprex™?

Mifeprex is a new option for American women. It is the first Food and Drug Administration (FDA) approved early option pill for ending early pregnancy. Mifeprex followed by misoprostol is a safe and effective non-surgical method for ending early pregnancy. Women in Europe have used this option for more than a decade.

Why choose Mifeprex?

Mifeprex is a non-invasive early option for ending pregnancy. Mifeprex is taken orally, allowing you to avoid anesthesia or surgery in most cases. Some women feel it is a more private option. When you choose the early option pill, you will receive counseling and support throughout the process.

A PROVEN REGIMEN

What experience has there been with Mifeprex?

Mifeprex has gone through the rigorous Food and Drug Administration (FDA) approval process for safety and effectiveness. Mifeprex is the only FDA approved pill for ending early pregnancy. You should tell your provider about any medications you are taking. You should discuss with your health care provider whether or not Mifeprex is right for you.

In Europe, over half a million women have used this drug. Worldwide, this early option has now been approved for use in eighteen countries.

How effective is Mifeprex?

Mifeprex followed by misoprostol is approximately 92–95 percent effective in ending pregnancy.

MIFEPREX AND YOU

How does Mifeprex work?

Mifeprex blocks a hormone needed to maintain pregnancy. When followed by another medicine, misoprostol, Mifeprex ends the pregnancy.

What are the side effects of Mifeprex?

Bleeding and cramping are a normal part of the process. You may experience bleeding similar to or greater than a heavy period and can expect bleeding or spotting for an average of 9–16 days. In some cases, women may have severe bleeding and need to contact their doctor right away. Side effects of the combined regimen that may occur include nausea, headache, vomiting, diarrhea, dizziness, fatigue and back pain. You can take a pain reliever to help alleviate discomfort.

NDA 20-687
Sample of Medication Guide
September 2001

MEDICATION GUIDE

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MIFEPREX™
(Mifepristone) Tablets, 200 mg

The Early Option Pill

DANCO LABORATORIES
P.O. Box 4816
New York, NY 10185

1.877.4 EARLY OPTION
(1.877.432.7596)

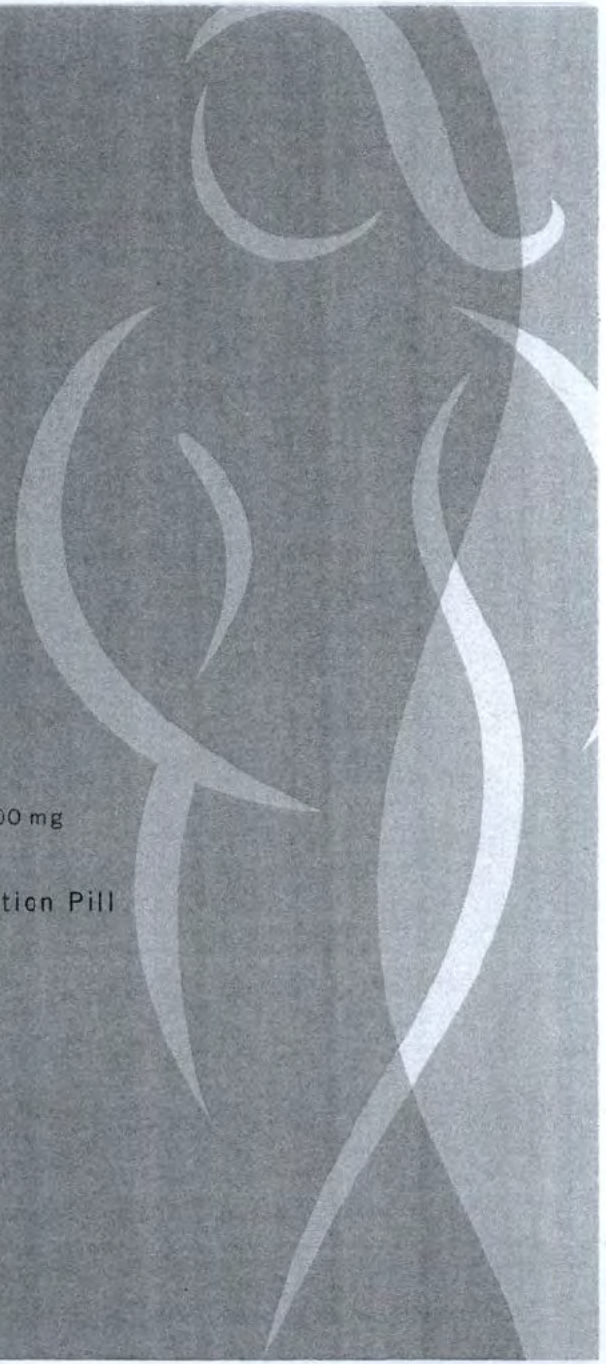
www.earlyoptionpill.com

MEDICATION GUIDE

MIFEPREX™

(Mifepristone) Tablets, 200 mg

The Early Option Pill



CONTACT INFORMATION

Danco Laboratories
P.O. Box 4816
New York, NY 10185

1.877.4 EARLY OPTION
(1.877.432.7596)
www.earlyoptionpill.com

MEDICATION GUIDE

MIFEPREX™ (Mifepristone) Tablets, 200 mg
For Oral Administration Only

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 the most important information I should know about Mifeprex?

Mifeprex is used to end an early pregnancy. 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. By using Mifeprex, you probably will not need a surgical procedure to end your pregnancy.

When you use Mifeprex, you also need to take another medicine called misoprostol. You take misoprostol 2 days after you take Mifeprex.

You need to sign a statement (PATIENT AGREEMENT). Before you get Mifeprex, you will need to read and understand the information in this Medication Guide. Then you will need to sign a statement that you have decided to end your pregnancy.

You must visit your provider on Day 1, Day 3, and about Day 14. See the section called "How should I take Mifeprex?" for information about what happens at each visit. If you do not follow all the steps in "How should I take Mifeprex?" you will not know if your pregnancy has ended.

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

* Mifeprex is a trademark of Danco Laboratories, LLC.

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

Symptoms to expect. This treatment causes cramping and bleeding. 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.

If you are not already bleeding after taking Mifeprex, you probably will begin to bleed once you take misoprostol. This is a 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 that come from your uterus. This is an expected part of ending the pregnancy.

Heavy bleeding and the need for surgery. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (curettage) to stop it. This is why you must talk with your provider about what to do if you need emergency care to stop heavy and possibly dangerous bleeding.

Before you take Mifeprex. Your provider will give you a telephone number to call if you have any questions, concerns, or problems. Your provider will also give you the name and phone number of who will handle emergencies.

Talk with your provider. You and your provider should discuss the benefits and risks for you of using Mifeprex.

What is Mifeprex?

Mifeprex blocks a hormone needed for your pregnancy to continue. When used together with another medicine called misoprostol, Mifeprex ends

your pregnancy. About 5-8 out of 100 women taking Mifeprex will need a surgical procedure to end the pregnancy or to stop too much bleeding.

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:**
  - Your provider will check to see if you are still pregnant.
  - If you are still pregnant, take 2 misoprostol tablets.
  - Misoprostol may cause cramps, nausea, diarrhea, and other symptoms. Your health care 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 2 weeks after you took 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?

You should not take certain other medicines, because they may interfere with the treatment. Ask your provider about what medicines you can take for pain. 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.

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

What are the possible side effects of using Mifeprex?

See the section "What is the most important information I should know about Mifeprex?" for symptoms to expect.

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

Other side effects of the 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.

If you are worried about any side effects you have, talk with your provider about them. Your provider will give you a telephone number to call if you have any questions, concerns, or problems. Your provider's telephone number is _____.

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.

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.
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 the 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:
    - 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.

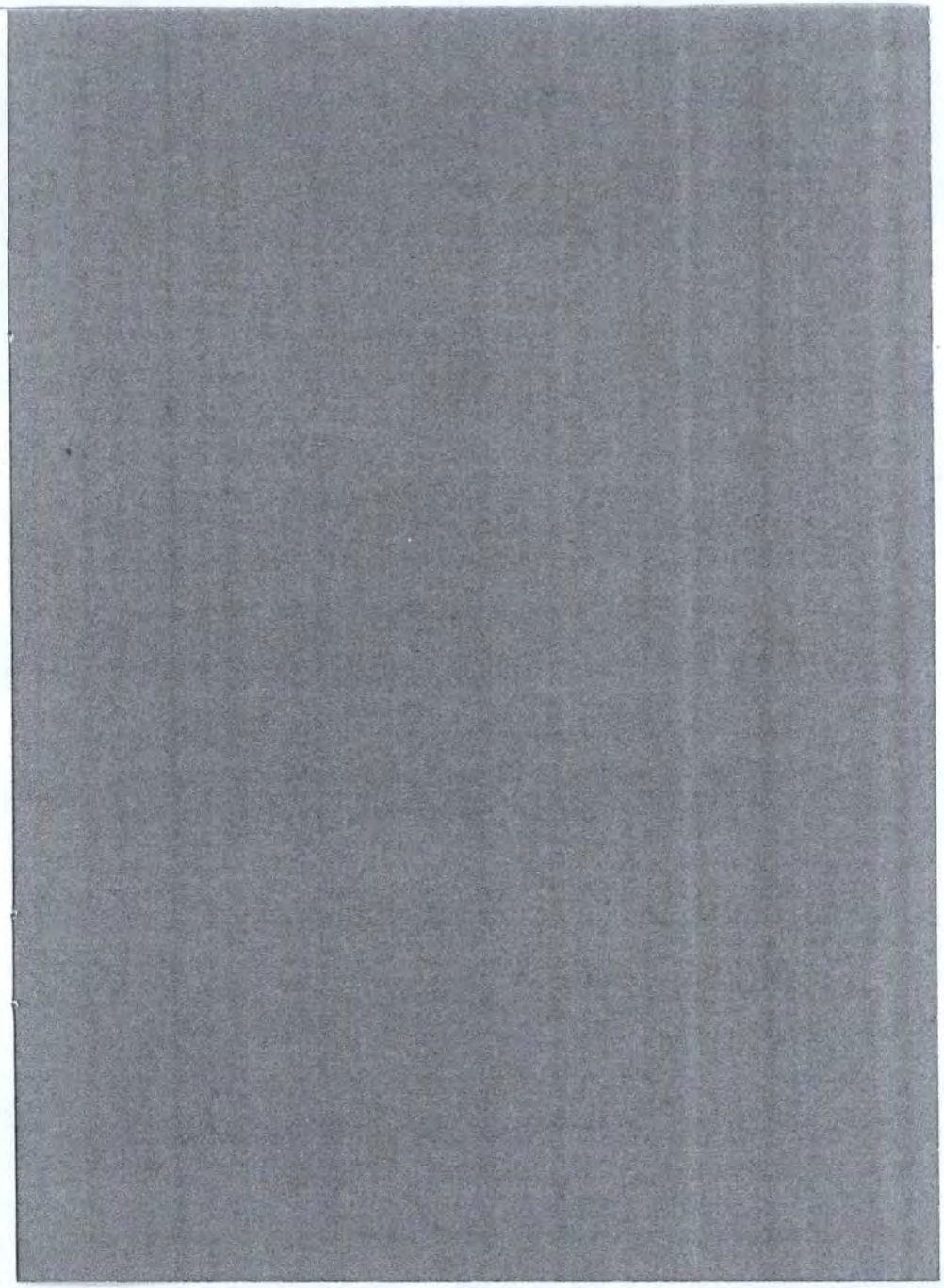
Provider's Signature: _____

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.

9/28/00



9(d) CHEMISTRY MANUFACTURING AND CONTROLS CHANGES

9(d) 1. Drug Substance

9(d) 1.1. Specifications and Test Methods

There were no changes in test methods or specifications during the reporting period.

9(d) 1.2. Manufacturing Procedure

There were no changes in manufacturing procedures during the reporting period. Batches of kg of Drug Substance remain the standard.

During the report period the code numbers for auxiliary materials were changed. In addition, two new suppliers were approved, one for and one for . The Table in the Substance CMC Section, pages 146 and 147 has been revised to show the new code numbers for Auxiliary Raw materials and the two new suppliers, which have been highlighted, in bold print. See Attachment 1.

9(d) 1.3. Packaging Procedure

There were no changes in the packaging materials or procedures during the reporting period.

9(d) 1.4. Stability Data

The three batches of Drug Substance submitted in the original Drug Substance CMC, lot numbers , remain on long-term stability. Additionally, new batches, lot numbers, , reflecting the altered manufacturing process in place prior to the September 2000 FDA Approval, remain on long term stability. Finally, three batches from 2001 lot numbers have been put on long term, stability during the year. Data on all those batches described above are included in Attachment 2.

All data to date on all batches continue to demonstrate the stability of the Drug Substance.

9(d) 2. Drug Product

9(d) 2.1. Specifications and Test Methods

There were no changes in test methods or specifications during the reporting period. A copy of the specifications is included as Attachment 3. The test methods had been previously submitted in Amendment 069 dated January 30, 2001.

As an update to our previous commitment to review the specification for residual [redacted] (NMT [redacted] %) in the Drug Product after [redacted] batches were manufactured, we have since manufactured [redacted] batches of Mifepristone Tablets, 200 mg and will finalize the specification upon completion of the [redacted] batch.

The results to date for the residual [redacted] for the [redacted] batches were "non-detectable" because the levels were below the limit of quantification for the method (LOQ is [redacted] %).

9(d) 2.2. Formulation

There were no changes in the formulation of the Drug Product.

9(d) 2.3. Manufacturers of Drug Substance and Inactive Ingredients

There were no changes in the manufacturer of the Drug Substance or the manufacturer of any of the inactive ingredients.

9(d) 2.4. Manufacturing Procedure

There were no changes in the manufacturing procedure. The current manufacturing procedure is designated as MPR # 100101 Rev # 03, dated November 11, 1999. This was previously submitted in Amendment 038, dated December 7, 1999 as Attachment 1.

9(d) 2.5. Packaging Procedure

There were no changes in the packaging materials (types or manufacturers) used to produce the blister cards.

There were minor changes to the blister packaging procedure. The changes were formatting and the inclusion of more detail to document the operations. A new labeling procedure was prepared and added to the packaging procedure to document the blister card labeling, the intermediate carton labeling and the shipping carton labeling.

The previously submitted procedure was designated as MPR P00101 Rev #02 dated 11/11/99. During the reporting period, two revisions were made to this procedure. They were designated as Rev # 03; dated 10/16/2000 and Rev #04 dated 11/6/2000. A summary of the changes is tabulated below.

Table comparing Procedure P00101 Rev #03 to P00101 Rev #02
(All steps refer to the step # in Rev #03.)

Step #	Change made

Table comparing Procedure P00101 Rev #04 to P00101 Rev #03
(All steps refer to the step # in Rev #04.)

Step #	Change made

Copies of the revised blister packaging and labeling procedures (P00101 Rev #03 and P00101 Rev #04) are included as Attachment 4 and Attachment 5, respectively.

9(d) 2.6. Stability Data

The batches that are in the current stability program are lot numbers These batches were placed in both the controlled room temperature and accelerated stability programs. All batches were manufactured by our approved contract manufacturer for the finished product and tested by our approved contract-testing laboratory. The stability data for each of the five batches are summarized in Attachment 6. The batches met all stability specifications at each time interval. The stability data continues to support the long-term stability of the Drug Product.

9(d) 2.7. Additional Stability Studies

Danco Laboratories committed to performing X-ray diffraction analysis on the first three batches of Drug Product that were stored for 6 months in the accelerated stability chamber. The data for the first two batches (lot numbers [redacted] were previously submitted in Amendment 044, dated April 20, 2000 as Attachment 4. The X-ray diffraction data from the third lot, number [redacted], is now available and is included as Attachment 7. The data from all three batches demonstrate that the crystal structure of the drug substance remains unchanged after 6 months of storage in the accelerated stability chamber.

9(e) Non-Clinical Laboratory Studies

9(e) 1. Unpublished Reports

During the reporting period, there were no unpublished reports of non-clinical studies conducted with mifepristone of which we are aware.

9(e) 2. Published Reports

Appended in Attachment 8 is an updated bibliography of non-clinical publications on mifepristone and copies of abstracts of selected references on the effects of mifepristone in non-clinical studies are appended in Attachment 9. Copies of listed references will be provided upon request.

9(f) Clinical Data

9(f) 1. Published Clinical Trials of the Drug

Appended in Attachment 10 is an updated bibliography of clinical references for mifepristone and in Attachment 11, abstracts of clinical publications on mifepristone related to abortion and to long-term use. Copies of these references will be provided upon request.

9(f) 2. Summaries of Completed Unpublished Clinical Trials

Summaries of completed unpublished clinical trials which have come to our attention are appended in Attachment 12.

9(f) 3. Other Clinical Trials

Below is a tabulation of clinical investigators to whom Danco has provided Drug Product. Investigational use of the drug is described in IND's held by the individual investigators.

[redacted]

In addition, Drug Substance has been provided to the [redacted] for two separate studies being conducted by [redacted]

9(g) Status Reports - Post Marketing Studies

9(g) 1. Status Reports – Post Marketing Study Commitments [21CFR 314.81(b)(2)(vii)]

Study Commitment Status Report Not for Public Release

Appended in Attachment 13 is a confidential status report of the postmarketing study commitments not for public release.

Study Commitment Status Report for Public Release

Appended in Attachment 14 is a status report of the postmarketing study commitments for public release.

9(g) 2. Other Post Marketing Studies [21CFR 313.81 (b)(2)(viii)]

Ongoing Clinical Studies

Status reports of other ongoing postmarketing studies are provided in Attachment 15.

Completed Clinical Studies

Other post marketing studies completed during this reporting period are provided in Attachment 16.

Stability Issues

Status reports for all product stability studies are provided in Section 9(d) 2.6.

ATTACHMENT 1

1.6.1 Auxiliary Raw materials and Suppliers

Code Number	Name	Supplier

Code Number	Name	Supplier

ATTACHMENT 2

LONG TERM STABILITY STUDIES

Lot No.

TESTS	SPECIFICATIONS	RESULTS & TEST DATE				
		1999.01.07	1999.02.09	1999.03.10	1999.04.09	1999.07.14

ENVIRONMENTAL CONDITIONS:

PACKING:

Tabulated by:

Reviewed by:

LONG TERM STABILITY STUDIES (2)

Lot No.

TESTS	SPECIFICATIONS	RESULTS & TEST DATE 1999.10.16	2000.01.16	2000.07.13	2001.01.13	

ENVIRONMENTAL CONDITIONS:

PACKING:

Tabulated by:

Reviewed by:

LONG TERM STABILITY STUDIES

Lot No.

TESTS	SPECIFICATIONS	RESULTS & TEST DATE				
		1999.01.15	1999.02.15	1999.03.22	1999.04.16	1999.07.14

ENVIRONMENTAL CONDITIONS:

PACKING:

Tabulated by:

Reviewed by:

LONG TERM STABILITY STUDIES (2)

Lot No.

TESTS	SPECIFICATIONS	RESULTS & TEST DATE 1999.10.16	2000.01.16	2000.07.13	2001.01.13	

ENVIRONMENTAL CONDITIONS:

PACKING:

Tabulated by:

Reviewed by:

[redacted]

LONG TERM STABILITY STUDIES

Lot No. [redacted]

TESTS	SPECIFICATIONS	RESULTS & TEST DATE				
		1999.01.20	1999.02.22	1999.03.24	1999.04.22	1999.07.28
[redacted]						

ENVIRONMENTAL CONDITIONS: [redacted]

PACKING: [redacted]

Tabulated by: [redacted]

Reviewed by: [redacted]

LONG TERM STABILITY STUDIES (2)

Lot No.

TESTS	SPECIFICATIONS	RESULTS & TEST DATE 1999.10.16	2000.01.16	2000.07.13	2001.01.13	

ENVIRONMENTAL CONDITIONS:

PACKING:

Tabulated by:

Reviewed by:

LONG TERM STABILITY STUDIES (1)

LOT No.

TESTS	SPECIFICATIONS	RESULTS & TEST DATE				
		2000. 01.21	2000.03.03	2000.04.03	2000.05.07	2000.08.09

ENVIRONMENTAL CONDITIONS:

PACKING:

Tabulated by: Reviewed by:

LONG TERM STABILITY STUDIES (2)

LOT No.		RESULTS & TEST DATE				
TESTS	SPECIFICATIONS	2000.11.06	2001.02.06	2001.08.10		

ENVIRONMENTAL CONDITIONS:

PACKING:

Tabulated by:

Reviewed by:

LONG TERM STABILITY STUDIES (1)

LOT No.

TESTS	SPECIFICATIONS	RESULTS & TEST DATE				
		2000.04.06	2000.05.07	2000.06.07	2000.07.05	2000.10.11

ENVIRONMENTAL CONDITIONS:

PACKING:

Tabulated by:

Reviewed by:

LONG TERM STABILITY STUDIES (2)

LOT No.		RESULTS & TEST DATE				
TESTS	SPECIFICATIONS	2001.01.13	2001.04.10	2001.07.05		

ENVIRONMENTAL CONDITIONS:

PACKING:

Tabulated by:

Reviewed by:

LONG TERM STABILITY STUDIES (1)

LOT No.

TESTS	SPECIFICATIONS	RESULTS & TEST DATE				
		2000. 05.31	2000.07.14	2000.08.17	2000.09.14	2000.12.13

ENVIRONMENTAL CONDITIONS:

PACKING:

Tabulated by: Reviewed by:

LONG TERM STABILITY STUDIES (2)

LOT No.		RESULTS & TEST DATE				
TESTS	SPECIFICATIONS	2001.03.12	2001.06.11			

ENVIRONMENTAL CONDITIONS:

PACKING:

Tabulated by:

Reviewed by:

ACCELERATED STABILITY STUDIES

LOT No.		RESULTS & TEST DATE				
TESTS	SPECIFICATIONS	2000. 05.31	2000.07.14	2000.08.17	2000.09.14	2000.12.13

ENVIRONMENTAL CONDITIONS:

PACKING:

LONG TERM STABILITY STUDIES (1)

LOT No.

TESTS	SPECIFICATIONS	RESULTS & TEST DATE				
		2000.05.31	2000.07.14	2000.08.17	2000.09.14	2000.12.15

ENVIRONMENTAL CONDITIONS:

PACKING:

Tabulated by:

Reviewed by:

LONG TERM STABILITY STUDIES (2)

LOT No.		RESULTS & TEST DATE				
TESTS	SPECIFICATIONS	2001.03.12	2001.06.11			

ENVIRONMENTAL CONDITIONS:

PACKING:

Tabulated by:

Reviewed by:

ACCELERATED STABILITY STUDIES

LOT No.

TESTS	SPECIFICATIONS	RESULTS & TEST DATE				
		2000.05.31	2000.07.14	2000.08.17	2000.09.14	2000.12.15

ENVIRONMENTAL CONDITIONS:

PACKING:

Tabulated by:

Reviewed by:

LONG TERM STASBILITY STUDIES (1)

LOT No.

TESTS	SPECIFICATIONS	RESULTS & TEST DATE				
		2000.05.31	2000.07.14	2000.08.17	2000.09.14	2000.12.16

ENVIRONMENTAL CONDITIONS:

PACKING:

Tabulated by:

Reviewed by:

LONG TERM STABILITY STUDIES (2)

LOT No.		RESULTS & TEST DATE				
TESTS	SPECIFICATIONS	2001.03.15	2001.06.11			

ENVIRONMENTAL CONDITIONS:

PACKING:

Tabulated by: Reviewed by:

ACCELERATED STASBILITY STUDIES

LOT No.

TESTS	SPECIFICATIONS	RESULTS & TEST DATE				
		2000.05.31	2000.07.14	2000.08.17	2000.09.14	2000.12.16

ENVIRONMENTAL CONDITIONS:

PACKING:

LONG TERM STABILITY STUDIES (1)

LOT No.

TESTS	SPECIFICATIONS	RESULTS & TEST DATE				
		2001.01.17	2001.03.15	2001.04.09	2001.05.09	2001.08.10

ENVIRONMENTAL CONDITIONS:

PACKING:

Tabulated by:

Reviewed by:

LONG TERM STABILITY STUDIES (1)

LOT No.

TESTS	SPECIFICATIONS	RESULTS & TEST DATE				
		2001.02.09	2001.03.16	2001.04.09	2001.05.09	2001.08.10

ENVIRONMENTAL CONDITIONS:

PACKING:

Tabulated by:

Reviewed by:

LONG TERM STASBILITY STUDIES (1)

LOT No.

TESTS	SPECIFICATIONS	RESULTS & TEST DATE				
		2001.02.09	2001.03.16	2001.04.10	2001.05.09	2001.08.10

ENVIRONMENTAL CONDITIONS:

PACKING:

Tabulated by: Reviewed by:

ATTACHMENT 3

SPECIFICATIONS FOR MIFEPRISTONE TABLETS, 200 mg

IN-PROCESS SPECIFICATIONS

Test	Specification	Method
[redacted]		

Prepared by: [redacted] Approved by: [redacted] Issue Date: 8/31/05

SPECIFICATIONS FOR MIFEPRISTONE TABLETS, 200 mg

FINISHED PRODUCT AND STABILITY SPECIFICATION

Test	Specification	Method
[redacted]		

Prepared by: [redacted] Approved by: [redacted] Issue Date: 8/31/05

Danco Laboratories, Inc.

SPECIFICATIONS FOR MIFEPRISTONE TABLETS, 200 mg

HISTORY OF CHANGE

Date	Changes Made	Prepared by
10/6/99	[redacted]	[redacted]
8/21/00		

Prepared by: [redacted] Approved by: [redacted] Issue Date: 8/31/00

ATTACHMENT 4

DANCO LABORATORIES, INC.

PKG MPR: P00101	Rev.#: 03	Effective Date: October 16,2000	Batch #	Exp. Date:
Product Name: Mifepristone Tablets: (200 mg)			Issue Date: October 16,2000	Page 1 of 16

BLISTER PACKAGING OPERATION

A. **BLISTER PACK SIZE**: 1 X 3 Blister/Mini carton

B. **BLISTER PACK COMPONENTS:**

[redacted]

Calculated By: _____ Checked By: _____ Date: _____

PREPARED BY: [redacted]	DATE: 10/14/00	APPROVED [redacted]	DATE: 10/14/00

PKG MPR: P00101	Rev.#: 03	Effective Date: October 16,2000	Batch #	Exp. Date:
Product Name: Mifepristone Tablets: (200 mg)			Issue Date: October 16,2000	Page 2 of 16

BLISTER PACKAGING OPERATION

[redacted]

Performed By:	Date:
Checked By:	Date:
Quality Assurance Check:	Date:

[redacted]

PREPARED BY:	[redacted]	DATE: 10/14/00	APPROVED BY	[redacted]	DATE: 10/14/00

PKG MPR: P00101	Rev.#: 03	Effective Date: October 16,2000	Batch #	Exp. Date:
Product Name: Mifepristone Tablets: (200 mg)			Issue Date: October 16,2000	Page 3 of 16

Performed By:	Date:
Checked By:	Date:
Quality Assurance Check:	Date:

[redacted]

Performed By:	Date:
Checked By:	Date:
Quality Assurance Check:	Date:

[redacted]

Performed By:	Date:
Checked By:	Date:
Quality Assurance Check:	Date:

PREPARED BY: [redacted]	DATE: 10/14/00	APPROVED BY [redacted]	DATE: 10/14/00

PKG MPR: P00101	Rev.#: 03	Effective Date: October 16,2000	Batch #	Exp. Date:
Product Name: Mifepristone Tablets: (200 mg)			Issue Date: October 16,2000	Page 4 of 16

[redacted]

Date: _____ Time End:_____

Time	Start Up								
[redacted]									

PREPARED BY:	[redacted]	DATE: 10/14/00	APPROVED BY	[redacted]	DATE: 10/14/00

PKG MPR: P00101	Rev.#: 03	Effective Date: October 16,2000	Batch #	Exp. Date:
Product Name: Mifepristone Tablets: (200 mg)			Issue Date: October 16,2000	Page 5 of 16

[redacted]

[redacted]				

PREPARED BY: [redacted]	DATE: 10/14/00	APPROVED BY: [redacted]	DATE: 10/14/00

PKG MPR: P00101	Rev.#: 03	Effective Date: October 16,2000	Batch #	Exp. Date:
Product Name: Mifepristone Tablets: (200 mg)			Issue Date: October 16,2000	Page 6 of 16

(b) (4)

Visual Check of Blisters

Time (min)	Actual Time	Appearance [A] (Pass/Fail)	Count [A] (Pass Fail)	Performed By
(b) (4)				

PREPARED BY: (b) (4), (b) (6)	DATE: 10/14/02	APPROVED BY: (b) (4), (b) (6)	DATE: 10/14/02

PKG MPR: P00101	Rev.#: 03	Effective Date: October 16,2000	Batch #	Exp. Date:
Product Name: Mifepristone Tablets: (200 mg)			Issue Date: October 16,2000	Page 7 of 16

(b) (4)

Time Interval Inspected	Appearance [A] (Pass/Fail)	Count [A] (Pass Fail)	Performed By

(b) (4)

PREPARED BY: (b) (4), (b) (6)	DATE: 10/14/00	APPROVED BY (b) (4), (b) (6)	DATE: 10/14/00

PKG MPR: P00101	Rev.#: 03	Effective Date: October 16,2000	Batch #	Exp. Date:
Product Name: Mifepristone Tablets: (200 mg)			Issue Date: October 16,2000	Page 8 of 16

(b) (4)

[redacted]

PREPARED BY: (b) (4), (b) (6)	DATE: 10/14/00	APPROVED BY (b) (4), (b) (6)	DATE: 10/14/00

PKG MPR: P00101	Rev.#: 03	Effective Date: October 16,2000	Batch #	Exp. Date:
Product Name: Mifepristone Tablets: (200 mg)			Issue Date: October 16,2000	Page 9 of 16

LABELING AND FINAL PACKAGING OPERATION

(b) (4)

(b) (4)

#_____

#_____

#_____

#_____

#_____

(b) (4)

Performed By:	Date:
Checked By:	Date:
Quality Assurance Check:	Date:

PREPARED BY: (b) (4), (b) (6)	DATE: 10/14/00	APPROVED BY (b) (4), (b) (6)	DATE: 10/14/00

PKG MPR: P00101	Rev.#: 03	Effective Date: October 16,2000	Batch #	Exp. Date:
Product Name: Mifepristone Tablets: (200 mg)			Issue Date: October 16,2000	Page 10 of 16

(b) (4)

[redacted]

Performed By:	Date:
Checked By:	Date:
Quality Assurance Check:	Date:

PREPARED BY:	(b) (4), (b) (6) [redacted]	DATE: 10/14/00	APPROVED BY	(b) (4), (b) (6) [redacted]	DATE: 10/14/00

PKG MPR: P00101	Rev.#: 03	Effective Date: October 16,2000	Batch #	Exp. Date:
Product Name: Mifepristone Tablets: (200 mg)			Issue Date: October 16,2000	Page 11 of 16

(b) (4)

[redacted]

QA Label Check: Performed By: _____ Date: _____

PREPARED BY: (b) (4), (b) (6) [redacted]	DATE: 10/14/02	APPROVED BY: (b) (4), (b) (6) [redacted]	DATE: 10/14/02

PKG MPR: P00101	Rev.#: 03	Effective Date: October 16,2000	Batch #	Exp. Date:
Product Name: Mifepristone Tablets: (200 mg)			Issue Date: October 16,2000	Page 12 of 16

(b) (4)

[redacted]

Performed By: _____ Date: _____ Time Start: _____

Performed By: _____ Date: _____

Performed By: _____ Date: _____

Performed By: _____ Date: _____ Time Finished: _____

(b) (4)

[redacted]

System Started By: _____ Date: _____ Time: _____

(b) (4)

[redacted]

(b) (4), (b) (6)

PREPARED BY [redacted]	DATE: 10/14/00	APPROVED [redacted]	DATE: 10/14/00

PKG MPR: P00101	Rev.#: 03	Effective Date: October 16,2000	Batch #	Exp. Date:
Product Name: Mifepristone Tablets: (200 mg)			Issue Date: October 16,2000	Page 13 of 16

(b) (4)

[redacted]

QA Label Check: Performed By: _____ Date:_____

(b) (4)

[redacted]

Performed By: _____ Date: _____ Time Start: _____

Performed By: _____ Date: _____

Performed By: _____ Date: _____

Performed By: _____ Date: _____ Time Finished: _____

(b) (4)

[redacted]

(b) (4), (b) (6)

PREPARED BY: [redacted]	DATE: 10/14/00	APPROVED BY [redacted]	DATE: 10/14/00

PKG MPR: P00101	Rev.#: 03	Effective Date: October 16,2000	Batch #	Exp. Date:
Product Name: Mifepristone Tablets: (200 mg)			Issue Date: October 16,2000	Page 14 of 16

Performed By:	Date:

Quality Assurance Verification: _____

Date: _____

(b) (4)

[redacted]

Label reconciliation performed by: _____ Date: _____ Time: _____

Label reconciliation verified by: _____ Date: _____ Time: _____

(b) (4)

[redacted]

PREPARED BY: (b) (4), (b) (6) [redacted]	DATE: 10/14/00	APPROVED BY (b) (4), (b) (6) [redacted]	DATE: 10/14/0

PKG MPR: P00101	Rev.#: 03	Effective Date: October 16,2000	Batch #	Exp. Date:
Product Name: Mifepristone Tablets: (200 mg)			Issue Date: October 16,2000	Page 15 of 16

(b) (4)

[redacted]

QA Label Check: Performed By: _____ Date:_____

(b) (4)

[redacted]

Performed By: _____ Date: _____ Time Start: _____

PREPARED BY:	(b) (4), (b) (6) [redacted]	DATE: 10/14/00	APPROVED BY	(b) (4), (b) (6) [redacted]	DATE: 10/14/00

PKG MPR: P00101	Rev.#: 03	Effective Date: October 16,2000	Batch #	Exp. Date:
Product Name: Mifepristone Tablets: (200 mg)			Issue Date: October 16,2000	Page 16 of 16

Performed By: _____ Date: _____ Time Finished: _____

(b) (4)

[redacted]

26. Quality Assurance review of the batch record and approval for shipment
QA Approved By:_____ Date:_____
Danco QA: _____ Date: _____

PREPARED BY: (b) (4), (b) (6) [redacted]	DATE: 10/14/00	APPROVED BY (b) (4), (b) (6) [redacted]	DATE: 10/14/00

Request for a Change in a Master Production and Control Record

(To be filled in by the person requesting the change)

Product Name: Mifepristone Tablets Document # to Change: P00101 Rev #3

Change Requested: Statement to document retain Sampler.

Reason for change: There was no place to document retain Sample

Requested by: (b) (4), (b) (6) Date: ~~10/3~~ 11/6/00

(To be filled in by the senior member of the quality unit)

Change accepted?: ☒ yes ☐ no

Revalidation required?: ☐ yes ☐ no

FDA prior approval required?: ☐ yes ☐ no

If the "no" box was checked, enter the reason for the decision: _____

By: (b) (4), (b) (6) Date: 11/6/00

Title: _____

Send a copy of this completed form to the person requesting the change.
Attach a copy of the FDA approval letter to this form if it was requested and obtained.
File this completed form with the document that was obsoleted.

Form: 1802

ATTACHMENT 5

DANCO LABORATORI . INC.

PKG MPR: P000101	Rev.#: 04	Effective Date: November 7,2000	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001			Issue Date: November 6,2000	Page 1 of 14

BLISTER PACKAGING OPERATION

A. **BLISTER PACK SIZE:** 1 X 3 Blister/Mini carton

B. **BLISTER PACK COMPONENTS:**

(b) (4)

[redacted]

Calculated By: _____ Checked By: _____

PREPARED BY: (b) (4), (b) (6) [redacted]	DATE: 11/6/00	APPROVED (b) (4), (b) (6) [redacted]	DATE: 11.6.00

DANCO LABORATORIES, INC.

PKG MPR: P000101 .	Rev.#: 04	Effective Date: November 7,2000	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001			Issue Date: November 6,2000	Page 2 of 14

BLISTER PACKAGING OPERATION

(b) (4)

[redacted]

Performed By:	Date:
Checked By:	Date:
Quality Assurance Check:	Date:

(b) (4)

[redacted]

Performed By:	Date:
Checked By:	Date:
Quality Assurance Check:	Date:

(b) (4)

[redacted]

PREPARED BY:	(b) (4), (b) (6) [redacted]	DATE: 11/6/00	APPROVED BY:	[redacted]	DATE: 11-6-00

DANCO LABORATORI . INC.

PKG MPR: P000101	Rev.#: 04	Effective Date: November 7,2000	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001			Issue Date: November 6,2000	Page 3 of 14

(b) (4)

[redacted]

Performed By:	Date:
Checked By:	Date:
Quality Assurance Check:	Date:

(b) (4)

[redacted]

Performed By:	Date:
Checked By:	Date:
Quality Assurance Check:	Date:

(b) (4)

[redacted]

(b) (4), (b) (6)

[redacted]

PREPARED BY	DATE: 11/6/00	APPROVED BY:	DATE: 11.6.00

(b) (4), (b) (6)

[redacted]

DANCO LABORATORIES, INC.

PKG MPR: P000101	Rev.#: 04	Effective Date: November 7,2000	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001			Issue Date: November 6,2000	Page 4 of 14

Date: _____ Time End: _____

Time	Start Up								
(b) (4)									

(b) (4)

(b) (4)				

PREPARED BY: (b) (4), (b) (6)	DATE: 11/6/00	APPROVED BY (b) (4), (b) (6)	DATE: 11.6.00

(b) (4)
[redacted]

Visual Check of Blisters

Time(min)	Actual Time	Appearance [A] (Pass/Fail)	Count [A] (Pass Fail)	Performed By
(b) (4) [redacted]				

(b) (4)
[redacted]

PREPARED BY: (b) (4), (b) (6) [redacted]	DATE: 11/6/00	APPROVED BY: (b) (4), (b) (6) [redacted]	DATE: 11-6-00

DANCO LABORATORIES, INC.

PKG MPR: P000101	Rev.#: 04	Effective Date: November 7,2000	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001			Issue Date: November 6,2000	Page 6 of 14

(b) (4)

(b) (4)

PREPARED BY: (b) (4), (b) (6)	DATE: 11/6/00	APPROVED BY: (b) (4), (b) (6)	DATE: 11-6-00

DANCO LABORATORIES, INC.

PKG MPR: P000101	Rev.#: 04	Effective Date: November 7,2000	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001			Issue Date: November 6,2000	Page 7 of 14

Yield calculated by: _____ Calculation verified by: _____

(b) (4)

LABELING AND FINAL PACKAGING OPERATION

(b) (4)

Performed By:	Date:
Checked By:	Date:
Quality Assurance Check:	Date:

(b) (4)

PREPARED BY:	(b) (4), (b) (6)	DATE: 11/6/00	APPROVED BY	(b) (4), (b) (6)	DATE: 11,6.00

DANCO LABORATORIES, INC.

PKG MPR: P000101	Rev.#: 04	Effective Date: November 7,2000	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001			Issue Date: November 6,2000	Page 8 of 14

(b) (4)

[redacted]

Performed By:	Date:
Checked By:	Date:
Quality Assurance Check:	Date:

(b) (4)

[redacted]

System Started By: _____ Date: _____ Time: _____

PREPARED BY:	(b) (4), (b) (6) [redacted]	DATE: 11/6/00	APPROVED BY	(b) (4), (b) (6) [redacted]	DATE: 11.6.00

DANCO LABORATORIES, INC.

PKG MPR: P000101	Rev.#: 04	Effective Date: November 7,2000	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001			Issue Date: November 6,2000	Page 9 of 14

(b) (4)

[redacted]

QA Label Check: Performed By: _____ Date: _____

(b) (4)

[redacted]

Performed By: _____ Date: _____ Time Start: _____

Performed By: _____ Date: _____

Performed By: _____ Date: _____

Performed By: _____ Date: _____ Time Finished: _____

(b) (4)

[redacted]

PREPARED BY: (b) (4), (b) (6) [redacted]	DATE: 11/6/00.	APPROVED BY (b) (4), (b) (6) [redacted]	DATE: 11.6.00

DANCO LABORATORIES, INC.

PKG MPR: P000101	Rev.#: 04	Effective Date: November 7,2000	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001			Issue Date: November 6,2000	Page 10 of 14

(b) (4)

System Started By: _____ Date: _____ Time: _____

(b) (4)

QA Label Check: Performed By: _____ Date: _____

(b) (4)

Performed By: _____ Date: _____ Time Start: _____

Performed By: _____ Date: _____

Performed By: _____ Date: _____

Performed By: _____ Date: _____ Time Finished: _____

PREPARED BY: (b) (4), (b) (6)	DATE: 11/6/00	APPROVED BY (b) (4), (b) (6)	DATE: 11.6.00

DANCO LABORATORIES, INC.

PKG MPR: P000101	Rev.#: 04	Effective Date: November 7,2000	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001			Issue Date: November 6,2000	Page 11 of 14

(b) (4)

[redacted]

Performed By:	Date:
Quality Assurance Verification: _____ Date: _____	

(b) (4)

[redacted]

Label reconciliation performed by: _____ Date: _____ Time: _____

Label reconciliation verified by: _____ Date: _____ Time: _____

(b) (4)

[redacted]

PREPARED BY: (b) (4), (b) (6) [redacted]	DATE: 11/6/00	APPROVED BY (b) (4), (b) (6) [redacted]	DATE: 11-6-00

DANCO LABORATORIES, INC.

PKG MPR: P000101	Rev.#: 04	Effective Date: November 7,2000	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001			Issue Date: November 6,2000	Page 12 of 14

(b) (4)

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QA Label Check: Performed By: _____ Date: _____

(b) (4)

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Performed By: _____ Date: _____ Time Start: _____

Performed By: _____ Date: _____ Time Finished: _____

PREPARED BY: (b) (4), (b) (6) [redacted]	DATE: 11/6/00	APPROVED BY (b) (4), (b) (6) [redacted]	DATE: 11.6.00

DANCO LABORATORIES, INC.

PKG MPR: P000101	Rev.#: 04	Effective Date: November 7,2000	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001			Issue Date: November 6,2000	Page 13 of 14

(b) (4)

[redacted]

QUALITY ASSURANCE REVIEW OF PACKAGING BATCH RECORD:

Quality Assurance Review By: _____ Date: _____

Danco Quality Assurance Approval for Shipment

By: _____ Date: _____

PREPARED BY: (b) (4), (b) (6) [redacted]	DATE: 11/6/00.	APPROVED BY (b) (4), (b) (6) [redacted]	DATE: 11.6.00

DANCO LABORATORIES, INC.

PKG MPR: P000101	Rev.#: 04	Effective Date: November 7,2000	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001			Issue Date: November 6,2000	Page 14 of 14

History of Change

Revision Number	Date Of Revision	Revised By	Reason for Revision
1			
2			
3	October 16, 2000	(b) (4), (b) (6)	(b) (4)
4	November 7, 2000		

PREPARED BY: (b) (4), (b) (6)	DATE: 11/6/00.	APPROVED BY (b) (4), (b) (6)	DATE: 11.6.00

ATTACHMENT 6

STABILITY STUDY REPORT FOR BATCH # (b) (4)
CONTROLLED ROOM TEMPERATURE STUDY

Product: Mifepristone Tablets, 200 mg	**Batch #:** (b) (4)
Purpose of study: Controlled Room Temperature	**Manufacturing date**: 6/28/99
Batch size: (b) (4) tablets	**Expiration date:** 1/2001
Ingredient	**Manufacturer**

(b) (4)

CONTAINER/CLOSURE SYSTEM

(b) (4)

EVALUATION SCHEDULE

(b) (4)

STABILITY DATA

(b) (4)

STABILITY STUDY REPORT FOR BATCH # (b) (4)
ACCELERATED STABILITY STUDY

Product: Mifepristone Tablets, 200 mg	**Batch #:** (b) (4)
Purpose of study: Accelerated Stability	**Manufacturing date**: 6/28/99
Batch size: (b) (4) tablets	**Expiration date:** 1/2001
Ingredient	**Manufacturer**
(b) (4)	

CONTAINER/CLOSURE SYSTEM

(b) (4)

EVALUATION SCHEDULE

(b) (4)

STABILITY DATA

(b) (4)

STABILITY STUDY REPORT FOR BATCH # (b) (4)
CONTROLLED ROOM TEMPERATURE STUDY

Product: Mifepristone Tablets, 200 mg	**Batch #:** (b) (4)
Purpose of study: Controlled Room Temperature	**Manufacturing date**: 9/22/99
Batch size: (b) (4) tablets	**Expiration date**: 3/2001
Ingredient	**Manufacturer**
(b) (4)	

CONTAINER/CLOSURE SYSTEM

(b) (4)

EVALUATION SCHEDULE

(b) (4)

STABILITY DATA

(b) (4)

STABILITY STUDY REPORT FOR BATCH # (b) (4)
ACCELERATED STABILITY STUDY

Product: Mifepristone Tablets, 200 mg	**Batch #:** (b) (4)
Purpose of study: Accelerated Stability	**Manufacturing date**: 9/22/99
Batch size: (b) (4) tablets	**Expiration date:** 3/2001
Ingredient	**Manufacturer**
(b) (4)	

CONTAINER/CLOSURE

(b) (4)

EVALUATION SCHEDULE

(b) (4)

STABILITY DATA

(b) (4)

STABILITY STUDY REPORT FOR BATCH # (b) (4)
CONTROLLED ROOM TEMPERATURE STUDY

Product: Mifepristone Tablets, 200 mg	**Batch #:** (b) (4)
Purpose of study: Controlled Room Temperature	**Manufacturing date**: 8/3/00
Batch size: (b) (4) tablets	**Expiration date:** 2/2002

Ingredient	Manufacturer
(b) (4)	

CONTAINER/CLOSURE SYSTEM

(b) (4)

EVALUATION SCHEDULE

(b) (4)

STABILITY DATA

(b) (4)

STABILITY STUDY REPORT FOR BATCH # (b) (4)
ACCELERATED STABILITY STUDY

Product: Mifepristone Tablets, 200 mg	**Batch #:** (b) (4)
Purpose of study: Accelerated Stability	**Manufacturing date**: 8/3/00
Batch size: (b) (4) tablets	**Expiration date:** 2/2002
Ingredient	**Manufacturer**
(b) (4)	

CONTAINER/CLOSURE SYSTEM

(b) (4)

EVALUATION SCHEDULE

(b) (4)

STABILITY DATA

(b) (4)

STABILITY STUDY REPORT FOR BATCH # (b) (4)
CONTROLLED ROOM TEMPERATURE STUDY

Product: Mifepristone Tablets, 200 mg	**Batch #:** (b) (4)
Purpose of study: Controlled Room Temperature	**Manufacturing date**: 9/11/00
Batch size: (b) (4) tablets	**Expiration date:** 3/2002
Ingredient	**Manufacturer**
(b) (4)	

CONTAINER/CLOSURE SYSTEM

(b) (4)

EVALUATION SCHEDULE

(b) (4)

STABILITY DATA

(b) (4)

STABILITY STUDY REPORT FOR BATCH # (b) (4)
ACCELERATED STABILITY STUDY

Product: Mifepristone Tablets, 200 mg	**Batch #:** (b) (4)
Purpose of study: Accelerated Stability	**Manufacturing date**: 9/11/00
Batch size: (b) (4) tablets	**Expiration date:** 3/2002
Ingredient	**Manufacturer**
(b) (4)	

CONTAINER/CLOSURE SYSTEM

(b) (4)

EVALUATION SCHEDULE

(b) (4)

STABILITY DATA

(b) (4)

STABILITY STUDY REPORT FOR BATCH # (b) (4)
CONTROLLED ROOM TEMPERATURE STUDY

Product: Mifepristone Tablets, 200 mg	**Batch #:** (b) (4)
Purpose of study: Controlled Room Temperature	**Manufacturing date**: 10/11/00
Batch size: (b) (4) tablets	**Expiration date**: 4/2002
Ingredient	**Manufacturer**
(b) (4)	

CONTAINER/CLOSURE SYSTEM

(b) (4)

EVALUATION SCHEDULE

(b) (4)

STABILITY DATA

(b) (4)

STABILITY STUDY REPORT FOR BATCH # (b) (4)
ACCELERATED STABILITY STUDY

Product: Mifepristone Tablets, 200 mg	**Batch #:** (b) (4)
Purpose of study: Accelerated Stability	**Manufacturing date**: 10/11/00
Batch size: (b) (4) tablets	**Expiration date:** 4/2002
Ingredient	**Manufacturer**
(b) (4)	

CONTAINER/CLOSURE SYSTEM

(b) (4)

EVALUATION SCHEDULE

(b) (4)

STABILITY DATA

(b) (4)

ATTACHMENT 7

Memo

To: (b) (4), (b) (6)

From: (b) (4), (b) (6)

Date: May 1, 2001

Re: Our Commitment to FDA on stability of Mifepristone (b) (4) Completed.

During the FDA approval process we were able to convince FDA that although there were a number of crystal forms for mifepristone our process always generated (b) (4), (b) (6)

We would expect to report these data to the FDA in the annual update in September.

(b) (4), (b) (6)

(b) (4), (b) (6)

Danco Laboratories, LLC
P. O. Box 4816
New York, NY 10185

DATE: 4/25/01

LAB NO: (b) (4)

CLIENT P.O.

SAMPLE: Mifepristone, Batch #20001 - Pull Date 3/28/01

INFORMATION: (b) (4)

RESULTS:

(b) (4)

(b) (4), (b) (6) has FDA Registration Number (b) (4), (b) (6) DEA Registraion Number (b) (4), (b) (6) and (b) (4), (b) (6).

(b) (4), (b) (6)

(b) (4), (b) (6)

(b) (4), (b) (6)

ATTACHMENT 8

LITERATURE UPDATE – NONCLINICAL

The present update to the bibliography was generated by a search performed using PubMed with the keywords mifepristone and animal from all sources and languages. This bibliography covers the period of September 28, 2000 to September 27, 2001.

The bibliography generated by this strategy includes published articles on non-clinical investigations on mifepristone. A list of these references in alphabetical order is presented below. The reprints of these articles will be supplied upon request.

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ATTACHMENT 9

Contraception 2000 Oct;62(4):189-93

Synergistic effects of DL111-IT combined with mifepristone on termination of early pregnancy in rhesus monkeys.

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The objectives of this study were to determine the synergistic effects of DL111-IT in combination with mifepristone (RU486) on termination of early pregnancy in rhesus monkeys. Pregnancy was confirmed by tactile sensation of pregnant uterus via anus with finger and ultrasound examination. Pregnancy termination was obtained with vaginal bleeding and abortion materials including fetuses and placentae after treatment. With multiple doses of DL111-IT or RU486 given alone between d24 and d50 of gestation, pregnancy arrests were obtained in 40% (2/5) of monkeys treated with DL111-IT intramuscularly (im) (25 mg x kg(-1) x d(-1) x 3 days), in 20% (1/5) of monkeys treated with 9 mg x kg(-1) x d(-1) x 2 days, and 4.5 mg x kg(-1) on day 3 with RU486 intragastrically (ig). DL111-IT (25 mg x kg(-1) on day 1, im) in combination with RU486 (the same treatment as above) resulted in 100% (10/10) termination of pregnancy and uterine bleeding lasted 6.6 +/- 1.3 days. RU486 (as above treatment) in combination with misoprostal (Miso, 109 microg x kg(-1) on day 3, ig) showed 71.4% (5/7) termination of pregnancy, and uterine bleeding lasted 12.9 +/- 9.6 days. The synergistic effect of DL111-IT plus RU486 enhances termination of early pregnancy and significantly shortens the bleeding time than RU486 plus Miso does in rhesus monkeys.

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Biol Reprod 2000 Dec;63(6):1899-904

Altered fetal pituitary-adrenal function in the ovine fetus treated with RU486 and meloxicam, an inhibitor of prostaglandin synthase-II.

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Term and preterm labor are associated with increased fetal hypothalamic-pituitary-adrenal (HPA) activation and synthesis of prostaglandins (PGs) generated through the increased expression of prostaglandin H synthase-II (PGHS-II) in the placenta. Inhibition of PGHS-II has been advocated as a means of producing uterine tocolysis, but the effects of such treatment on fetal endocrine functions have not been thoroughly examined. Because PGE(2) is known to activate the fetal HPA axis, we hypothesized that administration of meloxicam, a PGHS-II inhibitor, to sheep in induced labor would suppress fetal HPA function. Chronically catheterized pregnant ewes were treated with RU486, a progesterone receptor antagonist, to produce active labor, and then treated with either high-maintenance-dose meloxicam, graded-maintenance-dose meloxicam, or a saline infusion. Maternal uterine contraction frequency increased 24 h after the RU486 injection and the animals were in active labor by 48 +/- 4 h. RU486 injection led to increased concentrations of PGE(2), ACTH, and cortisol in the fetal circulation, and increased concentrations of 13,14 dihydro 15-ketoprostaglandin F(2 alpha) (PGFM) in the maternal circulation. Uterine activity was inhibited within 12 h of beginning meloxicam infusion at both infusion regimes. During meloxicam infusion there were significant decreases in fetal plasma PGE(2), ACTH, and cortisol concentrations, and PGFM concentrations in maternal plasma. In control animals, frequency of uterine contractions, maternal plasma PGFM, fetal plasma PGE(2), ACTH, and cortisol concentrations increased after RU486 administration, and continued to rise during saline infusion until delivery occurred. We conclude that RU486-provoked labor in sheep is associated with activation of fetal HPA function, and that this is attenuated during meloxicam treatment to a level considered compatible with pregnancy maintenance.

PMID: 11090463 [PubMed - indexed for MEDLINE]

ATTACHMENT 10

LITERATURE UPDATE – CLINICAL

The present update to the bibliography was generated by a search performed using PubMed with the keywords mifepristone and human from all sources and languages. This bibliography covers the period of September 28, 2000 to September 27, 2001.

The bibliography generated by this strategy includes published articles on clinical investigations on mifepristone. The references are organized alphabetically by author. In addition, the references are subdivided into several sections: 1. Medical Abortion, 2. Long-term Treatment; 3. Termination for Fetal Anomaly or Death; 4. Cervical Ripening and 5. Other (Contraception, Ectopic Pregnancy, Biochemical Effects, etc.). The reprints of these articles will be supplied upon request.

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ATTACHMENT 11

1. Medical Abortion

Obstet Gynecol 2001 Apr;97(4):suppl 1-13

ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists. Medical management of abortion.

American College of Obstetricians and Gynecologists Committee on Practice Bulletins--Gynecology.

According to the U.S. Centers for Disease Control and Prevention, 1.18 million legal abortions were performed in the United States in 1997. Of these, 55.5% were performed at or before 56 days of gestation (calculated from the first day of the last menstrual period [LMP]) (I). Almost 98% of abortion procedures were performed by uterine curettage; all but 1% of these used suction curettage. There were 305 legal induced abortions per 1,000 live births, and the abortion rate was 20 per 1,000 women aged 15-44 years. For the first time in 1997, medical abortions were counted and comprised 0.25% of all abortions; 0.45% of those procedures were performed up to 56 days of gestation. Because of the lack of availability of mifepristone, these procedures mostly represent the use of a combination of methotrexate and misoprostol. Over the past two decades, medical methods of abortion have developed throughout the world and are now used clinically in the United States. This document will present evidence of effectiveness, benefits, and risks of medical methods of abortion and provide a framework for the evaluation and counseling of women who are considering such medical methods.

Publication Types:
Guideline
Practice Guideline

PMID: 11501565 [PubMed - indexed for MEDLINE]

Obstet Gynecol 2001 Jul;98(1):101-6

Curettage after mifepristone-induced abortion: frequency, timing, and indications.

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OBJECTIVE:To characterize women who underwent curettage after medical abortion with mifepristone and vaginal misoprostol, to describe when curettage occurred and the reasons for the intervention, and to categorize the indications for curettage according to a simple classification schema. METHODS: These analyses used data from two multisite, randomized controlled trials sponsored by Abortion Rights Mobilization. In the first study, women pregnant less than 63 days received 200 mg of mifepristone and 800 &mgr;g of vaginal misoprostol to use 48 hours after taking mifepristone. In the second study, women pregnant less than 56 days were randomly assigned to insert vaginal misoprostol at 1, 2, or 3 days after mifepristone administration. Case report forms and clinical case notes of all women who underwent curettage were examined. RESULTS: Of the 4393 women enrolled in both studies, 116 (2.6%, 95% confidence interval 2.1%, 3.1%) curettages were identified. The gestational age and a history of prior elective abortion were associated with the rate of curettage. The distribution of indications for curettage included bleeding, 61 (53%); continuing pregnancy, 17 (15%); patient request, 36 (31%); and indeterminate, 2 (1.7%). The timing of curettage differed by the indication and scheduled interval between study visits. The distribution of the timing was bimodal. One subset of women, 44 (38%), underwent curettage in the first study week and another subset, 43 (37%), during weeks 3-5. CONCLUSION: Curettage after medical abortion with mifepristone and vaginal misoprostol is rare. At least one half of the curettages were performed for persistent bleeding several weeks after treatment. Both acute heavy bleeding and continuing pregnancy are extremely rare.

PMID: 11430965 [PubMed - indexed for MEDLINE]

S Afr Med J 2000 Sep;90(9):889-91

Termination of early pregnancy with a reduced oral dose of mifepristone and vaginal misoprostol.

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OBJECTIVE: To determine the efficacy of termination of pregnancy with a reduced oral dose of mifepristone and vaginal misoprostol. DESIGN: A retrospective review of 369 medical terminations of pregnancy. SETTING: Northern General Hospital, Sheffield, UK. SUBJECTS: All women presenting for medical termination of pregnancy before 63 days' gestation between October 1996 and December 1997. INTERVENTIONS: Patients were pre-treated with mifepristone 200 mg orally, 36-48 hours before the prostaglandin E analogue, misoprostol, was administered vaginally. Two doses of misoprostol 400 micrograms, were given 2 hours apart. Women were allowed home 6 hours after the first dose of misoprostol. If the products of conception were not passed before going home, patients were to contact the hospital if bleeding did not take place within 4 days. OUTCOME MEASURES: Need for a surgical procedure and number of ongoing pregnancies after full treatment were considered primary outcome measures. RESULTS: A total of 369 women were treated with this regimen: 343 women (93.46%) aborted completely within a 6-hour observation period and did not require further intervention. A further 8 women aborted completely within the next 4 days. Overall, the complete abortion rate was 95.64%. Surgical intervention was necessary in 1.09% of the patients. No woman had serious complications. CONCLUSION: This combination is effective, safe and cost-effective in a clinical setting.

PMID: 11081141 [PubMed - indexed for MEDLINE]

Am J Obstet Gynecol 2000 Oct;183(4):998-1002

Mifepristone versus vaginally administered misoprostol for cervical priming before first-trimester termination of pregnancy: a randomized, controlled study.

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OBJECTIVE: This study was undertaken to compare the effectiveness of mifepristone orally administered at 24 or 48 hours before first-trimester vacuum aspiration abortion with that of vaginally administered misoprostol as a cervical priming agent. STUDY DESIGN: In a randomized comparative trial 90 women who requested surgical termination of pregnancy were randomly assigned to receive 200 mg mifepristone orally 24 or 48 hours before the operation or 800 microg misoprostol vaginally 2 to 4 hours before the operation. The main outcome measures were baseline cervical dilatation, cumulative force required to dilate the cervix to 9 mm, and intraoperative blood loss. RESULTS: The baseline cervical dilatation was significantly greater among women who received mifepristone 48 hours before the operation (P =.02). This group also required the least mechanical force to dilate the cervix (P =.06). There were no significant differences among the 3 groups in the intraoperative blood loss, in the operating time, or in patient acceptability. Side effects such as hot flushes and headaches were significantly higher among women who received mifepristone 24 or 48 hours before the operation than among those who received misoprostol (P =.01 and P =. 002, respectively). CONCLUSION: Mifepristone is an effective cervical priming agent when orally administered 48 hours before vacuum aspiration for termination of first-trimester pregnancy. Because of its cost and availability in comparison with misoprostol, however, selective use may have to be considered.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 11035353 [PubMed - indexed for MEDLINE]

Aubeny E.

The European Journal of Contraception and Reproductive Health Care 2001;6:54–57

Letters to the Editor

A two-stage increase in the dose of misoprostol improves the efficacy of medical abortion with mifepristone and prostaglandins

Since 1992 we have been using the drug regimen and protocol authorized in France for the medical termination of early pregnancy (up to 49 days of amenorrhea), i.e. day 1: oral mifepristone 600 mg; day 3: oral misoprostol 400 µg followed by observation for 3 h; days 10–15: follow-up visit. The results using this protocol have been reported[1]. A success rate of 95.4% has been achieved. The failures (4.6%) include cases of continuing pregnancy (1.5%), incomplete abortion (2.8%) and hemostatic curettage (0.3%).

We felt that the rate of failure of the method, although low, should be further decreased and we therefore investigated a new treatment regimen.

In France, women undergoing early medical termination of pregnancy must stay at the treatment center for 4h after the administration of misoprostol (this monitoring period was shortened to 3 h in 1998). Within the 4-h observation period, up to 69.1% women abort and, in approximately 90% of these women, pregnancy was terminated in the first 3 h[1].

We hoped to improve the success rate of the method by the administration of a second dose of misoprostol 3 h after the first, to women who had not aborted within this time. The rationale for this regimen is supported by the clinical observation that the majority of expulsions occur within 3 h of oral intake of misoprostol. After 3 h, the number of observed expulsions decreases rapidly. The clinical observation reflects the pharmacokinetic profile of misoprostol: 2 h after oral administration, a rapid decrease in plasma level is seen[2,3].

During 1993–94 and from 1995–97, two alternative drug regimens were studied in a sequential manner. The results are summarized in Table 1.

The decrease in the proportion of continuing pregnancies is highly important; both women and practitioners can be more confident with the procedure. As a consequence of the above observations, regimen 2 is now the routine treatment at Broussais Hospital.

We believe that the sequential administration of two 400-µg doses of misoprostol has a number of advantages, especially if gestation is limited to 49 days. First, it is more effective than a regimen using only a single dose of 400 µg misoprostol. The overall success rate is increased to a level not previously published and, although this may have been due to chance or an increase in operator experience, the 80% reduction in continuing pregnancies is less likely to be due to such factors. The proportion of continuing pregnancies has been reduced to that seen when gemeprost, a particularly potent prostaglandin, is used[5].

It is difficult to compare these results to those observed when misoprostol is given as a single dose of 800 µg. Only El Refaey and colleagues[4] have studied

Table 1 Success rates with a two-step regimen for the early therapeutic termination of pregnancy (≤ 49 days of amenorrhea)

Regimen	*Total number of subjects*	*Number receiving a single dose of misoprostol (400 µg)*	*Number receiving an additional dose of misoprostol*	*Overall success rate (%)*	*Continuing pregnancies (%)*
(1) Mifepristone 600mg + misoprostol 400 µg + 200 µg as required	487	206	281	95.5	1.2
(2) Mifepristone 600mg + misoprostol 400 µg + 400 µg as required	1973	1344	629	98.4*	0.2

*Failures include cases of incomplete abortion (1.4%) and continuing pregnancy (4 cases; 0.2%)

the use of 600 mg mifepristone followed by misoprostol given as a single 800 µg oral or vaginal dose. They reported a success rate lower than ours. However, the age of pregnancy in their series was up to 63 days of amenorrhea (success rate 87% with oral misoprostol).

Second, as the majority of side-effects related to medical termination of pregnancy are associated with the administration of prostaglandin and appear to be dose-related, it is desirable to use the lowest possible dose of prostaglandin. With this method, a large proportion (62.1%) of women will abort within the first 3 h after administration of only the first dose of 400 µg misoprostol. Administration of a larger dose would be unnecessary in the majority of women.

The incidence and severity of uterine pain were lower in our study than in the study by El Refaey and colleagues[4]; both the oral and vaginal routes of administration of 800 µg misoprostol were associated with use of *parenteral* narcotic analgesia in 16% and 10% of women, respectively. In our method, only non-narcotic analgesics were necessary. One may argue that this higher use of narcotic analgesia was due to the inclusion of more advanced pregnancies in the study by El Refaey[4]; however, other work has shown that use of narcotic analgesia is not related to gestation but to other factors (parity, history of dysmenorrhea)[5].

The data of the trials about gastrointestinal side-effects do not allow one to arrive at an assured conclusion because gastrointestinal side-effects were not registered in the same way. Figures about gastrointestinal side-effects in the 800-µg misoprostol trial relate to vomiting alone and diarrhea alone; in the 400 + 400-µg trial, all gastrointestinal side-effects are considered together (nausea + vomiting + diarrhea).

We conclude that, for the medical termination of early pregnancy (up to 49 days of gestation) with oral mifepristone 600 mg and misoprostol 400 µg, the administration of a second oral dose of 400 µg misoprostol to women who have not aborted within 3 h of the first dose increases the overall efficacy of the method. This regimen also appears to be better tolerated than a regimen in which misoprostol is given as a single 800-µg dose.

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: Eur J Contracept Reprod Health Care 2000 Sep;5(3):171-6

A randomized comparison of mifepristone and self-administered oral or vaginal misoprostol for early abortion.

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In France, mifepristone in association with orally administered misoprostol is widely used for the early termination of pregnancy (up to 49 days' gestation). In other centers, mifepristone in association with vaginally administered misoprostol has also been used. The aim of the present study was to compare the efficacy and tolerance of mifepristone in association with misoprostol administered orally or vaginally for the termination of pregnancy of up to 49 days' gestation. A total of 237 women were enrolled in the study. All women received 600 mg mifepristone administered orally and 400 microg misoprostol administered either orally (n = 119) or vaginally (n = 118). A second dose of 400 microg misoprostol was administered if women had not expelled the pregnancy within 3 h. Women were randomized into treatment groups according to the day of their admission. The overall success rate was 98.7% and there was no significant difference in efficacy between the two groups. There was one treatment failure in the group in which misoprostol was administered orally. Of those women who aborted within 3 h of administration of the first dose ofmisoprostol, the route of administration ofmisoprostol did not influence the time to abortion. Of the women who received a second dose ofmisoprostol, the time to abortion was shorter in those who received misoprostol orally (52 min versus 77 min). Tolerance was assessed by visual analog scales and was similar for both groups. In both groups, women preferred the oral route of administration.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

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Parity is a major determinant of success rate in medical abortion: a retrospective analysis of 3161 consecutive cases of early medical abortion treated with reduced doses of mifepristone and vaginal gemeprost.

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The antiprogesterone mifepristone in combination with a suitable prostaglandin provides an effective method for induction of abortion in early pregnancy up to 63 days of gestation. The combination of 600 mg mifepristone followed by 1 mg of gemeprost vaginal pessary 48 h later is one of the standard regimens in practice, which is registered in several countries in Europe. In 1995, we reduced the doses for both mifepristone and gemeprost to 200 mg and 0.5 mg respectively, as this was shown to decrease significantly the incidence of side effects whilst maintaining a high efficacy. In this article, we report our experience with this regimen in routine clinical practice by analysing 3161 consecutive medical abortions retrospectively. Twelve case notes (0.4%) were not available, and for 310 (9.8%) women, the outcome was not known with certainty as they did not return for their follow up visit. Of the remaining 2839 women, 2732 (96.2%) had a complete abortion following their treatment. One-hundred-two (3.6%) women required an evacuation of the uterus: for incomplete abortion in 63 (2.2%) and ongoing pregnancy in 39 (1.4%). Three women had to undergo surgery for ectopic pregnancies. The surgical intervention rate was significantly higher at gestation of >49 days compared to < or = 49 days (5.7% vs. 2.6%, p = 0.002) and at >56 days than among those at < or = 56 days (6.7% vs. 3.1%; p <0.001). However, for incomplete abortion a significant increase was only seen at gestation >49 days compared to < or = 49 days (3% vs. 1.6%, p = 0.017). The incidence of ongoing pregnancies increased significantly only after 56 days of gestation compared to < or = 56 days (3.8% vs. 0.9%; p <0.001). Parity was related to the outcome with parous women having significantly more incomplete/ongoing abortions compared to nulliparous women (5.4% vs. 2.0%; p <0.001), although parous women did present earlier in pregnancy for termination than nulliparous women (p = 0.01). The incidence of complications was low: 165 (5.8%) women were given antibiotics for presumed genital infection and severe haemorrhage occurred in 11 (0.4%) women, of whom only two required blood transfusion. In summary, the recommended regimen with the reduced doses of mifepristone and gemeprost is highly effective, meeting the anticipated efficacy with a complete abortion rate of >95%. We have concluded from the data that gestation and parity are strong predictors for clinicians to anticipate the probability of a successful medical termination of pregnancy.

PMID: 11239616 [PubMed - indexed for MEDLINE]

Journal of Family Planning and Reproductive Health Care 2001: 27(2):97-98

Experiences of termination of pregnancy in a stand-alone clinic situation

Boorer C, Murty J

Summary

This paper describes the authors' experience of conducting termination of pregnancy on conscious patients in community settings. If patients are appropriately selected and prepared, and the procedure conducted in the presence of well-trained and motivated nursing assistance, the method described is successful, safe and acceptable to patients.

Steroids 2000 Oct-Nov;65(10-11):801-5

Pregnancy termination.

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During pregnancy, the antiprogestin mifepristone will induce uterine contractions, increase the sensitivity of the myometrium to prostaglandin, and ripen the cervix. These effects indicate that mifepristone can be used for termination of pregnancy. The clinical experience has shown that mifepristone is sufficiently effective for this purpose only if combined with a suitable prostaglandin, e.g. gemeprost or misoprostol. The combined treatment has been used for termination of early pregnancy (up to 63 days of amenorrhea) and for termination of second trimester pregnancy. During early pregnancy, the recommended dose of mifepristone is 600 mg (although 200 mg seems sufficient), followed 36-48 h later by 0.4-0.8 mg misoprostol administered either orally or vaginally, or vaginal administration of 1.0 mg gemeprost. For termination of second trimester pregnancy, the treatment with mifepristone is most commonly combined with 1.0 mg gemeprost repeated at 3-6-h intervals. The combined treatment is as effective and safe during early pregnancy as is the alternative vacuum aspiration and is also equally acceptable if the woman is allowed to choose the method she prefers. During the second trimester, the pretreatment will significantly reduce the duration of labor, dose of prostaglandin, and the frequency of side effects.

Publication Types:

- Review
- Review, Tutorial

PMID: 11108891 [PubMed - indexed for MEDLINE]

Eur J Contracept Reprod Health Care 2001 Mar;6(1):39-45

Misoprostol for abortion at 9-12 weeks' gestation in adolescents.

Carbonell JL, Velazco A, Varela L, Tanda R, Sanchez C, Barambio S, Chami S, Valero F, Aragon S, Mari J.

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The objectives of the present clinical study were to evaluate the safety and efficacy of misoprostol (Cytotec), self-administered into the vagina for medical abortion, in adolescents under 18 years ofage. A group of 150 adolescents with gestations between 63 and 84 days, with previous written consent from the patient and parents or guardians, received 800 microg of vaginal misoprostol every 24 h, up to a maximum of three main doses, for abortion. Outcomes assessed included successful abortion (complete abortion without surgery), side-effects, decrease in hemoglobin, mean time of vaginal bleeding, mean expulsion time and mean time for the return of menses. Complete abortion occurred in 126/150 (84.0%, 95% confidence interval 77-89) patients. The frequencies of nausea and vomiting were statistically significantly higher when compared to those obtained for adult females. Vaginal bleeding lasted for 13.2 +/- 3.8 days (median 13 days, range 1-22 days). The mean expulsion time was 8.0 +/- 3.4 h (median 8 h, range 1-14 h) for all subjects who aborted after the first misoprostol dose. The mean drop in hemoglobin was statistically significant ($p = 0.001$), but without clinical relevance. From the high abortion rate obtained, we concluded that misoprostol alone is a valid method for terminating unwanted pregnancies at 10-13 weeks' gestation in adolescents under 18 years of age in the absence of mifepristone.

Publication Types:

- Clinical Trial

PMID: 11334475 [PubMed - indexed for MEDLINE]

Hum Reprod 2001 Jan;16(1):67-71

A comparative study of surgical and medical procedures: 932 pregnancy terminations up to 63 days gestation.

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The aim of this retrospective study was to compare the efficacy and complications associated with early medical and surgical pregnancy termination. The study population comprised 932 consecutive women undergoing pregnancy termination at gestations of 63 days or less. There were no age or parity differences between the study groups. Medical termination was performed with mifepristone 200 mg orally and misoprostol 800 microgram vaginally; surgical aspiration termination was performed under general anaesthesia. Outcome measures were: surgical curettage for presumed retained products of conception; ongoing pregnancy; and planned and emergency review in the unit. Early medical and surgical termination were associated with a 90.2 and 94.5% complete abortion rate respectively (P = 0.025). The complete abortion rate with medical termination decreased significantly with increasing parity; no such relationship with surgical abortion was found. Women of parity three or more were less likely to have a complete abortion following a medical (83.3%) compared to surgical procedure (97.7%) (P = 0.028). The ongoing pregnancy rate was 0.9% with medical and 0.5% with surgical termination (P = NS). Medical termination was associated with a lower complete abortion rate than surgical termination, particularly for women of higher parity. However, early medical termination allows over 90% of women to avoid the risks of surgical instrumentation of the uterus and anaesthesia.

Publication Types:

- Clinical Trial

PMID: 11139539 [PubMed - indexed for MEDLINE]

Lancet 2001 Jan 13;357(9250):120-2

Mifepristone abortion outside the urban research hospital setting in India.

Coyaji K, Elul B, Krishna U, Otiv S, Ambardekar S, Bopardikar A, Raote V, Ellertson C, Winikoff B.

Medical abortion holds great promise in less-developed countries, where abortion morbidity and mortality remain high. We tested the French mifepristone-misoprostol regimen in two urban outpatient family-planning clinics (n=600) and a rural hospital (n=300) in India. 4% of urban women and 1% of rural women were lost to follow-up. Perfect use and typical-use success rates were as high as European rates at all sites. Although rural women reported fewer side-effects, most women in urban and rural settings were satisfied with their medical abortions. Medical abortion can be offered safely, effectively, and acceptably in urban outpatient clinics and rural hospitals in India.

Publication Types:

- Letter

PMID: 11197403 [PubMed - indexed for MEDLINE]

Obstet Gynecol 2001 Sep;98(3):434-9

Mifepristone 100 mg in abortion regimens.

Creinin MD, Pymar HC, Schwartz JL.

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OBJECTIVE: To examine the clinical efficacy of mifepristone 100 mg followed 2 days later by misoprostol 400 microg orally or 800 microg vaginally in women at up to 49 days' gestation. METHODS: Eighty participants received mifepristone 100 mg and then were randomized to misoprostol, administered 48 hours later, at a dose of 400 microg orally (group 1) or 800 microg vaginally (group 2). Women returned for follow-up evaluations 24 +/- 1 hour after using the misoprostol and then 2-3 weeks later. If abortion still had not occurred and the pregnancy was nonviable, the subject returned again after an additional 3 weeks. RESULTS: Twenty-four hours after receiving misoprostol, 34 (85%; 95% confidence interval [CI] 71%, 94%) of the 40 women in group 1 and 38 (95%; 95% CI 85%, 99%) of the 40 women in group 2 had complete abortions. Overall, complete abortion without surgical intervention occurred in 34 women in group 1 (85%; 95% CI 71%, 94%) and 40 women in group 2 (100%; 95% CI 91%, 100%; P =.03). Four women in group 1 required suction aspiration for continuing pregnancy at the second follow-up, compared with none in group 2 (P =.12). Side effects occurred with similar frequency in both treatment groups. CONCLUSION: Low-dose mifepristone (100 mg) combined with vaginal misoprostol 800 microg may be an effective alternative to regimens using 200 or 600 mg of mifepristone with misoprostol.

Publication Types:
Clinical Trial
Randomized Controlled Trial

PMID: 11530125 [PubMed - indexed for MEDLINE]

BJOG 2001 May;108(5):469-73

Efficacy of mifepristone followed on the same day by misoprostol for early termination of pregnancy: report of a randomised trial.

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OBJECTIVE: To examine the clinical efficacy of mifepristone 600 mg followed on the same day or two days later by misoprostol 400 microg orally in women undergoing medical termination of pregnancy whose pregnancies have a gestational age up to 49 days. DESIGN: Prospective, randomised trial. SETTING: Clinical research office. PARTICIPANTS: Eighty-six women, requesting elective termination of a pregnancy which has a gestational age of < or = 49 days. METHODS: After administration of mifepristone 600 mg, participants were randomised to take misoprostol six to eight hours later (Group 1) or 48 hours later (Group 2). Women returned for a follow up evaluation 24 +/- 1 hours after taking the misoprostol. Participants in Group 1 who had not aborted received a second dose of misoprostol to take 48 hours after the mifepristone. All women returned approximately two weeks after receiving mifepristone. If termination of pregnancy had still not occurred and the pregnancy was non-viable, the woman returned again in three weeks. MAIN OUTCOME MEASURES: Rate of complete abortion 24 hours after administration of misoprostol. RESULTS: At 24 hours after receiving misoprostol, 21/42 (50%, 95% CI 35%, 65%) women in Group I and 40/44 (91%, 95% CI 82%, 99%) women in Group 2 had complete abortions. By follow up two weeks later after the administration of mifepristone, 40/42 (95%, 95% CI 89%, 100%) women in Group 1 and 43/44 (98%, 95% CI 93%, 99%) women in Group 2 were known to have complete abortions. Nausea, vomiting or diarrhoea in women using the standard regimen (Group 2) occurred in 68%, 36%, and 20%, respectively. CONCLUSIONS: After treatment with mifepristone 600 mg, administration of misoprostol 400 microg orally on the same day is not as effective at causing abortion within the first 24 hours compared with the standard time interval of 48 hours between medications.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 11368131 [PubMed - indexed for MEDLINE]

Ann Pharmacother 2001 Jun;35(6):707-19

Mifepristone.

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OBJECTIVE: To review the efficacy and safety of mifepristone (with misoprostol) for the termination of early pregnancy. DATA SOURCES: A MEDLINE search (1966-October 2000) was conducted, and additional references listed in articles were included; unpublished data obtained from the manufacturer were used to identify data from the scientific literature. Studies evaluating mifepristone were considered for inclusion. STUDY SELECTION: Human clinical studies in the English language were reviewed and evaluated. Clinical trials selected for detailed review were limited to those including the regimens of mifepristone and misoprostol, recently approved by the Food and Drug Administration for early pregnancy termination. DATA SYNTHESIS: Mifepristone is an antiprogestin available for pregnancy termination in combination with a prostaglandin such as misoprostol. Mifepristone offers efficacy similar to, if not better than, other drugs used for pregnancy termination, but appears less efficacious overall than surgical termination of pregnancy. Mifepristone in combination with misoprostol commonly causes adverse effects such as abdominal pain and, less commonly, can cause serious adverse effects such as incomplete abortion; endometritis; and bleeding warranting transfusion, hospitalization, or surgery. Mifepristone is metabolized by the cytochrome P450 system. Thus, the potential for drug interactions with this agent exists, although this has not been well studied. Data are included from clinical trials evaluating the safety, tolerability, efficacy, and pharmacoeconomics of mifepristone combined with misoprostol for early pregnancy termination. Data comparing the use of these agents with surgical abortion and other drugs used for pregnancy termination are included where available. CONCLUSIONS: Mifepristone in combination with misoprostol for the termination of early pregnancy (amenorrhea of < or = 49 d) is effective in 92-95% of women. Incomplete abortion requiring surgical abortion after the fact occurs in 3-5% of women, and pregnancy continues 1-2% of the time. Mifepristone with misoprostol treatment is not without significant risks, including hemorrhage, infection, and potential for long-term emotional consequences.

Publication Types:

- Review
- Review, Tutorial

PMID: 11408990 [PubMed - indexed for MEDLINE]

Contraception 2000 Dec;62(6):305-9

Timing of pain and bleeding after mifepristone-induced abortion.

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Previous studies of medical abortion with mifepristone and a prostaglandin have reported percentages of subjects who experience cramping and/or bleeding relative to prostaglandin use. This is the first analysis of cramping and bleeding onset patterns in subjects treated with low-dose (200 mg) mifepristone and 800 microg vaginal misoprostol at 24, 48, or 72 h after mifepristone. We analyzed the cramping and bleeding onset patterns in subjects up to 8 weeks pregnant who used 800 microg vaginal misoprostol at 24, 48, or 72 h after 200 mg of oral mifepristone. We collected data from subjects' symptom diaries and divided symptom onset into 3 categories: before misoprostol use, 0--12 h following misoprostol, and more than 12 h after misoprostol. Of the 2,302 subjects, cramping and bleeding onset data were available for 2,030 (88%) and 2,123 (92%), respectively. Across all groups, 230 (11%) experienced cramping and 445 (21%) experienced bleeding before misoprostol use. There was a significantly higher percentage of subjects who experienced early cramping and/or early bleeding between the three treatment groups, and this was related to the interval between mifepristone and misoprostol. In the 12 h following misoprostol administration, cramping and bleeding patterns were similar in the three groups. The longer subjects waited to insert misoprostol, the more likely they were to experience early cramping and/or bleeding. After misoprostol insertion, cramping and bleeding patterns are similar regardless of treatment group. Patients and providers cannot rely on symptom onset to predict treatment success.

Publication Types:

- Clinical Trial
- Multicenter Study
- Randomized Controlled Trial

PMID: 11239617 [PubMed - indexed for MEDLINE]

Lancet 2001 May 5;357(9266):1402-5

Can women in less-developed countries use a simplified medical abortion regimen?

Elul B, Hajri S, Ngoc NN, Ellertson C, Slama CB, Pearlman E, Winikoff B.

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BACKGROUND: Mifepristone-misoprostol abortion, consisting of oral pills, is potentially simple and safe enough for use in less-developed countries. But the labour-intensive, costly, clinic-based European protocols are not affordable or feasible in most less-developed countries. METHODS: We prospectively tested two simplifications to the French mifepristone-misoprostol regimen in Vietnam and Tunisia. Women (n=315) with amenorrhoea 8 weeks or less since their last menstrual period received 200 mg mifepristone in the clinic and then chose whether to take 400 mg oral misoprostol 2 days later either at home or in the clinic. FINDINGS: Despite the two-thirds reduction in mifepristone dose, success rates were high: Vietnam 93%, Tunisia 91%. About 88% of participants chose home administration of misoprostol. Most Vietnamese and Tunisian women were satisfied with their abortions, but efficacy and satisfaction rates were higher among those who used misoprostol at home. INTERPRETATIONS: A simplified medical abortion regimen of 200 mg mifepristone followed by the option of home administration of misoprostol seems feasible.

PMID: 11356438 [PubMed - indexed for MEDLINE]

Family Planning Perspectives 32(5):264, Sept./Oct. 2000.

Hollander D.

Most Abortion Patients View Their Experience Favorably, But Medical Abortion Gets a Higher Rating Than Surgical

A group of U.S. women who had a medical abortion reported a significantly higher level of satisfaction with the method than a similar group who underwent suction curettage at the same facility. Nearly all women in both groups (93–97%) said that they would recommend their method to a friend, but those who had a medical procedure were more likely than those who had surgery to say that they would choose the same method if they needed to terminate another pregnancy.[1]

Using self-administered questionnaires given to abortion patients just before and about three weeks after their procedure, researchers gathered information on women's expectations about and actual experiences with their method. To be included in the study, women had to be at least 18 years old and no more than nine weeks pregnant.

The analyses are based on data from 146 women who participated in an acceptability trial of abortion using mifepristone and misoprostol in 1994–1995 and 174 women who had a surgical procedure in 1995–1996. Women in both groups were predominantly white (90–92%), with an average age of 26–27. The average gestation of their pregnancies was 51–52 days, and roughly three in 10 had never been pregnant before.

Participants were asked to rate the amount of discomfort, anxiety and bleeding that they expected and experienced, on a scale from one (indicating none) to five (signifying extreme). They also were asked to rate their expected and actual length of bleeding on a scale from one (denoting 1–3 days) to five (indicating 13 or more).

The two groups both expected and experienced similar levels of discomfort, but differed on most other measures. Women undergoing surgical abortions anticipated a significantly higher level of anxiety (mean rating, 3.1) than those having medical procedures (2.9), yet ratings of the actual level were statistically indistinguishable (2.7–2.8). Those who had medical abortions expected significantly more bleeding than those who had surgical procedures (3.6 vs. 3.1) and experienced significantly more (3.4 vs. 2.6). Likewise, the medical abortion group thought they would bleed longer than women having surgical abortions (3.2 vs. 2.8) and rated the actual duration of bleeding higher (3.8 vs. 3.2).

Women's overall satisfaction with their abortion, rated on a scale from one (signifying very satisfied) to five (denoting very dissatisfied) was high, but those in the medical group gave the procedure a significantly more positive rating (1.4) than those in the surgical group (1.8). The overwhelming majority in both groups would recommend their method to a friend: 93% of those who had surgical procedures and 97% of those who had medical abortions. However, women in the medical abortion group were significantly more likely than surgical abortion patients to say that they would choose the same procedure if they had to have another abortion (91% vs. 58%).

Among women who had medical abortions, overall satisfaction with the method was reduced if bleeding was heavier than expected. Also in this group, overall satisfaction, the likelihood of recommending the procedure to a friend and the likelihood of choosing the same method to terminate a subsequent pregnancy declined if the method failed and the woman required a surgical procedure. Failure of surgical abortions, however, had no effect on these measures.

The researchers point out that their study has the advantage of directly comparing women undergoing medical and surgical abortion. However, they add, medical abortion patients "made a conscious decision to seek out a generally unavailable [procedure] as research subjects," whereas surgical abortion patients had no choice of procedure, and this difference may have biased the results. For example, women in the medical abortion study may have viewed the procedure more favorably and may have reported symptoms more accurately than those in the surgical abortion group. Furthermore, some surgical abortion patients might have chosen a medical procedure if given the option.

Despite the study's limitations, the investigators conclude that women's experiences with abortion depend to some extent on the procedure used. Although both medical and surgical abortion are safe and effective, they note, women contemplating abortion should receive thorough counseling and education about both methods before making their choice. In particular, "attitudes and expectations regarding fears of instrumentation and bleeding should be explored," to help ensure that women choose the procedure with which they are most likely to feel satisfied.—*D. Hollander*

Reference

1. Jensen JT, Harvey SM and Beckman LJ, Acceptability of suction curettage and mifepristone abortion in the United States: a prospective comparison study, *American Journal of Obstetrics and Gynecology*, 2000, 182(6):1292–1299.

Contraception 2000 Sep;62(3):125-30

A multicentre randomized comparative clinical trial of 200 mg RU486 (mifepristone) single dose followed by either 5 mg 9-methylene PGE(2) gel (meteneprost) or 600 microg oral PGE(1) (misoprostol) for termination of early pregnancy within 28 days of missed menstrual period. ICMR Task Force Study. Indian Council of Medical Research.

A multicentre, randomized, comparative clinical trial of 200 mg RU486 (Mifepristone) followed 48 h later by either 5 mg 9-methylene PGE(2) vaginal gel (meteneprost) or 600 microg oral PGE(1) (misoprostol) for termination of pregnancy within 28 days of the missed period, was carried out through the Indian Council of Medical Research's (ICMR) network of Human Reproduction Research Centres (HRRCs). A total of 893 subjects were assessed regarding their therapeutic responses to the two different treatment groups. The results indicated a success rate of 84.6% among 453 women treated with RU486 followed by 9 methylene PGE(2) vaginal gel, that was not significantly different from the success rate of 87.7% observed in 440 women treated with RU486 followed by oral PGE(1). The majority of study subjects (90%) started bleeding within 72 h. About 26% of the subjects had started bleeding before the administration of any prostaglandin. The average duration of bleeding in all the subjects was about 7 days. No life threatening side effects were observed among the subjects in two treatment groups. Gastro-intestinal complaints were reported more often by women treated with oral PGE(1) as compared to those treated with 9-methylene vaginal PGE(2) gel; nausea occurred in 25.7% and 19.2%, vomiting in 6.8% and 4.6%, and diarrhoea in 4.8% and 0.9% of the subjects in the 2 treatment groups, respectively. Fever higher than 38 degrees C and severe abdominal pain were reported by 4.2% and 5.0% of all subjects treated, respectively. Intravenous infusion of glucose and saline was required by 6 subjects in each treatment of the prostaglandin treated groups. Blood transfusion was required in 2 subjects, one in each treatment group, for profuse bleeding.

Publication Types:

- Clinical Trial
- Multicenter Study
- Randomized Controlled Trial

PMID: 11124359 [PubMed - indexed for MEDLINE]

Zhonghua Fu Chan Ke Za Zhi 2000 Dec;35(12):733-5

[Clinical study of four cases with malignant gestation trophoblastic tumor after mifepristone abortion]

[Article in Chinese]

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OBJECTIVE: To describe the clinical characteristics of malignant gestational trophoblastic tumor after medical abortion used by mifepristone combined with misoprostol and its diagnosis and differential diagnosis from incomplete abortion. METHODS: Four cases with malignant gestational trophoblast tumor after medical abortion were presented focusing on the clinical manifestation and the methods of diagnosis and differential diagnosis. RESULTS: Irregular vaginal bleeding and abnormal high level of beta-human chorionic gonadotropin (hCG) in plasma were the common manifestation of the gestational trophoblast tumour and incomplete abortion after medical abortion. However, beta-hCG of the former after curettage was still higher by dynamic monitoring. Malignant gestational trophoblast tumor showed rich blood flow signal and low blood flow resistance index (RI, RI < 0.5) in uterus in color doppler echography, digital subtraction angiography (DSA) with abnormal enlargement of the arteria of uterine, arteriovenous fistula beside the uterine were the main characteristics of malignant gestational trophoblast tumour. CONCLUSIONS: Pay attention to the early stage malignant gestational trophoblast tumour among patients with abnormal vaginal bleeding after medical abortion. beta-hCG and DSA were the most effective methods to diagnose and differentially diagnose choriocarcinoma from the incomplete abortion among the patients with abnormal vaginal bleeding after medical abortion.

PMID: 11286033 [PubMed - in process]

Contraception 2001 May;63(5):247-50

First trimester abortion with mifepristone and vaginal misoprostol.

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This study assessed the efficacy and side effects of first trimester medical abortion using mifepristone and vaginally administered misoprostol. Medical abortion was first introduced in Denmark in December 1997, and the acceptability of this new approach in a Danish population was evaluated. The study included the first 100 women seeking medical abortion. The gestational age was from 33 to 56 days. All received 600 mg mifepristone (RU 486) orally followed 2 days later by vaginally administered misoprostol 400 microg. Success was defined as achieving complete abortion without the need for surgical evacuation. Ninety-three percent achieved a successful medical termination of pregnancy. Side effects were few, and the acceptability was high. Ninety percent of the women would prefer medical abortion in case of a new unwanted pregnancy. The combination of mifepristone and vaginally administrated misoprostol is effective, safe, has few side effects and is well accepted by Danish women.

Publication Types: Clinical Trial

PMID: 11448463 [PubMed - indexed for MEDLINE]

Ugeskr Laeger 2000 Nov 27;162(48):6536-7

[Vasospastic angina pectoris following abortion induced by prostaglandin analogue]

[Article in Danish]

Lindhardt TB, Walker LR, Colov NS, Hansen PS.

Kardiologisk afdeling P, og gynaekologisk obstetrisk afdeling G, Amtssygehuset i Gentofte.

A case of vasospastic angina pectoris with loss of consciousness, bradycardia and seizures induced by medical abortion following administration of mifepristone and gemeprost is reported. The patient had a history of smoking and migraine, and former treatment with ergot alkaloids or serotonin agonists had also resulted in chest pain and lipothymia. The case underlines the importance of obtaining a detailed history of vasospastic disorders in women referred for medical abortion.

PMID: 11187221 [PubMed - indexed for MEDLINE]

Family Planning Perspectives 32 (5): 259, Sep./Oct. 2000.

Mahler K.

DIGEST

Early Medical Abortion Regimens Using Different Dosages of Mifepristone Are Equally Successful

A regimen of medical abortion consisting of 200 mg of mifepristone and 400 mcg of misoprostol is as likely to successfully terminate an early pregnancy as a regimen using the same dosage of misoprostol and 600 mg of mifepristone. In a study of treatment effectiveness conducted at 17 centers worldwide, 89% of women treated with the lower dose of mifepristone and 88% of those treated with the higher dose of the drug had a complete abortion.[1] The proportion of women in each group who experienced side effects such as lower abdominal pain, nausea, vomiting and diarrhea was similar. The success of both of the regimens was related to gestational age: The risk of a continuing pregnancy was more than twice as high among women who received treatment 4-5 weeks after the expected date of menses as it was among those who were treated no more than 15 days after they missed their menstrual period.

Women were eligible to enroll in the study if they had positive pregnancy test results, were in good health, had a history of regular menstrual periods and were no more than 35 days past the expected date of their menses; gestational age was confirmed through a pelvic exam. Exclusion criteria included medical conditions that would contraindicate use of either of the drugs in the treatment regimen, and a history of thromboembolism, liver disease or pruritus of pregnancy (an inflammatory skin condition characterized by severe itching). In addition, women could not participate in the study if they were heavy smokers (defined as having smoked 10 or more cigarettes per day over the prior two years), were using an IUD, were breastfeeding or had a known or suspected ectopic pregnancy.

A total of 1,589 women were randomly assigned to one of two treatment regimens. One group of women was treated with a single oral dose of 600 mg of mifepristone, followed 48 hours later by a 400 mcg oral dose of the prostaglandin misoprostol. Women in the second group received 200 mg of mifepristone, also followed by 400 mcg of misoprostol. The women's vital signs and any side effects of the drug were assessed hourly for three hours after the administration of misoprostol. All women were asked to maintain a diary of side effects (e.g., nausea, vomiting, diarrhea and lower abdominal pain) and to note any days of bleeding during the study period. Study participants were evaluated 15 days and 43 days after beginning treatment.

The mean age of the women in the sample was 27, and approximately two-thirds had ever given birth. At enrollment, the study participants were an average of 19 days past the expected date of menstrual onset. The two treatment groups did not differ significantly on any of these baseline characteristics.

Eighty-nine percent of women who received the 200 mg dose of mifepristone and 88% of those who received the 600 mg dose had a complete abortion without surgical intervention. When the data were reanalyzed to omit 41 cases in which the treatment regimen was not completed properly or the outcome was unknown, the success of the two regimens increased to 92% and 91%, respectively. Some 3% of patients who took the lower dose of mifepristone and 5% of those who took the higher dose had incomplete abortions and required curettage. Three percent of women who received the 200 mg treatment and 2% of those who received the 600 mg treatment had a continuing pregnancy. In about 2% of cases in each group, no cardiac activity was present after treatment, but the gestational sac was not expelled.

Regardless of mifepristone dosage, the likelihood of treatment failure rose with increasing delay in menses ($p<.01$). Overall, the failure rate was 8% among women with a menstrual delay of no more than 14 days, 11% among those with a delay of 15-21 days and 13% among those with a delay of 22-28 days; that rate rose to 20% among women with a menstrual delay of 29 days or more. Compared with women who had a menstrual delay of fewer than 15 days, women who had a menstrual delay of 22-28 days or 29 days or more had odds of abortion failure more than twice as high (2.2-2.3) after the effects of treatment center were accounted for.* In addition, the proportion of women with a continuing pregnancy after treatment increased significantly with the length of the delay ($p<.01$), from fewer than 2% among women with a delay of no more than 21 days and 3% among those with a delay of 22-28 days to 9% among those with a delay of 29-35 days.

The dose of mifepristone was not related to the occurrence of side effects. More than 80% of women receiving either dosage regimen reported experiencing lower abdominal pain at some point during treatment, and more than 65% reported experiencing nausea. Nearly 30% of the women in each group reported vomiting, and about 10% reported diarrhea. However, five women who took the higher dose of mifepristone needed a blood transfusion, compared with none of those who took the lower dose of the drug ($p=.03$).

The researchers conclude that, in combination with a 400 mcg dose of misoprostol, a 200 mg dose of mifepristone is as effective as a 600 mg dose for medical termination of pregnancy within the first three weeks after a missed menstrual period. They note, however, that the efficacy of either oral regimen among women with a menstrual delay of more than 21 days "is too low to justify [its use] in such pregnancies."--*K. Mahler*

Reference

1. World Health Organization Task Force on Post-Ovulatory Methods of Fertility Regulation, Comparison of two doses of mifepristone in combination with misoprostol for early medical abortion: a randomized trial, *British Journal of Obstetrics and Gynaecology*, 2000, 107(4):524-530.

*The center at which a woman received treatment was the only variable with a significant effect on the risk of failure ($p<.01$).

Hum Reprod 2000 Oct;15(10):2205-8

Randomized comparison of vaginal (200 microg every 3 h) and oral (400 microg every 3 h) misoprostol when combined with mifepristone in termination of second trimester pregnancy.

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It is known that when misoprostol is given at 200 microg every 3 h after mifepristone pretreatment, the vaginal route is more effective than the oral route. However, women prefer the oral route. This randomized study was to test our hypothesis that oral misoprostol 400 microg is as effective as vaginal misoprostol 200 microg when given every 3 h in termination of second trimester pregnancy after priming with mifepristone. A total of 142 patients was randomly assigned to group 1 (200 mg mifepristone + 400 microg oral misoprostol every 3 h up to five doses) or group 2 (200 mg mifepristone + 200 microg vaginal misoprostol every 3 h up to five doses). The incidence of side-effects and the preference study were assessed through a standardized questionnaire during and after the abortion. For the oral group, both the incidence of diarrhoea (40.0 versus 23.2%, $P = 0.03$) and the amount of drug used (1734 compared with 812 microg, $P < 0.0001$) were significantly higher than that of the vaginal group but the incidence of fever appeared to be lower (not significant). There was no significant difference in complete abortion rate: 81.4% in the oral group and 75.4% in the vaginal group. The median induction-abortion interval was similar in the two groups (10.4 versus 10.0 h). The percentage of women who aborted in 24 h was also similar: 57/70 (81.4%) in the oral group and 58/69 (87.0%) in the vaginal group. Overall, 82.0% of women preferred the oral route. Oral misoprostol (400 microg) given every 3 h up to five doses, when combined with mifepristone, was as effective as the vaginal (200 microg) route in second trimester termination of pregnancy. This regimen could also be offered to those women who found repeated vaginal administration unacceptable.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 11006200 [PubMed - indexed for MEDLINE]

Journal of Family Planning and Reproductive Health Care 2001 27(2):102

Time to relax the rules about administration of mifepristone

Omokanje S.

Summary

Pre-clinical and clinical data indicate that mifepristone is a safe and effective drug for the termination of pregnancy. The author suggests that it could be given by nursing staff rather than by a doctor, and that the 2-hour post-administration observation period is unnecessary in the majority of cases.

Contraception 64 (2001) 87–92

Original research article

Mifepristone followed on the same day by vaginal misoprostol for early abortion

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Received 13 December 2000; received in revised form 9 May 2001; accepted 10 May 2001

Abstract

We performed a pilot study to examine the clinical efficacy of mifepristone 200 mg followed on the same day by misoprostol 800 μg vaginally in women with pregnancies up to 49 days gestation. Forty women received mifepristone 200 mg after which they self-inserted misoprostol intravaginally 6 to 8 h later at home. Participants returned for an evaluation, including transvaginal ultrasonography, 24 ± 1 h after using the misoprostol. Participants who had not aborted received a second dose of misoprostol to administer 48 h after the mifepristone. All participants returned approximately 2 weeks after receiving mifepristone. At 24 h after receiving misoprostol, 37/40 (92%, 95% CI 81–98%) had ultrasonographic evidence of complete abortion. By follow-up 2 weeks after the mifepristone, 40/40 (100%, 95% CI 92–100%) women were felt to have complete abortions. One subject subsequently had a suction aspiration for an incomplete abortion on study Day 44. Nausea, vomiting, diarrhea, and warmth/chills occurred in 38%, 13%, 13%, and 60%, respectively. This pilot study suggests that mifepristone 200 mg, followed on the same day by misoprostol 800 μg vaginally, effects abortion at rates comparable to regimens using the standard time interval of 48 h between medications.

Keywords: Abortion; Medical abortion; Mifepristone; Misoprostol

The Journal of Family Practice • JANUARY 2001 • Vol. 50, No. 1
POEMs - Patient-Oriented Evidence That Matters

Can vaginal misoprostol be administered 1 to 3 days after mifepristone without loss of efficacy or an increase in adverse events?

Schaff EA, Fielding SL, Westhoff C, et al. Vaginal misoprostol administered 1, 2, or 3 days after mifepristone for early medical abortion: a randomized trial. JAMA 2000; 284:1948-53.

• BACKGROUND The United States Food and Drug Administration (FDA) has approved the use of mifepristone (RU 486) in a protocol for early medical abortion.[1] In that protocol, 600 µg of mifepristone is followed by 400 µg of oral misoprostol 48 hours later. Previous studies have shown that low-dose mifepristone (200 µg) followed 2 days later by 800 µg vaginal misoprostol has fewer side effects and is more effective than the approved protocol. Restricting administration of vaginal misoprostol to a narrow time window 2 days after the mifepristone dose may be inconvenient or unsafe.

• POPULATION STUDIED Healthy pregnant women aged 18 years and older who desired abortions were recruited from 16 sites including hospitals, abortion clinics, family practice offices, and gynecology offices. A total of 2295 women were recruited, and all underwent a transvaginal ultrasound to rule out ectopic pregnancy and to confirm fetal size consistent with a gestation of 56 days or less.

• STUDY DESIGN AND VALIDITY This is an unblinded randomized controlled trial with 3 arms. Subjects were assigned by concealed computer-generated randomization to self-administered 800 µg misoprostol vaginally either 1 (n=745), 2 (n=778), or 3 (n=772) days after a 200-µg dose of mifepristone.

This study is large enough to detect a difference in rate of complete medical abortion of 5% or greater. Very few patients were lost to follow-up (40/2295, 1.7%). Researchers first analyzed the data for all women in each group (intention-to-treat analysis) and then repeated the analysis on those subjects who actually complied with the study protocol by using the misoprostol on the assigned day.

• OUTCOMES MEASURED Complete medical abortion without surgical intervention was the primary outcome.

• RESULTS There was no statistically significant difference in the percentage of women who had complete medical abortions across the 3 groups. The percentages of complete medical abortions for the day 1 and day 2 groups were both 98% (95% confidence interval [CI], 97%-99%), and for the day 3 group it was 96% (95% CI, 95%-97%). More than 90% of subjects in all 3 arms agreed or strongly agreed that the overall procedure was acceptable. Those subjects assigned to the day 3 group were significantly less satisfied with the wait time to complete abortion. Among the subjects in the day 3 group, 56 (7%) admitted to not taking the misoprostol on the assigned day compared with 26 (3%) subjects in the day 1 group and 21 (3%) in the day 2 group.

RECOMMENDATIONS FOR CLINICAL PRACTICE

Low-dose mifepristone (200 µg) followed 1 to 3 days later by 800 µg of self-administered vaginal misoprostol is a safe and effective procedure for early medical abortion. Rigid adherence to the oral administration of misoprostol in a medical office 48 hours after mifepristone is not necessary either from a safety or efficacy perspective. Administration of misoprostol 1 or 2 days after mifepristone is preferable, since patients in the day 3 group found the wait less acceptable. Information is available on the Internet about FDA special requirements and approved protocols involving mifepristone.[1]

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REFERENCE

1. US Food and Drug Administration. Mifepristone information. Available on-line at: www.fda.gov/cder/drug/infopage/mifepristone. Accessed November 22, 2000.

Contraception 64 (2001) 81–85

Original research article

Randomized trial of oral versus vaginal misoprostol at one day after mifepristone for early medical abortion

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Abstract

Mifepristone was recently approved in the United States. Regimens with shorter intervals may be more acceptable. The objective of this study was to determine whether the oral route of misoprostol was as effective as the vaginal route of misoprostol 1 day after mifepristone. A prospective, open-labeled, randomized trial of healthy adult women up to 63 days pregnant and wanting a medical abortion were randomized to use either two doses of oral misoprostol 400 μg taken 2 h apart or misoprostol 800 μg vaginally. Women self-administered misoprostol 1 day after taking one-third of the standard dose of mifepristone (200 mg) orally. Women then returned to the clinic up to 5 days later for a repeat sonogram evaluation. A dose of vaginal misoprostol was administered to women with a continuing pregnancy who then returned 1 day later to Day 15. The primary outcome measures were a complete medical abortion by the first or by the second follow-up visits. Surgical intervention was indicated for continuing pregnancy at the second follow-up visit, excessive bleeding, or persistent products of conception 5 weeks later. One thousand one hundred sixty-eight women were enrolled. Of the 1144 (98%) women who complied with their random assignment, two oral doses of misoprostol (800 μg total) were 90% effective at inducing an abortion by the first follow-up visit, compared with one dose of misoprostol by vagina of 97% ($\chi^2 = 23.95$, $p = 0.001$). By the second follow-up visit, the complete abortion rate was 95% for oral misoprostol and 99% for vaginal misoprostol ($\chi^2 = 21.76$, $p = 0.001$). There were minimal differences in side effects. Women preferred the oral route. The trial demonstrated that although two doses of oral misoprostol were effective, the vaginal misoprostol was more effective at inducing an early medical abortion at 1 day after low-dose mifepristone, and the regimen could be extended to 63 days gestation.

Keywords: Abortion; Mifepristone; Misoprostol

Contraception 2001 May;63(5):251-4

Mifepristone and misoprostol for early abortion when no gestational sac is present.

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The study was conducted to determine whether the administration of mifepristone followed by vaginal misoprostol can induce an abortion in early pregnancy when no gestational sac is present on sonogram. This report presents a prospective, pilot study of 30 healthy adult women, pregnant and seeking an abortion, and with no gestational sac on sonogram. All women had a baseline serum chorionic gonadotropin (hCG) level measured prior to using mifepristone 200 mg orally followed by misoprostol 800 mcg vaginally 48 h later, and then returned up to 4 days later for a repeat sonogram and serum hCG level. Women with initial hCG levels > 2000 IU/L were evaluated for ectopic pregnancy. At the first follow-up visit, if the hCG decreased by >50%, the women were followed with home pregnancy (25 IU/L) tests weekly until negative. If the levels did not decrease by 50%, a second dose of misoprostol was given. Surgical intervention was indicated for persistent hCG levels or excessive bleeding. Of the 30 women enrolled, the mean number of days of amenorrhea was 40 (SD 9) days. Two women had surgical intervention for continuing pregnancy, 2 had ectopic pregnancies, and 1 was lost to follow-up. Complete medical abortions occurred in 25/30 (88%) women, but when recalculated, in 25/27 (93%) women who completed the protocol and who did not have an ectopic pregnancy. There was 1 adverse event in a woman with an ongoing pregnancy who then received methotrexate. She was hospitalized a day later with a complicated pelvic infection and likely methotrexate-induced pneumonitis. Twenty-three women had a decrease in hCG at first follow-up visit of >50%. All 27 women who completed the protocol found the overall regimen acceptable. Mifepristone followed at 48 h by vaginal misoprostol were effective and acceptable in inducing an abortion in very early pregnancy. There may be a higher incidence of failure in very early pregnancies. Documentation of a complete abortion by hCG level is necessary to ensure the pregnancy is neither ongoing nor ectopic.

Publication Types:

Clinical Trial

PMID: 11448464 [PubMed - indexed for MEDLINE]

JAMA 2000 Oct 18;284(15):1948-53

Erratum in:

- JAMA 2000 Nov 22-29;284(20):2597

Vaginal misoprostol administered 1, 2, or 3 days after mifepristone for early medical abortion: A randomized trial.

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CONTEXT: The conventional timing of misoprostol administration after mifepristone for medical abortion is 2 days, but more flexible intervals, which may make the regimen more convenient, have not been studied. OBJECTIVE: To determine whether vaginal misoprostol administered 1, 2, or 3 days after mifepristone influences safety or effectiveness for abortion at up to 56 days' gestation. DESIGN: Prospective, randomized, open-label trial conducted from March 1998 to June 1999. SETTING: Sixteen US primary care and referral abortion facilities. PATIENTS: A total of 2295 healthy patients aged 18 years or older who were 56 or fewer days pregnant. Forty (1.7%) were lost to follow-up. INTERVENTIONS: Patients received 200 mg of oral mifepristone and were randomly assigned to self-administer 800 microg of vaginal misoprostol at home 1 (n = 745), 2 (n = 778), or 3 (n = 772) days later. Women returned to the clinic up to 8 days after mifepristone for ultrasonographic evaluation. A second dose of misoprostol was administered if the abortion was not complete. Patients with continuing pregnancy, excessive bleeding, or retained pregnancy tissue 5 weeks later received an aspiration curettage. MAIN OUTCOME MEASURES: Effectiveness of the procedure (ie, a complete medical abortion without surgical intervention), adverse effects, acceptability of the procedure based on patient questionnaires, reasons for surgical intervention, and adverse outcomes, compared among the study groups. RESULTS: Of the 2255 women completing follow-up, complete medical abortion rates were 98% (95% confidence interval [CI], 97%-99%) among those using misoprostol after 1 day, 98% (95% CI, 97%-99%) for those using misoprostol after 2 days, and 96% (95% CI, 95%-97%) among those using misoprostol after 3 days. Fifty-five subjects aborted before taking misoprostol, 9 had early surgery, and 103 did not take misoprostol on their assigned day. No blood transfusions were required. Cramping and nausea were the most common adverse effects reported, with similar percentages of patients in all 3 groups reporting such effects. Thirteen unexpected or serious adverse events occurred: 6 in those using misoprostol after 1 day; 4 in those using it after 2 days; and 3 in those using it after 3 days. Nearly all women (>90%) found the procedure to be acceptable. CONCLUSIONS: Our results suggest that vaginal misoprostol, 800 microg, can be used from 1 to 3 days after mifepristone, 200 mg, for early medical abortion, and need not be administered strictly 48 hours after mifepristone. JAMA. 2000;284:1948-1953.

Publication Types:

- Clinical Trial
- Multicenter Study
- Randomized Controlled Trial

PMID: 11035891 [PubMed - indexed for MEDLINE]

Circulation. **2000;102:e9030.)**

Cardiovascular News

Ruth SoRelle, MPH, Circulation Newswriter

Abortion Pill Gets FDA Approval

The FDA approved the controversial abortion pill called mifepristone or RU 486 on September 28, 2000, provoking expected responses from both sides of the abortion issue. Supporters of abortion hailed the ruling for giving women the ability to have abortions in privacy and making abortion available through private physicians who have previously not provided that service when it involved a surgical procedure. Those opposed to abortions vowed to fight the decision legislatively and in the courts.

FDA officials denied that politics played a part in the decision. However, the road to approval for the abortion pill has been long and arduous. Approval has been opposed in Congress, and the FDA's newest ruling is destined to play a part in the ongoing race for the US Presidency.

Doctors who prescribe the drug must be able to determine how long a woman has been pregnant and to ensure that women who take it have access to and agree to have a surgical abortion if the pill does not work. In tests, the abortion pill failed to cause a complete abortion in 5% of cases. Women take RU 486 or mifepristone first to block the action of progesterone, the drug needed to maintain a pregnancy. After 36 to 48 hours, the woman takes a second drug called misoprostol to cause the body to expel the fetal tissue. Side effects include bleeding, cramping, headaches, vomiting, and diarrhea. All women must receive written instructions on using the pill and information about its side effects.

Contraception 2001 Jul;64(1):29-32

Second trimester medical abortion with mifepristone and gemeprost: a review of 956 cases.

Tang OS, Thong KJ, Baird DT.

Department of Obstetrics and Gynaecology, University of Edinburgh, Centre for Reproductive Biology, Edinburgh, Scotland, UK.

The treatment outcomes of 956 women undergoing second trimester termination of pregnancy with mifepristone and gemeprost were studied. The median gestational age was 16 weeks (range: 12-24 weeks). All women were treated with 200 mg mifepristone orally, followed 36 h later with 1 mg vaginal gemeprost administered every 6 h to a maximum of 4 doses in the first 24 h. A second course of 1 mg vaginal gemeprost was given 3-hourly in the next 12 h, if abortion had not occurred. Overall, 96.4% and 98.8% of the women aborted within 24 and 36 h, respectively. The median induction-to-abortion interval was 7.8 h (range: 0.5-109.9 h). The induction-abortion interval was longer in nulliparous women and women with a gestation age 17 weeks or above. Surgical evacuation of the uterus was performed in 11.5% of women for incomplete abortion or retained placenta. More multiparous women (16.7%) required surgical evacuation of uterus than did nulliparous women (7.3%; $p < 0.001$). Ten (0.1%) women failed to abort with gemeprost and required other methods for abortion. In conclusion, a combination of mifepristone and gemeprost is a safe, effective, and noninvasive method of medical abortion for second trimester pregnancy.

PMID: 11535210 [PubMed - indexed for MEDLINE]

BMJ 2000;321:1041 (28 October)

News roundup

Abortion pill withdrawn in Germany after financial losses

Annette Tuffs ***Heidelberg***

Distribution of the abortion pill, mifepristone (Mifegyne), in Germany is to be stopped by the end of 2000.

The company that distributes the drug, Femagen in Bavaria, announced last week that it will stop distributing it to doctors and hospitals by the end of 2000 because of huge financial losses. Femagen orders the pill from the French producer Exelgyn.

This year 96% of all abortions in Germany have still been carried out by surgery, and Femagen handled only 600 prescriptions a month instead of the expected minimum of 2000.

This recent development adds another chapter to the difficult story of the introduction of mifepristone in Germany. After long discussions and strong opposition from the church and conservative politicians, mifepristone was finally introduced last year as an alternative to surgery.

According to Petra Schoettler, managing director of Femagen, the main reason for the pill's failure is the low profit margin for pharmaceutical abortion compared with surgical abortion. Doctors are paid about DM500 (£148; $207) for a surgical abortion, but they receive just DM120 for prescribing mifepristone and the three necessary medical examinations of the patient, which, according to gynaecologists, does not cover their costs.

In addition, most women seeking an abortion have a very low income. Costs of the abortion are usually not paid by health insurance, and, when a patient's income falls below a certain level, the costs must be covered by the federal states.

Not all the states, however, cover the entire cost of mifepristone treatment. Women who do not receive social benefits are sometimes faced with a charge of DM800. Furthermore, the law permits direct distribution only to doctors and hospitals, which adds to the cost of mifepristone compared with drugs dispensed over the counter.

Meanwhile, Exelgyn is looking for a new partner firm in Germany. Politicians, although enraged by this recent development, see no direct possibility of intervening as it is the responsibility of the doctors' associations and the health insurance companies to set rates of payment for standard treatments.

Contraception 2000 Dec;62(6):311-4

Analgesia during at-home use of misoprostol as part of a medical abortion regimen.

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The objective of this study was to identify predictors of narcotic analgesic use during medical abortion. Two-thousand-seven-hundred-forty-seven women with pregnancies of 63 days gestational age or less received 200 mg mifepristone followed by at-home use of 800 microg vaginal misoprostol in two consecutive clinical trials in the United States, and also reported their use of analgesics. Overall, 79% of these subjects used narcotic analgesics. Women in the 2nd of the two studies were randomized to use misoprostol 24, 48, or 72 h after mifepristone. Those who were randomized to 24 h were more likely to use narcotic analgesics than those who were randomized to 48 or 72 h. In both studies, the use of narcotic analgesia during medical abortion was less prevalent among parous women and Asian women, and among those with a gestational age of 56 days or less. The clinic providing care for the patient was the most important determinant of narcotic analgesia use, even though the analgesia was used at home. Use of narcotic analgesics in these women undergoing medical abortion at home was more prevalent than use reported in previous studies where women underwent medical abortion in a clinical setting.

Publication Types:

- Clinical Trial
- Multicenter Study
- Randomized Controlled Trial

PMID: 11239618 [PubMed - indexed for MEDLINE]

Acta Obstet Gynecol Scand 2001 May;80(5):447-51

Medical abortion at 57 to 63 days' gestation with a lower dose of mifepristone and gemeprost. A randomized controlled trial.

World Health Organization Task Force on Post-ovulatory Methods of Fertility Regulation.

OBJECTIVE: To compare the abortifacient efficacy and side-effects of 200 mg and 600 mg of mifepristone, followed by gemeprost 1 mg vaginally, at 57 to 63 days' gestation. DESIGN: Double-blind, randomized controlled trial. SETTING: Ten international centers. SUBJECTS: Eight hundred and ninety-six healthy women requesting medical abortion. INTERVENTIONS: Participants were randomly assigned to receive a single oral dose of mifepristone of either 200 mg or 600 mg followed in 48 h by gemeprost 1 mg vaginally. The allocation sequence was concealed by using a central pharmacy, and double masking was maintained throughout the study. MAIN OUTCOME MEASURES: Complete abortion rate was the principal outcome measure. We also evaluated the incidence of side-effects and time to abort. RESULTS: The complete abortion rate with the lower dose of mifepristone was similar to that with the higher dose (92.4% vs. 91.7%). The relative risk of failure to achieve a complete abortion with the 200 mg dose compared to 600 mg dose was 0.9 (95% CI 0.6-1.4). The timing of the abortion and the incidence of side-effects were comparable in both groups, with the exception of reported nausea at one-week follow-up which was reported more frequently by women in the higher-dose group. CONCLUSIONS: The 200 mg dose of mifepristone is equally as effective as the 600 mg dose in the antiprogestogen-prostaglandin regimen for pregnancy termination. With vaginal gemeprost, the abortifacient efficacy of the regimen remains high at 57-63 days' gestation.

Publication Types:

- Clinical Trial
- Multicenter Study
- Randomized Controlled Trial

PMID: 11328223 [PubMed - indexed for MEDLINE]

BJOG 2001 Jul;108(7):738-42

Lowering the doses of mifepristone and gameprost for early abortion: a randomised controlled trial. World Health Organization Task Force on Post-ovulatory Methods for Fertility Regulation.

OBJECTIVE: To test the efficacy of lower doses of mifepristone and gemeprost for medical induction of early abortion. DESIGN: Randomised controlled trial. Participants were blinded as to the therapy and physicians to the dose of mifepristone. SETTING: Thirteen hospital gynaecological units in different continents. PARTICIPANTS: 1,224 healthy pregnant women requesting medical abortion at <57 days from last menses. INTERVENTION: Random allocation to one of four regimens: mifepristone 50 mg by mouth followed by either 0.5 mg or 1.0 mg gemeprost vaginally on day 3; mifepristone 200 mg by mouth followed by either 0.5 mg or 1.0 mg gemeprost vaginally. We concealed the allocation sequence from clinicians enrolling participants, and maintained double blinding throughout. MAIN OUTCOME MEASURES: Incidence of complete abortion; subordinate outcome measures included side effects such as vomiting and fall in haemoglobin, as well as the need for emergency curettage and blood transfusion. RESULTS: The success rate was significantly related to the dose of mifepristone. The relative risk of failure to have a complete abortion with the lower dose of mifepristone was 1.6 (95% CI: 1.1-2.3) times that with the higher dose. The relative risk of failure with the lower dose of gemeprost (1.3; 95% CI: 0.9-1.8) did not reach statistical significance. CONCLUSIONS: A single dose of mifepristone 50 mg followed by gemeprost is inadequate for early medical abortion. There was no significant difference in side effects between the four treatment groups.

Publication Types:
Clinical Trial
Multicenter Study
Randomized Controlled Trial

PMID: 11467701 [PubMed - indexed for MEDLINE]

Int J Gynaecol Obstet 2001 Mar;72(3):245-51

Termination of early pregnancy in the scarred uterus with mifepristone and misoprostol.

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OBJECTIVE: To analyze the safety and possibility of terminating early pregnancy up to 49 days gestation after cesarean section with mifepristone and misoprostol. METHODS: One-hundred and ninety-two early pregnant women were recruited, of which, 35 cases with uterine cicatrix and 157 cases were no-uterine cicatrix as control group. All of them took 25 mg of mifepristone, b.i.d. for 3 days and 600 microg of misoprostol on the 4th day. RESULTS: Of the 35 cases with uterine cicatrix, 33 achieved complete abortion after medical abortion. The complete abortion rate was 94.29% (95% CI 81-99%) in the cicatrix group and 89.81% (95% CI 75-91%) in the control group. There were no obvious complications detected in the cicatrix group. CONCLUSION: For the termination of early pregnancy in scarred uterus, administration of mifepristone and misoprostol is safe and effective, and a further large series study needs be done to confirm its acceptability as a routine medication in such situations.

Publication Types:

- Clinical Trial

PMID: 11226445 [PubMed - indexed for MEDLINE]

2. Long-term Treatment with Mifepristone

Clin Endocrinol Metab 2001 Aug;86(8):3568-73

Successful long-term treatment of refractory Cushing's disease with high-dose mifepristone (RU 486).

Chu JW, Matthias DF, Belanoff J, Schatzberg A, Hoffman AR, Feldman D.

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An extremely ill patient, with Cushing's syndrome caused by an ACTH-secreting pituitary macroadenoma, experienced complications of end-stage cardiomyopathy, profound psychosis, and multiple metabolic disturbances. Initially treated unsuccessfully by a combination of conventional surgical, medical, and radiotherapeutic approaches, he responded dramatically to high-dose long-term mifepristone therapy (up to 25 mg/kg x d). Treatment efficacy was confirmed by the normalization of all biochemical glucocorticoid-sensitive measurements, as well as by the significant reversal of the patient's heart failure, the resolution of his psychotic depression, and the eventual unusual return of his adrenal axis to normal. His 18-month-long mifepristone treatment course was notable for development of severe hypokalemia that was attributed to excessive cortisol activation of the mineralocorticoid receptor, which responded to spironolactone administration. This case illustrates the efficacy of high-dose long-term treatment with mifepristone in refractory Cushing's syndrome. The case also demonstrates the potential need for concomitant mineralocorticoid receptor blockade in mifepristone-treated Cushing's disease, because cortisol levels may rise markedly, reflecting corticotroph disinhibition, to cause manifestations of mineralocorticoid excess.

PMID: 11502780 [PubMed - indexed for MEDLINE]

Program/Proceedings American Society of Clinical Oncology,Thirty-Seventh Annual Meeting, May 12-15, 2001, SanFrancisco, CA Vol 20, page 56a, Poster 222

Phase III Double-Blind Randomized Placebo-Controlled Study of Mifepristone (RU) for the Treatment of Unresectable Meningioma

S.M. Grunberg, C. Rankin, J. Townsend, J. Ahmadi, L. Feun, R. Fredericks, C. Russell, F. Kabbinavar, G. R. Barger, K.J. Stelzer; Southwest Oncology Group, Burlington, VT; Eastern Cooperative Oncology Group, Brookline, MA

Meningiomas (M), which are 3 times more common in women as in men, are often progesterone receptor positive but seldom estrogen receptor positive. We have therefore studied the antiprogestin RU for the treatment of unresectable M. A previous open-label pilot study in which 8/28 patients (pts) receiving RU showed clinical benefit justified this trial. In the present study adults with unresectable histologically confirmed non-malignant M which had appeared (22%) or progressed (78%) within 2 years were ramdomized to receive blinded RU 200 mg po qd or placebo (P) with an endpoint of freedom from progression (FFP) for the next 2 years. Progression was defined as anatomic growth or neurologic deterioration. 193 pts were entered with 160 (80 per arm) fully evaluable. Median age was 57 with 30% male, 19% premenopausal female, and 51% postmenopausal female. 29% had received prior radiotherapy. There was no significant difference in response between the arms. 2 RU pts and 1 P pt had partial or unconfirmed responses. Median FFP was 10 months for RU and 12 months for P ($p=0.44$). Treatment was generally well tolerated with the most common toxicities being fatigue (72% RU vs 54% P), headache (44% RU vs 41% P), and hot flashes (38% RU vs 26% P). 9 RU pts (16% of female RU pts) also developed endometrial hyperplasia. Although increased FFP was not demonstrated in this population, prolonged treatment with an antiprogestin (RU) was safe and feasible. Antiprogestins may be useful in the chronic treatment of other progesterone-dependent conditions.

Steroids 2000 Oct-Nov;65(10-11):831-6

Alterations in sex steroids and gonadotropins in post-menopausal women subsequent to long-term mifepristone administration.

Heikinheimo O, Ranta S, Grunberg S, Spitz IM.

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Long-term administration of progesterone antagonists (PAs) and progesterone receptor modulators (PRMs) has been proposed as a novel hormonal therapy for various hormone dependent maladies. We studied the long-term endocrine effects of mifepristone on the kinetics of estradiol (E(2)) and its precursors, and on gonadotropin levels in five postmenopausal women treated for unresectable meningioma with mifepristone [200 mg/day] for at least 15 months. Serum samples were analyzed for LH, FSH and SHBG with fluoroimmunoassay; androstenedione (A), testosterone (T), estrone (E(1)) and E(2) were measured with radioimmunoassay (RIA). Serum levels of mifepristone were measured using both RIA and high performance-liquid chromatography (HPLC). Serum levels (mean +/- SD) of LH and FSH were suppressed from pretreatment values of 32 +/- 16 and 65 +/- 30 IU/l to 13 +/- 7 and 33 +/- 16 IU/l at 6 months ($P < 0.05$), respectively. Serum (mean +/- SD) A, T, E(1), and E(2) were increased from initial values of 6.9 +/- 0.9 nmol/l, 1.2 +/- 0.3 nmol/l, 77 +/- 25 pmol/l, and 29 +/- 14 pmol/l to 6 month values of 13.1 +/- 5.6 nmol/l, 1.8 +/- 0.6 nmol/l, 178 +/- 60 pmol/l, and 45 +/- 22 pmol/l (n.s.). The correlation coefficients between the levels of A, T, E(1), and E(2) were statistically significant, whereas the ratios of T/A, E(1)/A, E(2)/E(1), and E(2)/T remained unchanged. The levels of SHBG remained stable, and ranged from 48 +/- 10 to 65 +/- 9 nmol/l (mean +/- SD). Thus, prolonged mifepristone treatment marginally increased the serum levels of A, T, E(1) and E(2). These effects of mifepristone are likely due to its antiglucocorticoid effect and thus increased secretion of adrenal A. Serum levels of LH and FSH declined. The serum levels of gonadotropins and those of T, E(1) and E(2) were inversely, yet significantly, correlated. Therefore the decrease in LH and FSH might reflect the slightly increased levels of T, E(1) and E(2). However, the lack of change in SHBG and the low E(2) levels suggest that enhanced systemic estrogen effects are unlikely during long-term mifepristone treatment.

PMID: 11108895 [PubMed - indexed for MEDLINE]

Clin Endocrinol (Oxf) 2001 Mar;54(3):399-404

Long-term mifepristone (RU486) therapy resulting in massive benign endometrial hyperplasia.

Newfield RS, Spitz IM, Isacson C, New MI.

Department of Paediatrics, The New York Hospital--Cornell Medical Center, New York, NY, USA.

Mifepristone (RU486) is a potent antiprogestagen, and at high doses it also acts as an antiglucocorticoid drug. Mifepristone, administered as a single 600 mg dose, is commonly employed to induce medical abortion in conjunction with prostaglandins. The long-term safety profile of mifepristone, especially at high doses, is less well-established. Long-term mifepristone is considered efficacious in treating uterine myomas, endometriosis (25--100 mg/day), and possibly in inoperable meningiomas (200 mg/day), as well as inoperable Cushing's syndrome. Many animal studies document an antiproliferative effect (antioestrogenic), as do some reports in humans. However, there are also data to suggest that, as an antiprogestagen, mifepristone may promote an unopposed oestrogen milieu, and thus have a proliferative effect upon the endometrium. We hereby describe the first reported case of an adolescent female with Cushingoid features and morbid osteoporosis who was treated with mifepristone for its antiglucocorticoid effect (400 mg/day) in an attempt to prevent further bone loss. The patient's striae, weight gain, and buffalo hump markedly improved, and further bone loss was halted. However, with each of the two 6-month courses of mifepristone (9 months apart) she developed massive simple endometrial hyperplasia and a markedly enlarged uterus. This reversed to normal after cessation of mifepristone treatment. In conclusion, High doses of the antiprogestagen mifepristone over a prolonged period of time may promote an unopposed oestrogen milieu leading to endometrial hyperplasia. Therefore, interval pelvic imaging in women who receive long-term mifepristone may be prudent.

PMID: 11298094 [PubMed - indexed for MEDLINE]

3. Termination for Fetal Anomaly or Death

Eur J Obstet Gynecol Reprod Biol 2001 Mar;95(1):52-4

Second trimester termination of pregnancy for fetal anomaly or death: comparing mifepristone/misoprostol to gemeprost.

le Roux PA, Pahal GS, Hoffman L, Nooh R, El-Refaey H, Rodeck CH.

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OBJECTIVE: To assess the effect of changing the regimen for second trimester induction of labour from gemeprost to mifepristone/misoprostol. DESIGN and SETTING: A retrospective study at a university teaching hospital over the 5-year period 1993-1997. SUBJECTS, METHODS and REGIMENS: 68 patients, 34 in the gemeprost group and 34 in the mifepristone/misoprostol group. The gemeprost group received 1mg vaginally every 3h to a maximum of five doses. The mifepristone/misoprostol group were pre-treated with 600 mg mifepristone orally followed by 800 microg misoprostol vaginally and then 400 microg orally every 3h to a maximum of four oral doses. MAIN OUTCOME MEASURES: Induction to abortion interval; delivery within 24h. RESULTS: The mifepristone/misoprostol group had a lower induction to abortion interval compared to the gemeprost group (median 8.9h versus 19.8h, respectively, $p<0.01$). The mifepristone/misoprostol regimen was more successful than the gemeprost regimen; 94% versus 68%, respectively, aborted without extra medical or surgical intervention, $p=0.02$. There were no significant differences in side effects, analgesia requirements or complications between the two groups. Three patients with previous Caesarean sections had a ruptured uterus; two from the gemeprost group and one from the mifepristone/misoprostol group. CONCLUSIONS: The new mifepristone/misoprostol regimen was more effective in second trimester induction of labour. Induction of labour with misoprostol or gemeprost should be used with care in patients with a previous Caesarean section.

PMID: 11267720 [PubMed - indexed for MEDLINE]

4. Cervical Ripening

Eur J Obstet Gynecol Reprod Biol 2001 Jul;97(1):30-4

The effects of mifepristone on uterine sensitivity to oxytocin and on fetal heart rate patterns.

Giacalone PL, Daures JP, Faure JM, Boulot P, Hedon B, Laffargue F.

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OBJECTIVE: To compare the incidences of tachysystole, hypertonia and fetal heart rate (FHR) abnormalities in women treated by mifepristone plus prostaglandins (PGs), mifepristone alone or PGs alone for an unfavourable cervix. STUDY DESIGN: In this retrospective study, all women between 37 and 42 weeks were eligible for the study if they had undergone cervical ripening prior to labour induction. In group 1, the women were treated with mifepristone plus PGs (n=103). Group 2 women were treated with mifepristone alone (n=96) and group 3 women with PGs alone (n=100). Incidences of tachysystole, hypertonia and FHR abnormalities were compared. RESULTS: During induction of labour, tachysystole and hypertonia occurred more frequently in women treated with mifepristone. Severe bradycardia and recurrent late decelerations were more frequent after the initiation of oxytocin in groups 1 and 2 than in group 3. CONCLUSIONS: In this study, mifepristone increased the incidences of tachysystole, hypertonia and FHR abnormality.

PMID: 11435005 [PubMed - indexed for MEDLINE]

Obstet Gynecol 2000 Oct;96(4):543-8

Mifepristone for preinduction cervical ripening beyond 41 weeks' gestation: a randomized controlled trial.

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OBJECTIVE: To compare the effect of mifepristone with placebo on cervical ripening before labor induction in prolonged pregnancies. METHODS: One hundred eighty women with pregnancies beyond 41 weeks and undilated, uneffaced cervices were assigned randomly to receive mifepristone 200 mg or placebo and observed for 24 hours. We then gave intravaginal misoprostol 25 microg every 4 hours or intravenous oxytocin. We expected 60% of placebo-treated and 80% of mifepristone-treated women to deliver vaginally within 48 hours. RESULTS: Among 180 subjects, 97 received mifepristone and 83 received placebo. The mean interval (+/- standard deviation [SD]) from start of induction to delivery was 2209 +/- 698 minutes for mifepristone-treated subjects and 2671 +/- 884 minutes for placebo-treated subjects (P <.001, log-transformed data). Twelve (13. 6%) mifepristone-treated women and seven (10.8%) placebo-treated women delivered vaginally on day 1 (P =.60). After 24 hours, the median Bishop score for both groups was 3 (0-11) (P =.51). One hundred thirty-one subjects required misoprostol, 65 (67.0%) were mifepristone-treated women, and 66 (79.5%) placebo-treated women (P =.06). The median (range) oxytocin dose was 871.5 (0-22,174) mU for mifepristone-treated women and 2021.0 (0-24,750) mU for placebo-treated women (P =.02). Seventy-seven (87.5%) mifepristone-treated women and 46 (70.8%) placebo-treated women delivered vaginally 48 hours after the start of treatment (P =.01). There were nine cesareans in the mifepristone group and 18 in the placebo group (P =.02). More nonreassuring fetal heart rate patterns and uterine contractile abnormalities occurred in mifepristone-treated subjects. There were no statistically significant differences in neonatal outcomes between groups. CONCLUSION: Mifepristone had a modest effect on cervical ripening when given 24 hours before labor induction, appearing to reduce the need for misoprostol and oxytocin compared with placebo.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 11004356 [PubMed - indexed for MEDLINE]

ATTACHMENT 12

Completed Unpublished Clinical Trial

The following clinical trial was conducted with the Exelgyn drug product, Mifegyne®:

COMPARISON OF ABORTIONS INDUCED BY METHOTREXATE OR MIFEPRISTONE FOLLOWED BY MISOPROSTOL.

Ellen Wiebe, Sheila Dunn, Edith Guilbert, Francis Jacot, Lisa Lugtig.

A randomized non-blinded controlled trial.

Mifepristone has recently been approved in the US but is still unavailable in Canada and many other countries. It is much more expensive than methotrexate which is widely available. No other study has compared these two methods of inducing early abortion. Five abortion clinics across Canada were setting the study. 1001 women 16 years and older at 49 days gestation or less presenting for abortion were included. A randomised non-blinded controlled trial comparing methotrexate 50mg/m^2 followed 4-6 days later by 800µg vaginal misoprostol to mifepristone 600mg orally followed 36-48 hours by 400µg oral misoprostol.

There were 505 women in the methotrexate group and 494 women in the mifepristone group. In the methotrexate group, 20 women had surgery, 2 for continuing pregnancy, 8 due to doctor's request (usually for excessive bleeding) and 10 due to patient's request. In the mifepristone group, 22 women had surgery, 17 due to the doctor's request, 5 due to the patient's request and none for continuing pregnancy. By D8, only 374 in the methotrexate group had completed the abortion compared to 453 in the mifepristone group and the mean number of days from beginning to completion was 6.9 for methotrexate and 3.2 for mifepristone (p=.000). The mean worst pain on a scale from 0 to 10 was 6.4 for methotrexate and 5.8 for mifepristone (p=.001). The mean number of days of bleeding was 12.8 for methotrexate and 14.6 for mifepristone (p=.005). There were no differences in complications. Eleven women visited a hospital, 22 women were treated for excessive bleeding but no one needed a transfusion and 8 women received antibiotics for possible infection. Side effects were similar with mifepristone causing more headache and methotrexate causing more diarrhea. Acceptance was slightly higher with mifepristone (413/466) than with methotrexate (389/464). In conclusion, abortion induced with mifepristone completed faster than those induced with methotrexate but the overall success rates, side effects and complications were similar. Acceptance was slightly higher with mifepristone than methotrexate.

Source: Exelgyn Laboratory Periodic Safety Update Report No. 12, December 1, 2000 to May 31, 2001, Page 9.

Completed Unpublished Clinical Trial

The following clinical trial was conducted with the Exelgyn drug product, Mifegyne®:

MANAGEMENT OF MISSED ABORTION

Comparison of medical treatment with either mifepristone+misoprostol or misoprostol alone with surgical evacuation

A. Grønlund, L. Grønlund, L. Clevin, B. Andersen, N. Palmgren, Ø. Lidegaard.

Multi-centre trial, Copenhagen Country, Denmark

The objective is to compare the efficacy of two different medical treatment regimens: Mifepristone 600mg orally + misoprostol 0.4mg vaginally (Mf+Ms) or Misoprostol 0.4mg (Ms) vaginally with conventional surgical evacuation (SE) in women with missed abortion.

176 women with missed abortion accepted to participate in the study during the period October 1999 to October 2000.

A prospective crossover study with alternating regimens every four months.

The main outcome measures are the proportion of women, who needed surgical evacuation after medical treatment and the number of women who needed re-evacuation after primary surgical evacuation, duration of vaginal bleeding, treated infections, the need of analgesics, and subjective experiences from the participating women.

54, 73 and 49 patients were randomised to Mf+Ms, Ms and SE, respectively. Within one week, complete expulsion occurred in 40 (74%), 52 (71%), 47 (96%) of the three arms, respectively. Duration of bleeding was 7.0, 7.0 and 2.5 days, respectively. Women with an initial plasma chorionic gonadotrophin (β-hCG) between 2,000 and 20,000 IU/l had significantly better response to the medical treatment than women not fulfilling these criteria. Initial plasma – (p)-progesterone did not correlate to success of medical treatment.

In conclusion, vaginal misoprostol 0.4mg – 0.6mg is effective in most patients with missed abortion. Pre-treatment with the anti-progesterone mifepristone does not increase the success rate. Selection of women with missed abortion for medical treatment from gestational age (GA) and initial β-hCG level may increase the success of medical treatment significantly.

Source: Exelgyn Laboratory Periodic Safety Update Report No. 12, December 1, 2000 to May 31, 2001, Pages 10-11.

Completed Unpublished Clinical Trial

The following clinical trial was conducted with the Exelgyn drug product, Mifegyne®:

MIFEPRISTONE-MISOPROSTOL MEDICAL ABORTION:
Evaluation of a simplified regimen in the Taiwan medical environment.
A multi-center single-arm open-label study
FM601-080599

The study aimed to determine how two refinements of mifepristone-misoprostol regimen work together in Taiwan. In this study, the abortifacient efficacy and the tolerance of treatment comprising the consecutive administration of mifepristone (600mg) and misoprostol (400µg or 600µg orally) were evaluated in 42 patients with intrauterine pregnancy and gestational age less than or equal to 7 weeks.
Efficacy was assessed 15 days after administration of 600mg of mifepristone on the basis of clinical, ultrasonographic and/or biological (β-hCG levels) finding. Safety was evaluated on the basis of uterine bleeding duration, any adverse event occurrence or abnormal clinical finding and the adverse event linked to the prostaglandin analog.
The successful rate in the 42 patients was 95.2%. Only two patients failed (one ongoing pregnancy and incomplete abortion).
In terms of clinical tolerance, none of the patients were reported to have had any adverse events within 15 minutes following mifepristone intake. The most frequent adverse events were vaginal bleeding (83.3%), abdominal pain (81.0%), nausea (64.3%), vomiting (28.6%) and diarrhea (21.4%). Only one case required analgesic drugs, while in the other cases, no action was taken. Therefore, the clinical tolerance of this protocol can be rated as acceptable.
Some reports show that gastrointestinal upsets are related to the doses of misoprostol and suggest that the dose of misoprostol can be reduced to 400µg orally.
In conclusion, the consecutive administration of 600mg of mifepristone and 400µg or 600µg of misoprostol orally 36 to 48 hours later in women resulted in pregnancy termination in 95.2% of case. It is effective and safe and the clinical tolerance is excellent.

Source: Exelgyn Laboratory Periodic Safety Update Report No. 10, December 1, 1999 to May 31, 2000, Page 9.

ATTACHMENT 13

Not For Public Release
Status Report
Post Marketing Study Commitment

Date of Report:	December 2001
Applicant Name:	Population Council
Product Name:	Mifeprex™ (mifepristone) Tablets (Oral), 200 mg
Application Number:	NDA 20-687
Date of Application Approval:	September 28, 2000
Date of Post Marketing Study Commitment:	September 28, 2000
Description of Post Marketing Study Commitment:	Two studies are to be conducted. ***Study 1*** – A cohort-based study of safety outcomes of patients having medical abortions 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. ***Study 2*** – A surveillance study on outcomes of ongoing pregnancies.
Original Schedule for Post Marketing Study Commitment:	Final protocols for both studies to be submitted within six months of NDA approval.

Current Status of Post Marketing Study Commitment: *PENDING*

Explanation of Status Of Studies: ***Study 1 -***

Study Status – *Pending*
Explanation of Status – Protocol was submitted as scheduled on March 9, 2001. The final protocol has not been agreed upon by both FDA and the Population Council. Negotiations and revisions are in process. We are responding to comments sent to us by FDA on April 20, 2001 as well as a phone conversation between (b) (6) and (b) (4), (b) (6) on June 19, 2001. We plan for the negotiation process to be complete and the final protocol submitted to FDA in early 2002. Enrollment will begin when national sales of mifepristone support selection of the study sample.

The majority of the sales in the first year of distribution have been to (b) (4).
Currently, sales volume of mifepristone is too small to allow for the selection of a cohort of providers of mifepristone medical abortion who would refer their patients when surgical intervention is required. We anticipate that in the next year, with more time on the market, the population of referring providers of mifepristone medical abortion will increase sufficiently to allow for the selection of the sample.

Study 2 –

Study Status – *Pending*
Explanation of Status – Protocol was submitted on May 29, 2001, eight months after approval. We are currently revising the protocol in response to comments sent to us by FDA on August 20, 2001. We plan for the negotiation process to be complete and the final protocol submitted to FDA in early 2002. Again, given the rarity of the outcome of interest, numbers of users of the method is too low at this time for this study to begin.

ATTACHMENT 14

For Public Release
Status Report
Post Marketing Study Commitment

Date of Report: December 2001

Applicant Name: Population Council

Product Name: Mifeprex™ (mifepristone) Tablets (Oral), 200 mg

Application Number: NDA 20-687

Date of Application Approval: September 28, 2000

Commitment #1:

Commitment Date: September 28, 2000

Commitment: A cohort-based study of safety outcomes of patients having medical abortions 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.

Current Status: Pending

Explanation of Status: Discussions between the FDA and the Population Council on the final protocols are in process. Enrollment will begin when national sales of mifepristone support selection of the study sample.

Commitment #2:

Commitment Date: September 28, 2000.

Commitment: A surveillance study on outcomes of ongoing pregnancies.

Current Status: Pending

Explanation of Status: Discussion between the FDA and the Population Council on the final protocol are in process. Again, given the rarity of the outcome of interest, numbers of users of the method is too low at this time for this study to begin.

ATTACHMENT 15

STATUS REPORT OF OTHER POST MARKETING STUDIES – ONGOING STUDIES

STUDY STATUS SUMMARY (I) – September 28, 2001

Study Title: Mifepristone-Misoprostol Medical Abortion: Simplifying the Regimen

Protocol Number: 205-US

Study Phase:

Date of Study Initiation: January 19, 2001

Study Status (Ongoing/Completed/Discontinued): Ongoing

Investigator(s)/Study Center(s):

(b) (4), (b) (6)

1.
2.
3.
4.

Objective: To investigate the safety, efficacy and acceptability of a simplified regimen of mifepristone-misoprostol medical abortion, including home administration of misoprostol and a lower dose of mifepristone (200 mg).

Study Design: Prospective, non-comparative trial

Drugs:

Investigational Drug: Mifepristone + Misoprostol

Control Drug: None

Dosage: 200 mg oral mifepristone, 400 µg oral misoprostol (2 days later)

Description of Patients: Pregnant women with gestations under 49 days LMP

Number of Patients

Planned: 370
Enrolled: 255

Age Range: 18 - 45
Gender: female
Race: n/a

Dropped	0
Completed:	237

Safety Variables: Frequency of blood transfusion, administration of IV fluids and hospitalization

Efficacy Variables: Success, complete abortion without a surgical intervention

Safety Results:

Blood transfusion	= 0
Administration IV fluids	= 2
Hospitalization	= 1*

Efficacy Results: Success = 91.6% (217/237)

*IND Safety Reports on this serious adverse event were submitted to IND 22,047 (Initial Report, Submission Serial Number 215, June 19, 2001 and Follow-up Report, Submission Serial Number 217, August 21, 2001).

STATUS REPORTS OF OTHER POST MARKETING STUDIES – ONGOING STUDIES

STUDY STATUS SUMMARY (II) – September 28, 2001

Study Title: Comparison of abortions induced by mifepristone followed by vaginal versus oral misoprostol up to 56 days gestation

Protocol Number: 298

Study Phase:

Date of Study Initiation: February 27, 2001

Date of IND Submission: June 19, 2001 (Submission Serial Number: 216)

Study Status (Ongoing/Completed/Discontinued): Suspended

Investigator(s)/Study Center(s):

1. Ellen Wiebe, University of British Columbia, Vancouver, British Columbia, Canada
2. Francis Jacot, Clinique de Planification des Naissances de l'Éstrie, Centre Universitaire de Santé de l'Éstrie, Sherbrooke, Quebec
3. Edith Guilbert, The Family Planning Clinic of Le Center Hospitalier Universitaire de Quebec, Quebec City, Quebec
4. Sheila Dunn, Bay Center for Birth Control, University of Toronto, Toronto, Ontario
5. Lisa Lugtig, Klinic Community Health Centre, Inc., Winnipeg, Canada

Objective: To compare the use of vaginal misoprostol (800 µg) and oral misoprostol (400 µg or 600 µg) in combination with mifepristone (200 mg) to terminate pregnancies of up to 56 days gestation.

Study Design: Randomized, non-placebo controlled trial

Drugs:

Investigational Drug: Mifepristone + Misoprostol
Control Drug: None

Dosage: 200 mg oral mifepristone, 400 µg oral misoprostol or 600 mcg oral misoprostol or 800 mcg vaginal misoprostol (2 days later)

Description of Patients: Pregnant women with gestations ≤ 56 days gestation

Number of Patients

Planned:	1500
Enrolled:	940
Age Range:	18 - 45
Gender:	female
Race:	n/a
Dropped:	0
Completed:	940

Safety Variables: Frequency of blood transfusion, administration of IV fluids and hospitalization

Efficacy Variables: Success, complete abortion without a surgical intervention

Safety Results:

Blood transfusion	= 1
Administration IV fluids	= 2
Hospitalization	= 1*
Death	= 1*

Efficacy Results: Success (interim analysis of 817 cases)

Overall =		97.8%
400 µg oral misoprostol =		97.1%
600 µg oral misoprostol =		98.5%
800 µg vaginal misoprostol	=	97.8%

*IND Safety Reports were submitted to IND 22,047 (Initial Report, Submission Serial Number 218, September 5, 2001 and Follow-up Report, Submission Serial Number 219, September 19, 2001).

STATUS REPORT OF OTHER POST MARKETING STUDIES – ONGOING STUDIES

STUDY STATUS SUMMARY (III) – SEPTEMBER 28, 2001

Study Title: Mifepristone – Misoprostol Medical Abortion: Simplifying the Regimen

Protocol Number: 205-Vietnam

Study Phase:

Date of Study Initiation: January 1, 2001

Study Status (Ongoing/Completed/Discontinued): *Ongoing*

Investigator(s)/Study Center(s):

(b) (4), (b) (6)

Objective: To investigate the safety, efficacy and acceptability of a simplified regimen of mifepristone-misoprostol medical abortion, including home administration of misoprostol and a lower dose of mifepristone (200 mg).

Study Design: Prospective, non-comparative trial

Drugs:

Investigational Drug: Mifepristone + Misoprostol

Control Drug: None

Dosage: 200 mg oral mifepristone, 400 µg oral misoprostol (2 days later)

Description of Patients: Pregnant women with gestations under 56 days LMP

Number of Patients

Planned:	1600
Enrolled:	1560
Age Range:	18 - 45
Gender:	female
Race:	n/a
Dropped:	0
Completed:	1560

Safety Variables: Frequency of blood transfusion, administration of IV fluids and hospitalization

Efficacy Variables: Success, complete abortion without a surgical intervention

Safety Results:

Blood transfusion	= 0
Administration IV fluids	= 0
Hospitalization	= 0

Efficacy Results: Success = 87.5% (911/1041)

STATUS REPORT OF OTHER POST MARKETING STUDIES – ONGOING STUDIES

STUDY STATUS SUMMARY (IV) – SEPTEMBER 28, 2001

Study Title: Mifepristone – Misoprostol Medical Abortion: Expanding Access and Increasing Autonomy

Protocol Number: 283

Study Phase:

Date of Study Initiation:

Sweden: anticipated December 2001
Austria: anticipated early 2002
France: June 8, 2001

Study Status (Ongoing/Completed/Discontinued): *Ongoing*

Investigator(s)/Study Center(s):

Dr. Danielle Hassoun, MD, Hopital Delafontaine, Paris, France

Objective: To investigate the safety, efficacy and acceptability of a simplified regimen of mifepristone-misoprostol medical abortion, including a lower dose of mifepristone (200 mg) and two doses of misoprostol (400 mcg). All women are offered the option to administer their misoprostol at home.

Study Design: Prospective, non-comparative trial

Drugs:

Investigational Drug: Mifepristone + Misoprostol

Control Drug: None

Dosage: 200 mg oral mifepristone, 800 µg oral misoprostol (at day 1 and day 3 following administration of mifepristone)

Description of Patients: Pregnant women with gestations under 56 days LMP

Number of Patients

Planned: Austria=100, Sweden=100, France=30
Enrolled: 11
Age Range: 18 - 45
Gender: female

Race:	n/a
Dropped:	0
Completed:	11
Safety Variables:	Frequency of blood transfusion, administration of IV fluids and hospitalization
Efficacy Variables:	Success, complete abortion without a surgical intervention
Safety Results:	Blood transfusion = 0 Administration IV fluids = 0 Hospitalization = 0
Efficacy Results:	Success = n/a

ATTACHMENT 16

STATUS REPORT OF OTHER POST MARKETING STUDIES
COMPLETED STUDIES
STUDY STATUS SUMMARY (I)

Study Title: Mifepristone – Misoprostol Medical Abortion: Simplifying the Regimen

Protocol Number: 205 -Tunisia

Study Phase:

Date of Study Initiation: January 1, 2001

Study Status (Ongoing/Completed/Discontinued): *Completed*

Investigator(s)/Study Center(s):

(b) (4), (b) (6)

Objective: To investigate the safety, efficacy and acceptability of a simplified regimen of mifepristone-misoprostol medical abortion, including home administration of misoprostol and a lower dose of mifepristone (200 mg).

Study Design: Prospective, non-comparative trial

Drugs:

Investigational Drug: Mifepristone + Misoprostol

Control Drug: None

Dosage: 200 mg oral mifepristone, 400 µg oral misoprostol (2 days later)

Description of Patients: Pregnant women with gestations under 56 days LMP

Number of Patients

Planned: 360
Enrolled: 360
Age Range: 18 - 45

Gender:	female
Race:	n/a
Dropped:	0
Completed:	360
Safety Variables:	Frequency of blood transfusion, administration of IV fluids and hospitalization
Efficacy Variables:	Success, complete abortion without a surgical intervention
Safety Results:	Blood transfusion = 0 Administration IV fluids = 0 Hospitalization = 0
Efficacy Results:	Success = 93%

STATUS REPORT OF OTHER POST MARKETING STUDIES
COMPLETED STUDIES
STUDY STATUS SUMMARY (II)

Study Title: Mifepristone – Misoprostol Medical Abortion: Simplifying the Regimen

Protocol Number: 205 -Turkey

Study Phase:

Date of Study Initiation: August 2000

Study Status (Ongoing/Completed/Discontinued): *Completed*

Investigator(s)/Study Center(s):

(b) (4), (b) (6)

Objective: To investigate the safety, efficacy and acceptability of a simplified regimen of mifepristone-misoprostol medical abortion, including home administration of misoprostol and a lower dose of mifepristone (200 mg).

Study Design: Prospective, non-comparative trial

Drugs:

Investigational Drug: Mifepristone + Misoprostol

Control Drug: None

Dosage: 200 mg oral mifepristone, 400 µg oral misoprostol (2 days later)

Description of Patients: Pregnant women with gestations under 56 days LMP

Number of Patients

Planned:	200
Enrolled:	208
Age Range:	18 - 45
Gender:	female
Race:	n/a
Dropped:	0
Completed:	208

Safety Variables: Frequency of blood transfusion, administration of IV fluids and hospitalization

Efficacy Variables: Success, complete abortion without a surgical intervention

Safety Results:

Blood transfusion	= 0
Administration IV fluids	= 0
Hospitalization	= 0

Efficacy Results: Success = 84%

STATUS REPORT OF OTHER POST MARKETING STUDIES

COMPLETED STUDIES

STUDY STATUS SUMMARY (III)

Study Title: Mifepristone – Misoprostol Medical Abortion: Simplifying the Regimen

Protocol Number: 205 (Vietnam & Tunisia)

Study Phase:

Date of Study Initiation: December 1997

Study Status (Ongoing/Completed/Discontinued): *Completed and published in Lancet 357 (9266): 1402-5, May 5, 2001.*

Investigator(s)/Study Center(s):

(b) (4), (b) (6)

Objective: To investigate the safety, efficacy and acceptability of a simplified regimen of mifepristone-misoprostol medical abortion, including home administration of misoprostol and a lower dose of mifepristone (200 mg).

Study Design: Prospective, non-comparative trial

Drugs:

Investigational Drug: Mifepristone + Misoprostol

Control Drug: None

Dosage: 200 mg oral mifepristone, 400 µg oral misoprostol (2 days later)

Description of Patients: Pregnant women with gestations under 56 days LMP.

Number of Patients

Planned:	315
Enrolled:	315
Age Range:	18 - 45
Gender:	female
Race:	n/a

Dropped:	0
Completed:	315

Safety Variables: Frequency of blood transfusion, administration of IV fluids and hospitalization

Efficacy Variables: Success, complete abortion without a surgical intervention

Safety Results:

Blood transfusion	= 0
Administration IV fluids	= 0
Hospitalization	= 0

Efficacy Results: Success = 93% (Vietnam)
91% (Tunisia)

STATUS REPORT OF OTHER POST MARKETING STUDIES

COMPLETED STUDIES

STUDY STATUS SUMMARY (IV)

Study Title: The feasibility of mifepristone and misoprostol for the medical termination of pregnancy in urban family planning centers and in a well-delineated rural community in Maharastra State, India

Protocol Number: 172

Study Phase:

Date of Study Initiation: October 1995

Study Status (Ongoing/Completed/Discontinued): *Completed and published in Lancet 357 (9250): 120-2, Jan. 13, 2001.*

Investigator(s)/Study Center(s):

1. Usha Krishna, M.D., Bhatia Hospital, Bombay, India
2. Kurus Coyaji, M.D., K.E.M. Hospital, Pune, India
3. Kurus Coyaji, M.D., Shirdi Saibaba Hospital, Vadu, India

Objective: To evaluate whether the combination of mifepristone and misoprostol for early abortion can be safely delivered through a family planning clinic and through a rural health station.

Study Design: Prospective, non-comparative trial

Drugs:

Investigational Drug: Mifepristone + Misoprostol

Control Drug: None

Dosage: 600 mg oral mifepristone, 400 µg oral misoprostol (2 days later)

Description of Patients: Pregnant women with gestations under 56 days LMP in one rural site (300) and with gestation under 63 days in two urban sites (600) and with gestation between 63 and 70 days (20)

Number of Patients

Planned:	920
Enrolled:	912
Age Range:	18 - 45
Gender:	female
Race:	n/a
Dropped:	0
Completed:	912

Safety Variables: Frequency of blood transfusion, administration of IV fluids and hospitalization

Efficacy Variables: Success, complete abortion without a surgical intervention

Safety Results:

Blood transfusion	= 1*
Administration IV fluids	= 2*
Hospitalization	= 2*

Efficacy Results:

Success	= 95.3% (Pune) 90.3% (Bombay) 95% (Vadu) 83.3% (Pune, 63-70 days)

*IND Safety Reports were submitted to IND 22,047 (Initial Reports, Submission Serial Number 204, December 16, 1999).

LONG TERM STABILITY STUDIES (1)

LOT No. (b) (4)

TESTS	SPECIFICATIONS	RESULTS & TEST DATES				
		01.01.17	01.03.15	01.04.09	01.05.09	01.08.10
(b) (4)						

ENVIROMMENTAL CONDITIONS: (b) (4)

PACKING: (b) (4)

Tabulated by (b) (4), (b) (6)

Date: August 13th,2002

Reviewed by (b) (4), (b) (6)

Date: August 15th,2002

LONG TERM STABILITY STUDIES (2)

LOT No (b) (4)		RESULTS & TEST DATES				
TESTS	SPECIFICATIONS	01.11.09	02.02.28	02.08.12	/ /	/ /
(b) (4)						

ENVIROMMENTAL CONDITIONS: (b) (4)

PACKING: (b) (4)

Tabulated by (b) (4), (b) (6)

Date: August 13th,2002

Reviewed by (b) (4), (b) (6)

Date: August 15th,2002

LONG TERM STABILITY STUDIES (1)

LOT No. (b) (4)

TESTS	SPECIFICATIONS	RESULTS & TEST DATES				
		01.02.09	01.03.16	01.04.09	01.05.09	01.08.10
(b) (4)						

ENVIROMMENTAL CONDITIONS: (b) (4)

PACKING: (b) (4)

Tabulated by (b) (4), (b) (6)

Date: August 13th,2002

Reviewed by (b) (4), (b) (6)

Date: August 15th,2002

LONG TERM STABILITY STUDIES (2)

LOT No. (b) (4)

TESTS	SPECIFICATIONS	RESULTS & TEST DATES 01.11.09	02.02.28	02.08.12	/ /	/ /
(b) (4)						

ENVIROMMENTAL CONDITIONS (b) (4)

PACKING: (b) (4)

Tabulated by (b) (4), (b) (6)

Date: August 13th,2002

Reviewed by (b) (4), (b) (6)

Date: August 15th,2002

LONG TERM STASBILITY STUDIES (1)

LOT No. (b) (4)

TESTS	SPECIFICATIONS	RESULTS & TEST DATES				
		01.02.09	01.03.16	01.04.10	01.05.09	01.08.10
(b) (4)						

ENVIROMMENTAL CONDITIONS: (b) (4)

PACKING: (b) (4)

Tabulated by (b) (4), (b) (6)

Date: August 13th,2002

Reviewed by (b) (4), (b) (6)

Date: August 15th,2002

LONG TERM STABILITY STUDIES (2)

LOT No. (b) (4)

TESTS	SPECIFICATIONS	RESULTS & TEST DATES 01.11.09	02.02.28	02.08.12		
(b) (4)						

ENVIROMMENTAL CONDITIONS: (b) (4)

PACKING: (b) (4)

Tabulated by (b) (4), (b) (6)

Date: August 13th,2002

Reviewed by (b) (4), (b) (6)

Date: August 15th,2002

LONG TERM STABILITY STUDIES (1)

LOT No. (b) (4)

TESTS	SPECIFICATIONS	RESULTS & TEST DATES 02.07.12	02.08.14	02.09.16	/ /	/ /
(b) (4)						

ENVIROMMENTAL CONDITIONS: (b) (4)

PACKING: (b) (4)

Tabulated by (b) (4), (b) (6)

Date: September 17th,2002

Reviewed by (b) (4), (b) (6)

Date: September17th,2002

LONG TERM STABILITY STUDIES (1)

LOT No. (b) (4)

TESTS	SPECIFICATIONS	RESULTS & TEST DATES				
		02.07.12	02.08.14	02.09.16	/ /	/ /
(b) (4)						

ENVIROMMENTAL CONDITIONS: (b) (4)

PACKING: (b) (4)

Tabulated by (b) (4), (b) (6)

Date: September 17th,2002

Reviewed by (b) (4), (b) (6)

Date: September17th,2002

LONG TERM STASBILITY STUDIES (1)

LOT No. (b) (4)

TESTS	SPECIFICATIONS	RESULTS & TEST DATES				
		02.07.16	02.08.14	02.09.16	/ /	/ /
(b) (4)						

ENVIROMMENTAL CONDITIONS: (b) (4)

PACKING: (b) (4)

Tabulated by (b) (4), (b) (6)

Date: September 17th,2002

Reviewed by (b) (4), (b) (6)

Date: September17th,2002

ATTACHMENT 6

Danco Laboratories, Inc.

SPECIFICATIONS FOR MIFEPRISTONE TABLETS, 200 mg

IN-PROCESS SPECIFICATIONS

Test	Specification	Method
[redacted] (b) (4)		

Prepared by: [redacted] (b) (4), (b) (6) Approved by: [redacted] (b) (4), (b) (6) Issue Date: 8/31/05

SPECIFICATIONS FOR MIFEPRISTONE TABLETS, 200 mg

FINISHED PRODUCT AND STABILITY SPECIFICATION

Test	Specification	Method
[redacted] (b) (4)		

Prepared by: [redacted] (b) (4), (b) (6) Approved by [redacted] (b) (4), (b) (6) Issue Date: 8/31/05

Danco Laboratories, Inc.

SPECIFICATIONS FOR MIFEPRISTONE TABLETS, 200 mg

HISTORY OF CHANGE

Date	Changes Made	Prepared by
10/6/99	(b) (4)	(b) (4), (b) (6)
8/21/00		

Prepared by: (b) (4), (b) (6) Approved by: (b) (4), (b) (6) Issue Date: 8/31/00

ATTACHMENT 7

DANCO LABOR RIES, INC.

PKG MPR: P000101	Rev.#: 05	Effective Date: December 7,2001	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001				Page 1 of 16

BLISTER PACKAGING OPERATION

A. **BLISTER PACK SIZE**: 1 X 3 Blister/Mini carton

B. **BLISTER PACK COMPONENTS:**

(b) (4)

[redacted]

Calculated By: _____ Checked By: _____

PREPARED BY: (b) (4), (b) (6) [redacted]	DATE: 12/7/2001	APPROVED BY: (b) (4), (b) (6) [redacted]	DATE: 12/7/01
Issued for Blister Packaging by:		Date:	

PKG MPR: P000101	Rev.#: 05	Effective Date: December 7,2001	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001				Page 2 of 16

BLISTER PACKAGING OPERATION

(b) (4)

Performed By:	Date:
Checked By:	Date:
Quality Assurance Check:	Date:

(b) (4)

Performed By:	Date:
Checked By:	Date:
Quality Assurance Check:	Date:

PREPARED BY:	(b) (4), (b) (6)	DATE: 12/7/2001	APPROVED BY:	(b) (4), (b) (6)	DATE: 12/7/01

PKG MPR: P000101	Rev.#: 05	Effective Date: December 7,2001	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001				Page 3 of 16

(b) (4)

[redacted]

Performed By:	Date:
Checked By:	Date:
Quality Assurance Check:	Date:

(b) (4)

[redacted]

Performed By:	Date:
Checked By:	Date:
Quality Assurance Check:	Date:

(b) (4)

[redacted]

PREPARED BY:	(b) (4), (b) (6) [redacted]	DATE: 12/7/2001	APPROVED BY:	(b) (4), (b) (6) [redacted]	DATE: 12/7/01

PKG MPR: P000101	Rev.#: 05	Effective Date: December 7,2001	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001				Page 4 of 16

(b) (4)

performed by:_____; Date:_____ Time Start:_____
Date: _____ Time End:_____

Time	Start Up								
(b) (4)									

(b) (4)

	Date	Time	Performed By	Results (P/F)
(b) (4)				

PREPARED BY: (b) (4), (b) (6)	DATE: 12/7/2001	APPROVED BY: (b) (4), (b) (6)	DATE: 12/7/01

PKG MPR: P000101	Rev.#: 05	Effective Date: December 7,2001	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001				Page 5 of 16

(b) (4)

[redacted]

Visual Check of Blisters

Time(min)	Actual Time	Appearance [A] (Pass/Fail)	Count [A] (Pass Fail)	Performed By
(b) (4)				

PREPARED BY:	(b) (4), (b) (6) [redacted]	DATE: 12/7/2001	APPROVED BY:	(b) (4), (b) (6) [redacted]	DATE: 12/7/01

DANCO LABORATORIES, INC.

Pl[illegible]MPR: P000101	Rev.#: 05	Effective Date: December 7,2001	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001				Page 6 of 16

Note A [redacted] (b) (4)

Reason for Re-inspection:_____

Time Interval Inspected	Appearance A (Pass/Fail)	Count A (Pass Fail)	Performed By

[redacted] (b) (4)

PREPARED BY:	[redacted] (b) (4), (b) (6)	DATE:	12/7/2001	APPROVED BY:	[redacted] (b) (4), (b) (6) DATE 12/7/01

DANCO LABORATORIES, INC.

PKG MPR: P000101	Rev.#: 05	Effective Date: December 7,2001	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001				Page 7 of 16

(b) (4)

[redacted]

QA released by: _____ Date: _____

PREPARED BY:	(b) (4), (b) (6) [redacted]	DATE: 12/7/2001	APPROVED BY:	(b) (4), (b) (6) [redacted]	DATE: 12/7/01

PKG MPR: P000101	Rev.#: 05	Effective Date: December 7,2001	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001				Page 8 of 16

LABELING AND FINAL PACKAGING OPERATION

(b) (4)

(b) (4)

#_____

#_____

#_____

#_____

#_____

(b) (4)

Performed By:	Date:
Checked By:	Date:
Quality Assurance Check:	Date:

(b) (4)

QA Release for Final labeling and Packaging: Performed By: _____ Date: _____

PREPARED BY: (b) (4), (b) (6)	DATE: 12/7/2001	APPROVED BY: (b) (4), (b) (6)	DATE: 12/7/01
Issued for Packaging by:		Date	

Pkg MPR: P000101	Rev.#: 05	Effective Date: December 7,2001	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001				Page 9 of 16

(b) (4)

[redacted]

Performed By:	Date:
Checked By:	Date:
Quality Assurance Check:	Date:

(b) (4)

[redacted]

System Started By: _____ Date: _____ Time: _____

PREPARED BY:	(b) (4), (b) (6) [redacted]	DATE: 12/7/2001	APPROVED BY:	(b) (4), (b) (6) [redacted]	DATE 12/7/01

MPR: P000101	Rev.#: 05	Effective Date: December 7,2001	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001				Page 10 of 16

(b) (4)

System Set up By: _____ Date: _____ Time: _____

(b) (4)

QA Label Check: Performed By: _____ Date: _____

(b) (4)

Performed By: _____ Date: _____ Time Start: _____ Label # _____

Performed By: _____ Date: _____

Performed By: _____ Date: _____

Performed By: _____ Date: _____ Time Finished: _____ Label # _____

(b) (4)

PREPARED BY: (b) (4), (b) (6)	DATE: 12/7/2001	APPROVED BY (b) (4), (b) (6)	DATE 12/7/01

PKG MPR: P000101	Rev.#: 05	Effective Date: December 7,2001	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001				Page 11 of 16

(b) (4)

System Started By: _____ Date: _____ Time: _____

(b) (4)

QA Label Check: Performed By: _____ Date: _____

(b) (4)

Performed By: _____ Date: _____ Time Start: _____ Label # _____

Performed By: _____ Date: _____ Label # _____

Performed By: _____ Date: _____ Label # _____

Performed By: _____ Date: _____ Time Finished: _____ Label # _____

PREPARED BY: (b) (4), (b) (6)	DATE: 12/7/2001	APPROVED BY: (b) (4), (b) (6)	DATE 12/7/01

PKG MPR: P000101	Rev.#: 05	Effective Date: December 7,2001	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001				Page 12 of 16

(b) (4)

[redacted]

Performed By:	Date:
Quality Assurance Verification: _____ Date: _____	

(b) (4)

[redacted]

Label reconciliation performed by: _____ Date: _____ Time: _____

Label reconciliation verified by: _____ Date: _____ Time: _____

(b) (4)

[redacted]

PREPARED BY: (b) (4), (b) (6) [redacted]	DATE: 12/7/2001	APPROVED BY: (b) (4), (b) (6) [redacted]	DATE 12/7/01

PKG MPR: P000101	Rev.#: 05	Effective Date: December 7,2001	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001				Page 13 of 16

(b) (4)

[redacted]

System Started By: _____ Date: _____ Time: _____

(b) (4)

[redacted]

QA Label Check: Performed By: _____ Date: _____

PREPARED BY: (b) (4), (b) (6) [redacted]	DATE: 12/7/2001	APPROVED BY: (b) (4), (b) (6) [redacted]	DATE 12/7/01

PKG MPR: P000101	Rev.#: 05	Effective Date: December 7,2001	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001				Page 14 of 16

[redacted] (b) (4)

Performed By: _____ Date: _____ Time Start: _____

Performed By: _____ Date: _____ Time Finished: _____

[redacted] (b) (4)

PREPARED BY: [redacted] (b) (4), (b) (6)	DATE: 12/7/2001	APPROVED BY: [redacted] (b) (4), (b) (6)	DATE 12/7/01

PKG MPR: P000101	Rev.#: 05	Effective Date: December 7,2001	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001				Page 15 of 16

QUALITY ASSURANCE REVIEW OF PACKAGING BATCH RECORD:

Quality Assurance Review By: _____ Date: _____

Danco Quality Assurance Approval for Shipment

By: _____ Date: _____

PREPARED BY: (b) (4), (b) (6)	DATE: 12/7/2001	APPROVED BY: (b) (4), (b) (6)	DATE 12/7/01

PRO MPR: P000101	Rev.#: 05	Effective Date: December 7,2001	Lot #	Expiration Date:
Product Name(#): Mifepristone Tablets: (200 mg) 001				Page 16 of 16

History of Change

Revision Number	Date Of Revision	Revised By	Reason for Revision
1			
2			
3	October 16, 2000	(b) (4), (b) (6)	(b) (4)
4	November 7, 2000		
5	December 07, 2001		

PREPARED BY: (b) (4), (b) (6)	DATE: 12/7/2001	APPROVED BY: (b) (4), (b) (6)	DATE 12/7/01 .

ATTACHMENT 8

STABILITY STUDY REPORT FOR BATCH # (b) (4)
CONTROLLED ROOM TEMPERATURE STUDY

Product: Mifepristone Tablets, 200 mg	**Batch #:** (b) (4)
Purpose of study: Controlled Room Temperature	**Manufacturing date:** 6/28/99
Batch size: (b) (4) tablets	**Expiration date:** 1/2001
Ingredient	**Manufacturer**
(b) (4)	

CONTAINER/CLOSURE SYSTEM

(b) (4)

EVALUATION SCHEDULE

(b) (4)

STABILITY DATA

(b) (4)

STABILITY STUDY REPORT FOR BATCH # (b) (4)

ACCELERATED STABILITY STUDY

Product: Mifepristone Tablets, 200 mg	**Batch #:** (b) (4)
Purpose of study: Accelerated Stability	**Manufacturing date:** 6/28/99
Batch size: (b) (4) tablets	**Expiration date:** 1/2001
Ingredient	**Manufacturer**
(b) (4)	

CONTAINER/CLOSURE SYSTEM

(b) (4)

EVALUATION SCHEDULE

(b) (4)

STABILITY DATA

(b) (4)

STABILITY STUDY REPORT FOR BATCH # (b) (4)
CONTROLLED ROOM TEMPERATURE STUDY

Product: Mifepristone Tablets, 200 mg	**Batch #:** (b) (4)
Purpose of study: Controlled Room Temperature	**Manufacturing date:** 9/22/99
Batch size: (b) (4) tablets	**Expiration date:** 3/2001
Ingredient	**Manufacturer**
(b) (4)	

CONTAINER/CLOSURE SYSTEM

(b) (4)

EVALUATION SCHEDULE

(b) (4)

STABILITY DATA

(b) (4)

STABILITY STUDY REPORT FOR BATCH # (b) (4)
ACCELERATED STABILITY STUDY

Product: Mifepristone Tablets, 200 mg	**Batch #:** (b) (4)
Purpose of study: Accelerated Stability	**Manufacturing date:** 9/22/99
Batch size: (b) (4) ablets	**Expiration date:** 3/2001
Ingredient	**Manufacturer**
(b) (4)	

CONTAINER/CLOSURE

(b) (4)

EVALUATION SCHEDULE

(b) (4)

STABILITY DATA

(b) (4)

STABILITY STUDY REPORT FOR BATCH # (b) (4)
CONTROLLED ROOM TEMPERATURE STUDY

Product: Mifepristone Tablets, 200 mg	**Batch #:** (b) (4)
Purpose of study: Controlled Room Temperature	**Manufacturing date:** 8/3/00
Batch size: (b) (4) tablets	**Expiration date:** 2/2002
Ingredient	**Manufacturer**
(b) (4)	

CONTAINER/CLOSURE SYSTEM

(b) (4)

EVALUATION SCHEDULE

(b) (4)

STABILITY DATA

(b) (4)

STABILITY STUDY REPORT FOR BATCH # (b) (4)
ACCELERATED STABILITY STUDY

Product: Mifepristone Tablets, 200 mg	**Batch #:** (b) (4)
Purpose of study: Accelerated Stability	**Manufacturing date:** 8/3/00
Batch size: (b) (4) tablets	**Expiration date:** 2/2002
Ingredient	**Manufacturer**
(b) (4)	

CONTAINER/CLOSURE SYSTEM

(b) (4)

EVALUATION SCHEDULE

(b) (4)

STABILITY DATA

(b) (4)

STABILITY STUDY REPORT FOR BATCH # (b) (4)
CONTROLLED ROOM TEMPERATURE STUDY

Product: Mifepristone Tablets, 200 mg	**Batch #:** (b) (4)
Purpose of study: Controlled Room Temperature	**Manufacturing date:** 9/11/00
Batch size: (b) (4) tablets	**Expiration date:** 3/2002
Ingredient	**Manufacturer**
(b) (4)	

CONTAINER/CLOSURE SYSTEM

(b) (4)

EVALUATION SCHEDULE

(b) (4)

STABILITY DATA

(b) (4)

STABILITY STUDY REPORT FOR BATCH # (b) (4)

ACCELERATED STABILITY STUDY

Product: Mifepristone Tablets, 200 mg	**Batch #:** (b) (4)
Purpose of study: Accelerated Stability	**Manufacturing date:** 9/11/00
Batch size: (b) (4) tablets	**Expiration date:** 3/2002
Ingredient	**Manufacturer**
(b) (4)	

CONTAINER/CLOSURE SYSTEM

(b) (4)

EVALUATION SCHEDULE

(b) (4)

STABILITY DATA

(b) (4)

STABILITY STUDY REPORT FOR BATCH # (b) (4)
CONTROLLED ROOM TEMPERATURE STUDY

Product: Mifepristone Tablets, 200 mg	**Batch #:** (b) (4)
Purpose of study: Controlled Room Temperature	**Manufacturing date:** 10/11/00
Batch size: (b) (4) tablets	**Expiration date:** 4/2002
Ingredient	**Manufacturer**
(b) (4)	

CONTAINER/CLOSURE SYSTEM

(b) (4)

EVALUATION SCHEDULE

(b) (4)

STABILITY DATA

(b) (4)

STABILITY STUDY REPORT FOR BATCH # (b) (4)
ACCELERATED STABILITY STUDY

Product: Mifepristone Tablets, 200 mg	**Batch #:** (b) (4)
Purpose of study: Accelerated Stability	**Manufacturing date:** 10/11/00
Batch size: (b) (4) tablets	**Expiration date:** 4/2002
Ingredient	**Manufacturer**
(b) (4)	

CONTAINER/CLOSURE SYSTEM

(b) (4)

EVALUATION SCHEDULE

(b) (4)

STABILITY DATA

ATTRIBUTE	SPECIFICATION	INITIAL	1 MO.	2 MO.	3 MO.	6 MO.	12 MO.
(b) (4)							

STABILITY STUDY REPORT FOR BATCH # (b) (4)
CONTROLLED ROOM TEMPERATURE STUDY

Product: Mifepristone Tablets, 200 mg	**Batch #:** (b) (4)
Purpose of study: Controlled Room Temperature	**Manufacturing date:** 12/18/01
Batch size: (b) (4) tablets	**Expiration date:** 12/2003
Ingredient	**Manufacturer**
(b) (4)	

CONTAINER/CLOSURE SYSTEM

(b) (4)

EVALUATION SCHEDULE

(b) (4)

STABILITY DATA

(b) (4)

ATTACHMENT 9

LITERATURE UPDATE – NONCLINICAL

The present update to the bibliography was generated by a search performed using PubMed with the keywords mifepristone and animal from all sources and languages. This bibliography covers the period of September 28, 2001 to September 27, 2002.

The bibliography generated by this strategy includes published articles on non-clinical investigations on mifepristone. A list of these references in alphabetical order is presented below. The reprints of these articles will be supplied upon request.

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ATTACHMENT 10

LITERATURE UPDATE – CLINICAL

The present update to the bibliography was generated by a search performed using PubMed with the keywords mifepristone and human from all sources and languages. This bibliography covers the period of September 28, 2001 to September 27, 2002.

The bibliography generated by this strategy includes published articles on clinical investigations on mifepristone. The references are organized alphabetically by author. In addition, the references are subdivided into several sections: 1. Medical Abortion, 2. Cervical Softening, Surgical Abortion, Management of Late Intrauterine Death and Cesarean Section, 3. Other (Alzheimer's Disease, Contraception, Depression, Emergency Contraception and Biochemical Effects, etc.). The reprints of these articles will be supplied upon request.

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[No authors listed]
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3. Other (Alzheimer's Disease, Contraception, Depression, Emergency Contraception and Biochemical Effects, etc.)

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ATTACHMENT 11

1. Medical Abortion

Tidsskr Nor Laegeforen 2001 Nov 20;121(28):3261

[Interrupted pregnancy, mifepristone and patient rights]

[Article in Norwegian]

Aavitsland P.

Publication Types:

- Editorial

PMID: 11826453 [PubMed - indexed for MEDLINE]

Hum Reprod 2002 Jan;17(1):92-8

A randomized comparison of medical abortion and surgical vacuum aspiration at 10-13 weeks gestation.

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BACKGROUND: Since 1991, mifepristone in combination with a prostaglandin analogue has been licensed for termination of pregnancy in the UK at up to 9 weeks amenorrhoea, and since 1995, beyond 13 weeks. Surgical methods are used almost exclusively at 10-13 weeks amenorrhoea. METHODS: A patient-centred, partially randomized, controlled trial was carried out. Those who expressed a strong preference for either medical (n = 15) or surgical (n = 62) abortion were allocated to that method. The remainder agreed to be randomized. The medical method (n = 188) was mifepristone 200 mg followed by misoprostol up to 3 doses, and surgery (n = 180) was by vacuum aspiration under general anaesthesia. Outcome measures included efficacy rates, medical complications within 8 weeks of the procedure, patient preferences and acceptability. RESULTS: Among women who underwent medical abortion, 5.4% required a second procedure compared with 2.1% who had surgery, although this difference was not statistically significant. Side effects experienced were higher in women who underwent medical abortion compared with those who underwent surgery. There were no significant differences in the rates of major complications up to 8 weeks. Prior to termination, 80% of women had a preference for a method, with 72% preferring medical and 28% preferring surgical abortion. Following abortion, 70% of those who underwent medical termination and 79% who underwent surgery would opt for the same method in the future. CONCLUSION: Medical abortion is safe and effective at 10-13 weeks gestation and should be considered an option for those women who wish to avoid surgery and anaesthesia.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 11756368 [PubMed - indexed for MEDLINE]

Best Pract Res Clin Obstet Gynaecol 2002 Apr;16(2):221-36

Medical abortion in the first trimester.

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Pregnancy can be terminated safely by inducing abortion medically at any stage of gestation. Antagonists such as mifepristone block the action of progesterone and hence result in uterine contractions and increase the sensitivity of the uterus to prostaglandins. In the last 15 years the combination of a single dose of mifepristone (600 mg) followed 48 hours later with a suitable prostaglandin (1 mg gemeprost vaginal pessary or 400 microg oral misoprostol) has been licensed in most countries in Europe and the USA for induction of abortion in the early weeks of pregnancy. The safety and efficacy of these methods is comparable to vacuum aspiration at the same gestation. The complete abortion rate is related to the type and dose of prostaglandin, the route of administration as well as the gestation and parity. Published data suggest that the dose of mifepristone can be reduced from 600 mg to 200 mg without loss of efficacy. Although misoprostol tablets are formulated for oral use, extensive clinical experience has demonstrated vaginal administration is more effective and is associated with fewer side-effects. Successful abortion using medical methods requires a well organized service which includes referral without delay and a robust system of follow up to identify failures. The failure rate as reflected by the number of women who require surgical intervention falls with increasing experience. In those countries where medical abortion has been freely available for about 10 years, such as France, Scotland and Sweden, about 60-70% of eligible women elect for this method.

Publication Types:

- Review
- Review, Tutorial

PMID: 12041964 [PubMed - indexed for MEDLINE]

Hum Reprod 2001 Oct;16(10):2098-102

Double-blind randomized trial of mifepristone in combination with vaginal gemeprost or misoprostol for induction of abortion up to 63 days gestation.

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BACKGROUND: Gemeprost and misoprostol are two of the most widely used prostaglandins in combination with mifepristone for medical abortion in early pregnancy. However, the efficacy and side-effects of those two drugs given vaginally have not been assessed in a randomized trial. METHODS: Randomized double-blind controlled trial involving 999 women undergoing an abortion at gestational age < or =63 days who received either 0.5 mg gemeprost (group I, n = 499) or 800 microg misoprostol (group II, n = 500) vaginally approximately 48 h after taking 200 mg mifepristone by mouth. The rate of complete abortion and the side-effects were compared between the groups. RESULTS: A total of 89 cases was excluded from full analysis of outcome because either they aborted after mifepristone alone (n = 2), had an ectopic pregnancy (n = 1), or because the outcome was uncertain as they failed to attend their follow-up appointment (n = 86). The rate of complete abortion was very high (>95%) in both groups but significantly higher after treatment with misoprostol than with gemeprost [436/453 (98.7%) versus 451/457 (96.2%), P = 0.019, difference 2.5%, confidence interval 0.4-4.7%] and there were fewer ongoing pregnancies (n = 1 versus n = 8, P < 0.018). Surgical intervention rose significantly with gestation in women who received gemeprost (P < 0.03) but not with misoprostol. The incidence of side-effects such as diarrhoea (13.7 versus 16.4%) and vomiting (27.8 versus 29.7%) was similar in women who received misoprostol or gemeprost respectively, as was the duration and amount of bleeding. CONCLUSIONS: (i) Both regimens using a reduced dose of mifepristone are highly effective methods of inducing abortion in early pregnancy; (ii) vaginal misoprostol is the preferred prostaglandin because it is it is associated with fewer failures than low-dose gemeprost, particularly at gestation > or =49 days.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 11574498 [PubMed - indexed for MEDLINE]

Hum Reprod 2001 Oct;16(10):2243-4

Mifepristone (RU486) and voluntary termination of pregnancy: enigmatic variations or anecdotal religion-based attitudes?

Baulieu EE, Seidman DS, Hajri S.

Letters to the Editor

Mifepristone (RU486) and voluntary termination of pregnancy: enigmatic variations* or anecdotal religion-based attitudes?

Dear Sir,

Mifepristone (RU486), the first clinically efficient antiprogesterone (Herrmann *et al.*, 1982; Baulieu, 1989), has made the concept of medical abortion a reality (Ulmann *et al.*, 1992). Here we only refer to the voluntary termination of early pregnancy, which sustains so much controversy in the vast and evolving domain of women's reproductive health (Van Look, 2000). Legally on the market for years in France, Britain and Sweden and massively produced and used in China, the compound has become available to women in need in Israel, Tunisia and Germany, where what might be called religion-based attitudes have been observed.

Of course the biology of pregnancy is quasi-identical for women all over the world, and its termination with an antagonist to the hormone of pregnancy, progesterone, should also be the same everywhere. But the use of this antagonist, mifepristone (RU486), does not mean the same thing to everybody everywhere.

In Israel, mifepristone was approved and has been sold to the public since September 1999. Remarkably, its reception by religious fundamentalist Jews was not hostile and even the opposite: on the grounds that under Jewish law, although the fetus is considered to be a potential person from the moment of conception, before 40 days of gestation it is 'mayim b'alma' (mere water) according to the Talmud (Eisenberg, 1998). Although disagreement does exist, many Jewish scholars believe that prior to 40 days one cannot 'wound' or 'murder' that which does not have the status of an existing person. Since fear of injury to the mother by abortion within these 40 days still remains an objection by Jewish law, a safe medical termination with mifepristone, which is easy to perform and efficient earlier than with an instrumental technique, may thus be preferable. This should be appreciated when attempting to avoid real or foreseen obstacles to the introduction of new forms of contraception or abortion. This argument of a spiritual nature may be important for confronting other objections: apparently some Israeli physicians are not over-enthusiastic about a method which is less financially rewarding than an instrumental intervention.

Clearly, the strong opposition from fundamentalist Christian groups should not automatically be extended to another (monotheist) religion. This can also be deduced from the Tunisian experience. In Tunisia, trials have been conducted by the Population Council and the Tunisian 'Planning familial' and confirm the Israeli case with respect to the opinion of religious Muslims. Tunisian trials have involved Muslim women practising the five daily prayers and regularly following Ramadan, sometimes even wearing a tchador during the consultations. They found the procedure more acceptable because it is early and 'natural' (non instrumental), and imams cite a 'hadith' also describing the first 40 days of embryogenesis as that preceding 'unity' ('God's breath' being insufflated on ~120th day) (Banwell and Paxman, 1992). One unexpected favourable argument was provided by seven young single women (20–29 years old) who chose mifepristone which, not involving instrumental intrusion, would 'protect their virginity' in conformity with their fiancés' indication that they had only had a 'superficial' sexual relationship, and, of course, this was eventually also approved by their family. The preservation of future fertility (unpublished observations in cases reported in Ulmann *et al.*, 1992) is one more favourable reason for accepting mifepristone.

In Europe, mifepristone has recently been approved for use in a further eight countries, including Germany. In Germany, opposition came not directly from religious groups but from the German Society for Gynecology and Obstetrics (DGGG). This association reacted rapidly to the application for mifepristone, presented by the Bounder Institut für Arzneumittei and Medizin Products, and insisted on the 'considerable mental duress for women, the (frequently life long) psychosomatic consequences' caused by an abortion. The appointed DGGG committee recommended certain diagnosis of intact intrauterine pregnancy using vaginal sonographic proof of embryonic cardiac activity (German Society for Gynecology and Obstetrics, 1999), which is not possible before day 38–42 after the last menstrual period at the earliest. They tried to convince the Health Authorities and the public that mifepristone, which may be used to interrupt pregnancy very early—a physiologically and psychologically beneficial property— should be only used after the 42nd day because earlier intervention could constitute abortion 'of an unfit object' which would have been spontaneously eliminated anyway in up to 30% of cases (Blanch *et al.*, 1998). The delay would avoid future remorse for these women, and thus it would be better to wait (and possibly suffer more from use of an instrumental method). One of the rare cases when an appropriate medical treatment becomes improper because of its very early application! The story did end with the regular registration of mifepristone in Germany. At last.

The next 'interesting' case will be the USA, where the majority of religiously oriented professionals (pharmacists) supporting the right to refuse to dispense abortifacients, indicated abortion should remain a legal option including that using RU486 (Gianetti, 1996). The Food and Drug Administration has approved the drug (*Time Magazine*, 2000), a decision that generated debate between the candidates in the Presidential election (*The New York Times*, 2000).

How interesting the diversity of confrontations of human beings with a drug. It is not unexpected that pregnancy interruption generates behavioural variations which are, after all, not so enigmatic...

*The play *Enigmatic variations* by Eric-Emmanuel Schmitt has been performed in several countries. It is based on the symphonic 'Enigma variations' by Edward Elgar.

Tidsskr Nor Laegeforen 2001 Nov 20;121(28):3286-91

[Mifepristone--a controversial drug with great potential]

[Article in Norwegian]

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BACKGROUND: Antiprogestins, agents that inhibit the action of progesterone, are among the most controversial and yet the more interesting therapeutic compounds developed over the past 20 years. MATERIAL AND METHODS: We present a review of the literature identified through limited searches on Medline, Cochrane and the Internet, with a discussion of the biological, clinical, political and ethical aspects of this important drug. RESULTS: The first effective antiprogestin in clinical use was mifepristone (also known as RU 486). This agent provides the most effective and safest means of medical abortion. It may also be used as a contraceptive and delivery-inducing agent and in the treatment of spontaneous abortion, ectopic pregnancies, leiomyoma, endometriosis, intrauterine fetal death, Cushing's syndrome and progesterone-dependent malignancies. INTERPRETATION: The introduction of mifepristone as an abortion-inducing agent has created intense political, ethical and moral controversies which have delayed clinical investigations and evaluations for potential expanded use.

Publication Types:

- Historical Article
- Review
- Review, Tutorial

PMID: 11826459 [PubMed - indexed for MEDLINE]

Acta Obstet Gynecol Scand 2001 Nov;80(11):1056-61

Early pregnancy termination with mifepristone and misoprostol in Norway.

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OBJECTIVES: Medical abortion was first introduced in Norway in April 1998. The aims of this study were to assess the efficacy, side effects, and acceptability of medical abortion using mifepristone orally and misoprostol vaginally in a Norwegian population. DESIGN: The study included the first 226 pregnant women with gestational age of <63 days who requested nonsurgical abortion during the first year in the first Norwegian hospital using this regimen. METHODS: All women received a single dose of mifepristone 600 mg orally, followed at 48 hours by 800 microg misoprostol vaginally. Treatment outcome and complications were the principal outcome measures. We also measured the rates of side effects such as abdominal pain and bleeding and the women's acceptability of treatment. RESULTS: Abortion was successful in 95%, surgical evacuation became necessary in 4%, and the pregnancy continued in one woman. During the study period the method was chosen by 23% of those requesting abortion before 63 days amenorrhea; 80% would use the method again; 81% would recommend it to a friend; in retrospect, 69% would not have been willing to be randomly allocated to either a medical or a surgical method. CONCLUSIONS: The combination of orally administrated mifepristone and vaginally administrated misoprostol is an abortion method that is both effective and safe, has few side effects and is well accepted by Norwegian women.

Publication Types:

- Clinical Trial

PMID: 11703208 [PubMed - indexed for MEDLINE]

Obstet Gynecol 2001 Dec;98(6):1149-50

Curettage After Mifepristone-Induced Abortion: Frequency, Timing, and Indications

To the Editor:

Allen et al reported the outcome of 4393 medical abortions at gestations up to 63 days using 200 mg of oral mifepristone plus 800 μg of vaginal misoprostol.[1] One hundred sixteen (2.6%) women subsequently underwent curettage ("failed abortion"). The authors found that gestational age and prior elective abortion were associated with curettage, whereas age and parity were not. (The 17 centers participating in the study are to be congratulated in obtaining such a high success rate with medical abortion.)

We recently reported a comparative study of 533 medical and 399 surgical aspiration abortions up to 63 days' gestation.[2] The age and parity distributions were similar in the two treatment groups. Medical abortions were performed using the same drug regimen as that used by Allen et al.[1] The rate of curettage after medical abortion was 8.3% for incomplete or missed abortions and 0.9% for ongoing pregnancy and after surgical abortion 5.0% and 0.5%, respectively. This was an audited analysis within a general gynecologic service in a single institution providing all necessary follow-up.

We found a significantly higher rate of subsequent curettage with increasing parity irrespective of gestation for medical abortion ($P = .012$) but not surgical abortion (Table 1). The difference was particularly significant between the two abortion methods for para 3 and greater ($P = .028$), although the denominators were small. Allen et al[1] analyzed outcomes for nulliparous and multiparous groups and found no difference in curettage rates. It would, therefore, be of clinical value to know, with their large data set, whether increasing parity was associated with a higher rate of curettage after medical abortion.

Table 1. Complete Abortion Rates for Women Undergoing Medical or Surgical Procedures at up to 63 Days' Gestations

	Medical	Surgical	*P*
Parity			
0	304/330 (92.0%)*	238/251 (94.8%)†	NS‡
1	66/72 (91.7%)*	46/51 (90.2%)†	NS§
2	76/89 (85.4%)*	50/53 (94.3%)†	NS§
≥3	35/42 (83.3%)*	43/44 (97.7%)†	.028§

Values are complete abortions/total abortions (percentage).
*† Mantel-Haenszel χ^2 test for trend, controlling for gestation: * $P = .012$; † P = NS.
‡ χ^2 test, two-tailed P value.
§ Fisher's exact test (two-tailed).

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REFERENCES

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2. Child TJ, Thomas J, Rees M, MacKenzie IZ. A comparative study of surgical and medical procedures: 932 pregnancy terminations up to 63 days gestation. Hum Reprod 2001; 16:67–71.

In Reply:

In our study of curettage after medical abortion, we had 341 subjects with a parity of three or greater.[1] The rate of curettage in these women was 2.3%, which is similar to our overall rate. Other studies of the success of medical abortion, as cited by Child et al, also found no effect of parity on the rate of curettage; thus, their recent finding remains unconfirmed.[2] Our two studies used similar protocols with 200 mg of mifepristone and 800 μg of vaginal misoprostol to terminate pregnancies up to 63 days' gestation. The larger difference between our results is an overall curettage rate of 2.6% in our patients and 9.8% rate in theirs. These results represent the full range seen in the current literature and demand explanation. If all of the 59 women lost to follow-up in our study underwent curettage, then our rate would increase to only 4.0%. A possibly relevant protocol difference is that we allowed women a second dose of misoprostol in our study to assist expulsion rather than proceeding directly to aspiration; this intervention might have avoided a few curettages. These explanations bring our results only slightly closer together. The remaining difference in our curettage rates confirms that subtleties of practice style will continue to have a large impact on the success of medical abortion regimens.

Carolyn Westhoff, MD
Rebecca Allen, MD

Contraception 2002 Jul;66(1):33-40

Mifepristone-misoprostol abortion: a trial in rural and urban Maharashtra, India.

Coyaji K, Elul B, Krishna U, Otiv S, Ambardekar S, Bopardikar A, Raote V, Ellertson C, Winikoff B.

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As several important policy questions remain regarding the use of medical abortion in developing countries, we investigated the safety, efficacy, and acceptability of mifepristone-misoprostol abortion in the outpatient family planning departments of two urban hospitals and one rural hospital in India. Nine-hundred women (with gestations of < or =63 days in the urban sites and < or =56 days in the rural site) received 600 mg mifepristone followed 48 h later by 400 microg oral misoprostol in the clinic. Four point four percent or fewer urban women and 1.0% rural women were lost to follow-up. Perfect and typical-use failure rates were low at all sites. While rural women reported fewer side effects at all sites, the vast majority of women were satisfied with their medical abortions. Medical abortion can be offered safely, effectively, and acceptably in the outpatient family planning departments of urban and rural hospitals in India.

Publication Types:

- Clinical Trial
- Multicenter Study

PMID: 12169379 [PubMed - indexed for MEDLINE]

Curr Womens Health Rep 2001 Dec;1(3):184-90

The mifepristone-misoprostol regimen for early medical abortion.

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The combination of mifepristone, an antiprogesterone known in the United States as Mifeprex (Danco Laboratories, New York, NY), and misoprostol, a prostaglandin analogue marketed in the United States under the brand name Cytotec (Pharmacia [formerly Searle], Peapack, NJ), provides a nonsurgical abortion in the early stages of a pregnancy. Mifepristone blocks the action of progesterone, a hormone necessary to sustain a pregnancy, whereas misoprostol causes contractions that expel the embryo and other pregnancy tissue. Since September 2000, mifepristone has been approved by the United States Food and Drug Administration for induced abortions of gestations of 49 days or less since the last menstrual period, but is not yet approved for any other uses. Misoprostol has long been approved to prevent and treat stomach ulcers.

Publication Types:

- Review
- Review, Tutorial

PMID: 12112968 [PubMed - indexed for MEDLINE]

Perspect Sex Reprod Health 2002 Jan-Feb;34(1):34-40

Having an abortion using mifepristone and home misoprostol: a qualitative analysis of women's experiences.

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CONTEXT: Women choose medical over surgical abortion because it is more natural, more private and less painful. Whether their perceptions change during the medical abortion process has not been explored. METHODS: A nonprobabilitysample of 43 participants in a clinical trial of abortion using mifepristone completed two open-ended questionnaires about this method, one before taking mifepristone and the second during their follow-up clinic visit 4-8 days after taking misoprostol. Thirty women participated in in-depth interviews 1-6 weeks following their abortion. Researchers analyzed transcripts to identify common themes. RESULTS: On the first visit to the clinic, women expressed anxiety and uncertainty about the effectiveness of medical abortion, guilt or ambivalence, and a desire to avoid surgery. For most women, emotional distress decreased after their abortion. Control was the overarching theme women expressed regarding the meaning of the procedure: Women stressed the importance of being able to select the type of abortion procedure, to maintain control over their future and to preserve their family's quality of life, given the constraints of time, finances and emotional resources. In in-depth interviews, eight women remained concerned about long-term health effects; 18 said that having an abortion at home was a comfortable experience. CONCLUSIONS: Learning whether women are concerned about personal control may help clinicians identify appropriate candidates for medical abortion. In addition, clinicians could help allay women's anxiety at their first abortion visit by explaining that the uncertainties posed by any medical procedure create similar feelings. Clinicians also should reemphasize at the follow-up visit that there are no long-term health effects related to abortion.

Publication Types:

- Evaluation Studies

PMID: 11990637 [PubMed - indexed for MEDLINE]

Nurse Pract 2001 Nov;26(11):44-54

Professional considerations for providing mifepristone-induced abortion.

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Primary care clinicians who provide comprehensive reproductive heath care can now offer patients mifepristone (Mifeprex) as an abortifacient option. Clinicians, however, must first determine if the state in which they practice has regulations specifying who can perform abortions and dispense drugs, and they must consider clinical office zoning ordinances, staffing, public relations issues, and reimbursement. This article discusses the pharmacology of mifepristone and misoprostol, professional considerations, and how to prevent and manage adverse effects and complications of medical abortion.

Publication Types:

- Review
- Review, Tutorial

PMID: 11759615 [PubMed - indexed for MEDLINE]

Contraception 2002 Jul;66(1):27-31

Clinicians' perception of sonogram indication for mifepristone abortion up to 63 days.

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One barrier in the US to wider acceptance of mifepristone for abortion is the additional cost of the routine use of two sonograms, that is, for pregnancy dating and confirmation of a complete abortion. The purpose of this study is to document how the accuracy of medical abortion clinicians experienced with pelvic exams and dating pregnancies in assessing gestational age at the first visit compared with sonograms, and to identify the factors influencing whether they perceive that sonograms are desired or indicated at the first and follow-up visits. This was a prospective study of 1016 women wanting to participate in a medical abortion trial. After informed consent, clinicians (1) dated the pregnancy before routine sonography and (2) determined whether a sonogram was indicated. Women with sonographic pregnancies of less than 63 days were eligible for mifepristone followed by misoprostol 48 h later. Women returned on Day 4 to Day 8, and clinicians performed a clinical assessment of whether the abortion was complete and determined whether a sonogram was indicated. Fifteen sites participated. Advanced-level providers performed 56% of the assessments. When clinicians assessed a pregnancy under 43 days gestation, they perceived that a sonogram was "not indicated" in 60% of these women. This percentage increased to 66% at 43-49 days gestation, and declined to 46% of women assessed at more than 49 days. Clinicians correctly assessed gestational age as no more than 63 days in 87% of women. In only 1% (14/1013) of their assessments did clinicians underestimate gestational age. In 7/24 (29%) women with a persistent gestational sac, clinicians did not indicate the need for sonography when it was likely indicated. We conclude that the clinicians in our study felt confident in not using sonography in most cases. If clinicians monitor hCG levels to identify any ectopic or continuing pregnancies, medical abortion can be safely performed without sonography.

Publication Types:

- Multicenter Study

PMID: 12169378 [PubMed - indexed for MEDLINE]

J Ky Med Assoc 2001 Nov;99(11):499-500

RU-486: is it hot, or is it not?

Garcia DP.

Publication Types:

- Editorial

PMID: 11816952 [PubMed - indexed for MEDLINE]

AWHONN Lifelines 2002 Feb-Mar;6(1):46-50

Pregnancy termination. Understanding and supporting women who undergo medical abortion.

Goss GL.

California State University-Dominguez Hills, Carson, CA, USA.

Publication Types:

- Review
- Review, Tutorial

PMID: 11913202 [PubMed - indexed for MEDLINE]

Contraception 2002 Feb;65(2):133-42

Could American women use mifepristone-misoprostol pills safely with less medical supervision?

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Medical methods of early abortion differ from surgical methods in that women themselves can potentially administer the regimens. As currently researched and offered, however, the main regimen used for medical abortion, mifepristone-misoprostol, is highly medicalized, involving several clinic visits and extensive physician involvement. We re-examined the role of clinical supervision in each step of the abortion process, using data collected during a large clinical trial of mifepristone-misoprostol abortions in the US, fielded during 1994-1995. The trial was carried out in 17 geographically diverse centers, including private, public, and nongovernmental organization clinics, and enrolled 2121 women, aged 18-45 years, seeking early abortion (< or =63 days since last menstrual period). Women received 600 mg oral mifepristone, followed 48 h later by 400 microg oral misoprostol. Evidence suggests that most women can handle most steps of the medical abortion process themselves, effectively and safely. The utility of clinic visits to ingest mifepristone and misoprostol is questionable. For many women, even the follow-up visit could perhaps be replaced by telephone follow-up, combined with home pregnancy tests. Alternatives to the present protocol might allow greater control, comfort, and convenience at lower cost. Where clinician involvement might be useful, mid-level health care providers typically possess the skills necessary to offer the method safely, implying that physicians might be necessary only as complications arise. Future research useful for determining the optimal amount of medical involvement to provide mifepristone-misoprostol safely and effectively should include self-screening tests, label comprehension tests, calendars to aid in calculating gestational age, and the development of special pregnancy tests with telephone follow-up.

Publication Types:

- Clinical Trial

PMID: 11927116 [PubMed - indexed for MEDLINE]

BJOG 2002 Apr;109(4):437-42

Use of mifepristone as an example of conflicting and misleading medical information on the internet.

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OBJECTIVE: To evaluate the accuracy and reliability of medical information available on the internet regarding medical abortion using mifepristone, with special emphasis on the possible bias of the internet websites providing the information. METHODS: A systematic search of the internet identified patient-oriented websites distributing medical information about mifepristone. The sites were divided into three groups according to their views of the drug (i.e. in favour, against or indifferent). RESULTS: Forty sites met the criteria for inclusion in our analysis: 15 sites (37.5%) were in favour of using mifepristone, 16 (40%) were against and nine (22.5%) were indifferent. Incorrect information, found in 12 sites (30%), was significantly more common ($P < 0.006$) in websites that opposed the use of mifepristone than in websites that favoured it, 56.3% and 6.7%, respectively. Websites against the use of mifepristone provided significantly more ($P < 0.05$) graphic descriptions (31.3% vs 0%) and significantly fewer ($P < 0.03$) links (18.8% vs 60%), than the sites in favour of the use of mifepristone. CONCLUSIONS: We found that information provided on the internet regarding the use of mifepristone was significantly less complete and accurate and included more graphic descriptions when the site opposed medical termination of pregnancy. These findings reinforce the concerns regarding the reliability and credibility of medical information on the internet and the need for quality control.

PMID: 12013165 [PubMed - indexed for MEDLINE]

Rev Med Brux 2002 Feb;23(1):A52-3

[Voluntary pharmacologic termination of pregnancy]

[Article in French]

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Centre d'Orthogenie, C.H. de Roubaix, France.

PMID: 11913092 [PubMed - indexed for MEDLINE]

Contraception 2001 Dec;64(6):339-43

Mifepristone abortion in minors.

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Approximately one-third of pregnant teenagers in the U.S. choose abortion. This prospective study evaluated whether medical abortion with mifepristone and misoprostol is physically and emotionally acceptable in adolescents. Adolescents 14- to 17-years-old, with pregnancies < or =56 days gestation, and seeking abortion services with parental consent from at least one parent were enrolled. Mifepristone (200 mg) was administered, followed 2 days later by 800 microg of misoprostol administered vaginally. Follow-up visit occurred on Day 4-8 to confirm abortion completion. Questionnaires regarding acceptability of the procedure as well as emotional coping were administered at the initial visit, at the follow-up visit, and by phone at 4 weeks postabortion. All 28 adolescents had complete medical abortions without complications or surgical intervention, and five minors did not require misoprostol. At the Day 4-8 follow-up visit, 75% of teens found the procedure acceptable, and that increased to 96% by the 4-week visit. Although 57% reported stress and 43% reported fear initially, by 4 weeks postabortion only 21% of the teens reported stress, and 8% were still experiencing fear. In addition, the minors' satisfaction with their abortion decision increased from 43% to 79% by 4 weeks postabortion. Medical abortion with mifepristone and misoprostol was highly effective and well tolerated, physically and emotionally, by adolescents in our sample. A larger clinical trial is needed to generalize these findings to other adolescent populations seeking medical abortion services.

Publication Types:

- Clinical Trial

PMID: 11834231 [PubMed - indexed for MEDLINE]

Eur J Obstet Gynecol Reprod Biol 2002 Mar 10;101(2):113-20

Mifepristone: bioavailability, pharmacokinetics and use-effectiveness.

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The potentiality of mifepristone as an abortifacient and contraceptive drug along with its pharmacokinetic parameters is reviewed. Mifepristone or RU486 acts as antagonist to progestational and glucocorticoid functions. It is an orally active compound with nearly 70% absorption rate but its bioavailability is reduced to around 40% because of the first-pass effect. Peak plasma concentrations of 1.9 +/- 0.8, 3.8 +/- 0.9 and 5.3 +/- 1.3 micromol/l are reached within 1-2 h after oral administration of 50, 200 and 600 mg mifepristone in women, respectively, and are maintained at relatively high level up to 48 or 72 h depending on the ingested dose. The plasma kinetics of mifepristone followed two-compartment open model with a mean alpha-half-life of 1.4h, volume of distribution 1.47 l/kg and beta-half-life of 20-30 h in most of the subjects studied. Clearance from the body was mainly through feces (83%). Biologically active mono-demethylated, di-demethylated and hydroxylated metabolites were found in plasma soon after oral administration of mifepristone. RU486 and its mono-demethylated metabolite bind to progesterone receptors with high affinity. Mifepristone-bound receptor dimers suppress transcription activation and thus, bring about anti-progestational activity that makes mifepristone a potential abortifacient and contraceptive agent. Clinical trials for termination of early pregnancy with 50-600 mg mifepristone plus a prostaglandin analogue achieved a success rate of 82-97%. However, abdominal pain, cramping, nausea, vomiting, bleeding and delay in onset of the next menstrual cycle were the side effects. Administration of 25 mg mifepristone twice 12h apart, as a post-coital contraceptive showed 100% contraceptive efficacy. A low dose of mifepristone which does not inhibit ovulation reduced fertility significantly by affecting endometrial milieu. These findings suggest that reduced dose(s) of mifepristone, 200 mg or less, may be used as a post-coital contraceptive and in combination with vaginal misoprostol for termination of early pregnancy with high efficacy and minimal or no side effects.

Publication Types:

- Review
- Review, Tutorial

PMID: 11858883 [PubMed - indexed for MEDLINE]

Best Pract Res Clin Obstet Gynaecol 2002 Apr;16(2):237-46

Medical abortion in the second trimester.

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The introduction of prostaglandin analogues and mifepristone has changed the management of second trimester abortion in the last 2 decades. Gemeprost and misoprostol are the two most extensively studied prostaglandin analogues that are used in this period. The combination of either gemeprost or misoprostol with mifepristone is most effective. With these regimens, over 90% of women abort within 24 hours and the mean induction to abortion interval is about 6 hours. Mifepristone is expensive and is not available in many countries. Therefore, prostaglandin analogue-only regimens might be the only option. These regimens are still effective with an abortion rate of >90% in 48 hours. However, the induction to abortion interval (15 hours) is much longer. Intra-cervical tents can be used to shorten the induction to abortion intervals. Copyright 2002 Elsevier Science Ltd.

Publication Types:

- Review
- Review, Tutorial

PMID: 12041965 [PubMed - indexed for MEDLINE]

Hum Reprod 2002 Jan;17(1):99-102

The effect of contraceptive pills on the measured blood loss in medical termination of pregnancy by mifepristone and misoprostol: a randomized placebo controlled trial.

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BACKGROUND: A prospective randomized placebo controlled trial was performed to assess the immediate use of oral contraceptive (OC) on the amount of blood loss in the post-abortion period in women undergoing medical abortion by mifepristone and misoprostol. METHODS: One hundred women were randomized by computer to receive either OC pills or placebo, immediately after medical abortion. RESULTS: There was no difference in the complete abortion rate between the two groups. The complete abortion rate was 98 and 92% in the OC and placebo groups respectively. The side-effects and duration of bleeding were also similar. The median days of vaginal bleeding were 17 (range: 3-41) and 15 (range: 5-48) in the OC and placebo groups respectively. There was a statistically significant decrease in the mean haemoglobin level on day 15 in the OC group (from 12.0 to 11.5 g/dl) whereas the mean haemoglobin level in the placebo group remained stable. The median measured blood loss was 69.9 ml in the OC group and 72.8 ml in the placebo group and there was no statistically significant difference between the two groups. CONCLUSION: We conclude that it is safe to offer women combined OC pills immediately after medical abortion as an option of contraception, as it does not affect the duration or amount of vaginal bleeding or the complete abortion rate.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 11756369 [PubMed - indexed for MEDLINE]

Medscape Womens Health 2001 Dec;6(6):4

Medical abortion: overview and management.

Trupin SR, Moreno C.

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Medical abortion regimens are safe, effective, and offer a new range of choices for patients and providers. In September 2000, the US Food and Drug Administration (FDA) approved a regimen of mifepristone and misoprostol, which effects abortion by luteolysis, uterine contractions, and expulsion of the products of conception without surgical instrumentation. The regimen requires that a provider be capable of diagnosing ectopic gestations and be able to make arrangements for a surgical abortion in the case of failure or medical emergencies. With a medical abortion, the pregnancy is passed spontaneously, and there may not be tissue obtained for confirmation. Physicians must be aware of their state requirements with regard to expulsed tissue examination. Completion of the procedure can be established by ultrasound or by measurement of serum levels of human chorionic gonadotropin (hCG). The FDA-approved protocol allows for use up to 49 days after the first day of the last menstrual period (LMP) and consists of mifepristone 600 mg orally on day 1, misoprostol 400 mcg orally on day 3, and a follow-up appointment on days 12-20. Half of all patients pass their pregnancy in the first few hours after the second visit. It is important to be able to determine the difference between expected bleeding, 14 days on average, and the complication of hemorrhage, as 2% to 10% of patients require a surgical abortion. Continuing viable pregnancies are rare. Several other regimens can safely expand options and reduce expense, including protocols using methotrexate. Medication indications and contraindications, management strategies for patients undergoing treatment with these regimens, and safety issues are reviewed.

PMID: 11965218 [PubMed - indexed for MEDLINE]

J Formos Med Assoc 2002 Apr;101(4):277-82

Medical abortion with mifepristone and misoprostol: a clinical trial in Taiwanese women.

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BACKGROUND AND PURPOSE: Medical abortion was not officially approved in Taiwan until the end of 2001. We investigated the efficacy of combination mifepristone and misoprostol therapy for medical abortion (which has now been approved) in early pregnant Taiwanese women and whether the attitudes of women who received this treatment affected the clinical outcome of medical abortion. METHODS: Eighty healthy women in early pregnancy (< 49 d of gestation) were enrolled into two studies of medical abortion using mifepristone and misoprostol regimens. The outcomes were evaluated based on complete expulsion of intrauterine contents, with or without surgical intervention. Study 1 used treatment with mifepristone (200 mg or 600 mg) and misoprostol (400 micrograms), and the decision to perform surgical intervention was made mainly on the basis of the patient's request. Study 2 used treatment with mifepristone (200 mg or 600 mg) and misoprostol (600 micrograms) where the decision to perform surgical intervention was made exclusively by the physician. Serum or urinary human chorionic gonadotropin (hCG) concentration was measured serially after abortion. RESULTS: In general, the success rate was 95% as judged by complete expulsion of intrauterine contents without surgical intervention. However, the success rate in Study 1 was only 62.5%. The mean duration of bleeding after abortion was 16.7 to 21.7 days. Serum or urinary hCG concentration remained positive in one woman (1.2%) studied during 43 to 60 days after abortion. CONCLUSION: A combination of mifepristone and misoprostol for medical abortion in Taiwanese women during early pregnancy can achieve a high success rate. Our study showed that a mifepristone dose of 200 mg and a misoprostol dose of 400 micrograms were most effective. Our results suggest that sufficient physician and patient communication regarding medical abortion affects the clinical outcome.

PMID: 12101864 [PubMed - indexed for MEDLINE]

Best Pract Res Clin Obstet Gynaecol 2002 Apr;16(2):205-20

Unsafe abortion: an avoidable tragedy.

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An estimated 60 000-70 000 women die annually from complications of unsafe abortion and hundreds of thousands more suffer long-term consequences which include chronic pelvic pain and infertility. The reasons for the continuing high incidence of unwanted pregnancy leading to unsafe abortion include lack of access to, or misuse of and misinformation about, effective contraceptive methods, coerced sex which prohibits women from protecting themselves, and contraceptive failure. Unsafe abortion is closely associated with restrictive legal environments and administrative and policy barriers hampering access to existing services. Vacuum aspiration and medical methods combining mifepristone and a prostaglandin for early abortion are simple and safe. For second trimester abortion, the main choices are repeat doses of prostaglandin with or without prior mifepristone, and dilatation and evacuation by experienced providers. Strategies for preventing unsafe abortion include: upgrading providers' skills; further development of medical methods for pregnancy termination and their introduction into national programmes; improving the quality of contraceptive and abortion services; and improving partner communication.

Publication Types:

- Review
- Review, Tutorial

PMID: 12041963 [PubMed - indexed for MEDLINE]

ELSEVIER

Contraception

Contraception 64 (2001) 271–273
Commentary

Monitoring serum chorionic gonadotropin levels after mifepristone abortion

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1. Introduction

Mifepristone was approved in September 2000 as the first medical abortifacient in the US for up to 7 weeks of pregnancy. Approximately 1.4 million abortions occur each year [1], and almost half are eligible (less than 8 weeks gestation) for a medical abortion [2]. Medical abortion has the potential to offer many US women an earlier abortion option than surgical abortion.

Medical abortion requires careful monitoring by the clinician to ensure that the abortion is complete. There are several options for monitoring the process: (a) clinical parameters at 2 weeks with a history of vaginal bleeding and expulsion of the pregnancy and physical examination demonstrating the involution of the uterus; (b) measurement of the decline in human chorionic gonadotropin (hCG); and (c) sonogram examination to document the absence of the gestational sac. Clinical examination may not be sufficiently reliable to detect an incomplete abortion or ectopic pregnancy. Routine sonography, whereas accurate, can be expensive and may not be readily available.

Knowing the rate of decline in serum hCG levels would help clinicians determine the best time to have women return for follow-up care. In a retrospective analysis, Thonneau reported a significant decrease in the serum hCG levels at 2 weeks after mifepristone and misoprostol for abortion [3]. Among the 25 women with a failed medical abortion (retained tissue or continuing pregnancy), 23 had a persistent hCG level of greater than 500 IU/L, demonstrating the correlation between unsuccessful abortion and the continued elevation of hCG.

A study using hCG to monitor methotrexate abortions found that hCG dropped only 10% on average on Day 7 if bleeding had not occurred versus >90% with a history of significant vaginal bleeding [4]. Creinin et al. concluded that a successful abortion is accompanied by at least a 48% decrease in hCG levels within 24 h following a methotrexate medical abortion [5]. In studies following hCG values after confirmed medical abortions by using methotrexate and misoprostol, the hCG decreased to <26 IU/L by a mean of 32 days [6] and <10 IU/L by a mean of 39 days [7] after misoprostol was administered.

Following induced abortions by surgical aspiration, Van der Lugt and Drogendijk [8] demonstrated two different rates of decrease of serum hCG. Within the first 2 days, the serum hCG decreased with a half-life of 0.63 days, and in the next 2 weeks, the serum hCG decreased with a half-life of 3.85 days. This study demonstrated an exponential drop in serum hCG levels, with the fastest rate of decline in the first 2 days. This same study also followed the decline in urine hCG levels after a surgical aspiration. The rate of decrease of urine hCG was less than that of the initial decrease in serum hCG. They found that an urine pregnancy test with a sensitivity of 1000 IU/L will nearly always be negative 2 weeks after abortion.

To help clinicians monitor a medical abortion without the use of ultrasound, we performed a small study, approved by the University of Rochester Institutional Review Board, to determine the rate of decline in serum hCG and the absolute hCG values in women using mifepristone for an induced abortion.

2. Materials and methods

Women were recruited from mifepristone abortion trials in Rochester. There were 29 women in the study, the mean gestational age was 45 days (95% CI 43–48), and 53% of the women had one or more prior pregnancies. The medical abortion protocol included sonogram confirmation of dating, 200 mg of mifepristone administered orally on Day 1, misoprostol self-administered at home on Day 3 (orally or vaginally depending on the study), and return visit within the first week after misoprostol administration for sonogram evaluation. The inclusion and exclusion criteria, methods, and results of these studies have been reported elsewhere

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PII: S0010-7824(01)00266-9

Obstet Gynecol 2002 May;99(5 Pt 1):813-9

Comparison of abortions induced by methotrexate or mifepristone followed by misoprostol.

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OBJECTIVE: To compare the effectiveness, side effects, and acceptability of medical abortions induced by methotrexate and misoprostol with abortions induced by mifepristone and misoprostol. METHODS:This was a multicenter, randomized, nonblinded, controlled trial comparing 50 mg/m(2) of methotrexate followed 4-6 days later by 800 microgram of vaginal misoprostol with 600 mg of oral mifepristone followed 36-48 hours by 400 microgram of oral misoprostol. RESULTS: There were 518 women in the methotrexate group and 524 women in the mifepristone group. In the methotrexate group, 21 women required suction curretage, two for continuing pregnancy, eight because of physician request (usually for excessive bleeding), and 11 because of patient request. In the mifepristone group, 22 women needed surgical termination, 17 because of physician request, and five because of patient request. By day 8, only 386 (74.5%) in the methotrexate group had completed the abortion compared with 474 (90.5%) in the mifepristone group, and the mean number of days from beginning to completion was 7.1 for methotrexate and 3.3 for mifepristone (P </=.001). There were no differences in complications, and side effects were similar. Acceptance was slightly higher with mifepristone (88.0%) than with methotrexate (83.2%). CONCLUSION: Abortions induced with mifepristone completed faster than those induced with methotrexate, but the overall success rates, side effects, and complications were similar. Acceptance rates were slightly higher with mifepristone than methotrexate (P =.03).

Publication Types:

- Clinical Trial
- Multicenter Study
- Randomized Controlled Trial

PMID: 11978292 [PubMed - indexed for MEDLINE]

2. Cervical Softening, Surgical Abortion, Management of Late Intrauterine Death and Cesarean Section

Prescrire Int 2001 Oct;10(55):135-40

Mifepristone: new preparation. Avoids or facilitates cervical dilatation before vacuum aspiration of pregnancy.

(1) Cervical softening with prostaglandins or laminaria before vacuum aspiration of pregnancy can avoid or facilitate mechanical dilatation. (2) Mifepristone is now licensed in France for cervical softening before vacuum aspiration of pregnancy. (3) The clinical file on mifepristone in this indication contains data from about 20 comparative clinical trials using surrogate end points, namely the need for and/or ease of cervical dilatation. (4) In these trials the cervix was easier to dilate in women who received mifepristone than in women who received a placebo. (5) A few comparative trials showed comparable efficacy of prostaglandins, laminaria (small hydrophilic stents inserted into the cervix that gradually swell, leading to cervical dilatation) and mifepristone in this indication. (6) Before vacuum aspiration, metrorrhagia occurred more frequently in women on mifepristone than in those on a placebo. Blood losses during vacuum aspiration were comparable in women who had received prostaglandins and those who had received mifepristone. (7) The incidence of abdominal pain may be lower on mifepristone than with laminaria or prostaglandins.

PMID: 11824427 [PubMed - indexed for MEDLINE]

BJOG 2002 Sep;109(9):1069-71

Not assuming the obvious: failed surgical termination of pregnancy and multiple fetal abnormalities.

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PMID: 12269685 [PubMed - indexed for MEDLINE]

Am J Obstet Gynecol 2002 Aug;187(2):407-11

Early surgical abortion: efficacy and safety.

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Department of Obstetrics and Gynecology, University of Massachusetts Medical School, Boston, MA, USA.

OBJECTIVE: Because of concern over the higher rates of failed abortion, many clinicians defer surgical abortion until 7 menstrual weeks or later. We conducted this study to evaluate the efficacy and safety of early surgical abortions that are performed by numerous physicians in a community-based setting. STUDY DESIGN: We prospectively gathered data on all eligible patients who had surgical abortions at <6 weeks of gestation at 3 Planned Parenthood clinics from January 1, 1998, to August 31, 2000. Outcomes were evaluated with the use of proportions with 95% CI and chi(2) analysis. RESULTS: A total of 1132 women had early surgical abortions during the study interval, and follow-up was available for 750 of those women (66%). Seventeen women (2.3%; 95% CI, 1.4%, 3.7%) had failed attempted abortions. Other complications occurred in 13 women. CONCLUSION: Early surgical abortion is safe and effective. In this series, the frequency of complications that required curettage was similar to that reported with mifepristone and vaginal misoprostol.

Publication Types:

- Clinical Trial

PMID: 12193934 [PubMed - indexed for MEDLINE]

BJOG 2002 Apr;109(4):443-7

Medical management of late intrauterine death using a combination of mifepristone and misoprostol.

Wagaarachchi PT, Ashok PW, Narvekar NN, Smith NC, Templeton A.

Department of Obstetrics and Gynaecology, Aberdeen Maternity Hospital, UK.

OBJECTIVE: To assess the efficacy and safety of mifepristone in combination with misoprostol in the management of late fetal death. DESIGN: Observational study. SETTING: Aberdeen Maternity Hospital, Aberdeen. METHODS: A consecutive series of 96 women with intrauterine death after 24 weeks of gestation were studied. Each woman received a single dose of 200 mg mifepristone orally, following which a 24-48 hour interval was recommended before administration of misoprostol. For gestations of 24-34 weeks, 200 microg of intravaginal misoprostol was administered, followed by four oral doses of 200 microg at three hourly intervals. Gestations over 34 weeks were given a similar regimen but a reduced dose of 100 microg misoprostol. RESULTS: The average induction to delivery interval was 8.5 hours. Ninety-five women (98.9%) were delivered within 72 hours of administration of first dose of misoprostol, with 66.7%, 87.5%, 92.7% and 95.8% women delivering within 12, 24, 36 and 48 hours, respectively. No significant correlation was found between mean induction to delivery interval and maternal age, parity, Bishop's score, birthweight and mifepristone/ misoprostol interval. The induction to delivery interval was shorter with increasing gestation (P = 0.04). Mild side effects were noted in eight (8.3%) women. Three (3.1%) women had treatment for presumed or proven pelvic sepsis. No cases of uterine tachysystole, haemorrhage or coagulopathy were recorded. CONCLUSION: The combination of mifepristone and misoprostol for induction of labour following late fetal death is an effective and safe regimen. The induction to delivery interval with this regimen appears shorter than studies using mifepristone or misoprostol.

PMID: 12013166 [PubMed - indexed for MEDLINE]

BJOG 2002 Apr;109(4):462-5

Medical management of early fetal demise using sublingual misoprostol.

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The aim of this study was to determine the efficacy of mifepristone in combination with sublingual misoprostol for the medical management of early fetal demise. Fifty-six consecutive women were studied prospectively. The mean (SD) gestation at diagnosis was 9.6 weeks (1.84). Four women had complete miscarriage with mifepristone alone. The overall success rate was 83.9% and the median induction-miscarriage interval was 8.19 hours (range 0.83 to 37.50 hours). Of those women who had a successful outcome, 91.5% were satisfied with the regimen. Sublingual misoprostol in combination with mifepristone is an effective and safe alternative to vaginal or oral misoprostol in the management of early fetal demise.

PMID: 12013170 [PubMed - indexed for MEDLINE]

Chin Med J (Engl) 2002 Feb;115(2):242-6

Complication of cesarean section: pregnancy on the cicatrix of a previous cesarean section.

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OBJECTIVE: To probe into the clinical manifestation, diagnosis, as well as treatment of pregnancy on the cicatrix of a previous cesarean section at the uterine isthmus in the first trimester. METHODS: Analysis of 14 patients with pregnancy on the cicatrix of a previous cesarean section at the uterine isthmus in the first trimester was made after conservative treatment by drugs from January 1996 to December 1999. RESULTS: The 14 patients with a pregnancy on the cicatrix of a previous cesarean section at the uterine isthmus in the first trimester were painless, had slight vaginal bleeding, and concurrently had increased serum beta-subunit human chorionic gonadotropin (beta-HCG). Doppler ultrasonic examination revealed an obvious enlargement of the previous cesarean section cicatrix in the uterine isthmus, and found a gestational sac or mixed mass attached to the cicatrice, with a very thin myometrium between the gestational sac and bladder walls. Among the 14 patients, 12 patients had crystalline trichosanthes injected into the cervix, mifepristone taken orally, or methotrexate in the form of intramuscular injection. Following this procedure, their serum beta-HCG dropped to normal. The other 2 patients had a total hysterectomy. CONCLUSIONS: Pregnancy on the cicatrix of a previous cesarean section at the uterine isthmus in the first trimester is a complication of cesarean section. Early diagnosis and effective conservative treatment by drugs are instrumental in decreasing the potential occurrence of uterine rupture, which is also conducive to preserving the patient's future fertility.

PMID: 11940341 [PubMed - indexed for MEDLINE]

Int J Gynaecol Obstet 2002 Jun;77(3):201-7

Effect of early pregnancy on a previous lower segment cesarean section scar.

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OBJECTIVE: To summarize the manifestation, diagnosis, and early management of early pregnancy on a previous cesarean section scar. METHOD: Fifteen cases of early pregnancies implanted on previous cesarean section scars were diagnosed and treated in two obstetrical centers. RESULTS: The 15 patients had light, painless vaginal bleeding and their serum beta-subunit human chorionic gonadotropin (beta-HCG) was elevated. The interval between cesarean section and admission ranged from 6 months to 12 years (7.1+/-3.6 years). Doppler and real-time ultrasonic examinations demonstrated an enlargement of the previous cesarean section scar in the lower segment, a gestational sac or a mixed mass attached to the cicatrix, and a very thin myometrium between the gestational sac and the bladder wall. Serum beta-HCG dropped to normal in 12 of the 15 patients following treatment with crystalline trichosanthin injected into the cervix followed by oral mifepristone, intramuscular injections of methotrexate, or other appropriate treatment. Two patients underwent total hysterectomy due to massive vaginal bleeding. The remaining patient was misdiagnosed with choriocarcinoma and also had total hysterectomy. CONCLUSION: Pregnancy on a previous lower segment cesarean section scar is rare but very dangerous. Early diagnosis and effective conservative drug treatment may be instrumental in decreasing the occurrence of uterine rupture.

Publication Types:

- Review
- Review, Tutorial

PMID: 12065130 [PubMed - indexed for MEDLINE]

3. Other
(Alzheimer's Disease, Contraception, Depression, Emergency Contraception and Biochemical Effects, etc.)

Cancer Res 2002 Jan 1;62(1):79-88

Effect of normal endometrial stroma on growth and differentiation in Ishikawa endometrial adenocarcinoma cells.

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Endometrial cancer is characterized by alterations in the stromal cells and the supporting extracellular matrix in addition to the intrinsic alterations of the malignant epithelial cells. We have developed a cell culture model that demonstrates the role of stromal cells in the regulation of proliferation, hormone responsiveness, and differentiation of an endometrial adenocarcinoma cell line (Ishikawa). Conditioned medium (CM) was collected from normal primary human endometrial stromal cells grown on plastic or within the basement membrane extract, Matrigel. The CM produced by stromal cells cultured in contact with Matrigel markedly inhibited Ishikawa cell proliferation compared with CM from stromal cells cultured on plastic. Ishikawa cell proliferation varied with steroid hormone treatment in the presence of CM from stromal cells embedded in Matrigel. When the Ishikawa cells were placed in coculture in contact with stromal cells in Matrigel, production of a differentiated epithelial secretory product, glycodelin, was induced. Gene expression of stromal cell hormone receptors, growth factors, and integrins was analyzed by reverse transcription-PCR in the presence of Matrigel to determine the potential factors involved in stromal regulatory function. These combined studies imply that the phenotype of the Ishikawa cells can be induced to differentiate to more closely resemble normal endometrial epithelium by reintroduction of stromal factors and appropriate extracellular matrix. Additionally, the study shows that basement membrane proteins influence the regulatory function of stromal cells as they mediate epithelial cell growth.

PMID: 11782363 [PubMed - indexed for MEDLINE]

BJOG 2002 May;109(5):553-60

A randomised study comparing a low dose of mifepristone and the Yuzpe regimen for emergency contraception.

Ashok PW, Stalder C, Wagaarachchi PT, Flett GM, Melvin L, Templeton A.

Department of Obstetrics and Gynaecology, University of Aberdeen, Aberdeen Maternity Hospital, UK.

OBJECTIVE: To compare 100 mg mifepristone with the standard Yuzpe regimen for emergency contraception. DESIGN: Randomised controlled trial. SETTING: Family Planning Clinic, Aberdeen. SAMPLE: One thousand women seeking emergency contraception within 72 hours after an episode of unprotected sexual intercourse. METHODS: Women were randomised to receive either 100 mg (half tablet) of mifepristone as a single dose or the Yuzpe regimen (two tablets each with 50 microg ethinyloestradiol and 0.25 mg levonorgestrel, to be repeated 12 hours later). OUTCOME MEASURES: Crude pregnancy rates, proportion of pregnancies prevented, side effects and patient acceptability. RESULTS: The crude pregnancy rates (95% CI) for the Yuzpe regimen and mifepristone were 3.6% (2.3-5.7) and 0.6% (0.2-1.8), respectively, with a significant difference between the two groups (RR 6.04; 95% CI 1.75-20.75). Mifepristone prevented 92% of pregnancies and the Yuzpe regimen preventing 56%. An increasing coitus to treatment interval was associated with contraceptive failure in the Yuzpe group ($P = 0.03$) with no association seen with mifepristone. Following administration of mifepristone 24.5% and 13.1% given the Yuzpe regimen had a delayed period (RR 2.14; 95% CI 1.46-3.15). Overall, mifepristone was better tolerated than the Yuzpe regimen with significantly fewer side effects. More women were satisfied ($P < 0.0001$) with mifepristone as an emergency contraceptive and would recommend it to a friend ($P = 0.02$). CONCLUSION: Mifepristone administered in a 100 mg dose is a highly effective post-coital contraceptive with high patient acceptability and fewer side effects compared with the standard Yuzpe regimen. Delay in the onset of menstruation did not decrease patient acceptability.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 12066946 [PubMed - indexed for MEDLINE]

J Clin Psychopharmacol 2001 Oct;21(5):516-21

Rapid reversal of psychotic depression using mifepristone.

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The rationale for treating psychotic major depression with glucocorticoid receptor (GR) antagonists is reviewed. Five patients with psychotic major depression were given 600 mg of mifepristone in a 4-day, double-blind, placebo-controlled crossover study. All the patients completed the protocol and adverse effects were not observed or reported. All of the five patients showed substantial improvements in their Hamilton Rating Scale for Depression scores while they were receiving mifepristone, and four of the five patients showed substantial improvement in their Brief Psychiatric Rating Scale scores. Little, if any, improvement was seen with placebo. These preliminary results suggest that short-term use of GR antagonists may be effective in the treatment of psychotic major depression and that additional study, perhaps using higher doses or more treatment days, seems warranted.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 11593077 [PubMed - indexed for MEDLINE]

J Clin Endocrinol Metab 2002 Jan;87(1):63-70

Daily low-dose mifepristone has contraceptive potential by suppressing ovulation and menstruation: a double-blind randomized control trial of 2 and 5 mg per day for 120 days.

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Daily administration of progesterone (P) antagonists to women inhibits ovulation and disrupts endometrial function. In this double-blind randomized trial, we have explored the contraceptive potential of two doses of the P antagonist mifepristone in healthy volunteers in Edinburgh and Shanghai. Ninety-eight women (58 in Edinburgh and 40 in Shanghai) were randomized to receive either 2 or 5 mg mifepristone daily for 120 d. Ovarian activity was monitored by the weekly measurement of steroid metabolites in urine and of E2 and P in plasma every month. Endometrial function was assessed by menstrual records, and ultrasound measurement of endometrial thickness was assessed every month. Endometrial biopsy was collected on d 12 of the control cycle and after 60 and 120 d of treatment. Ninety women (50 in Edinburgh and 40 in Shanghai) completed the study. Follicular activity continued during treatment with both doses in Edinburgh women, although ovulation was suppressed in the majority of cycles (90 and 95% of cycles in 2- and 5-mg groups, respectively). The women in Shanghai showed evidence of ovulation in only 3 of 160 months of treatment (2 in 2-mg group and 1 in 5-mg group). The majority of women in both centers were amenorrheic (65% in 2-mg group and 88% in 5-mg group in Edinburgh, and 90% in both dose groups in Shanghai). The endometrial thickness increased significantly in women in Edinburgh and decreased in Shanghai; histology showed either atrophic or cystic changes without evidence of hyperplasia. There was no pregnancy reported in the 200 months of exposure in 50 sexually active women who had used no other method of contraception during the study. We conclude that mifepristone in low daily doses inhibits ovulation and induces amenorrhea in the majority of women and has the potential to be developed as a novel estrogen- free oral contraceptive pill.

Publication Types:

- Clinical Trial
- Multicenter Study
- Randomized Controlled Trial

PMID: 11788624 [PubMed - indexed for MEDLINE]

Hum Gene Ther 2002 Jun 10;13(9):1075-80

The epidermis as a bioreactor: topically regulated cutaneous delivery into the circulation.

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Previous studies have documented that the skin can be used as a bioreactor to produce proteins for systemic release to treat diseases. A gene-switch system has been developed that allows regulated expression of therapeutic genes. To determine whether this system could be used in the skin, we developed a transgenic mouse model in which expression of a therapeutic gene could be topically induced in epidermal keratinocytes. After a single induction, high levels of the therapeutic protein, human growth hormone (hGH), were released from keratinocytes into the circulation. The serum levels of hGH were dependent on the amount of inducer applied, and repeated induction resulted in increased weight gain by transgenic versus control mice. Furthermore, physiological levels of hGH were detected in the serum of nude mice after topical induction of small transgenic skin grafts. These results clearly demonstrate the feasibility of using the gene-switch system to regulate the delivery of therapeutic proteins into the circulation via genetically modified keratinocytes.

PMID: 12067440 [PubMed - indexed for MEDLINE]

Mol Endocrinol 2001 Dec;15(12):2078-92

Differential role of PR-A and -B isoforms in transcription regulation of human GnRH receptor gene.

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The presence of progesterone response element (PRE) in the 5'-flanking region of the human GnRH receptor (GnRHR) suggests the possible regulation of this gene by progesterone (P). In the present study, we examined the effects of P in transcriptional regulation of human GnRHR gene expression at the pituitary and placenta levels since the GnRHR has been detected in both tissues. By the use of transient transfection assays, a differential regulation of human GnRHR promoter activity by P was observed. P treatment resulted in a decrease in promoter activity in the pituitary alphaT3-1 cells, suggesting a P-mediated inhibitory action. Interestingly, P is found to have a stimulatory role at the placental expression of this gene. Addition of RU486 to, or inhibition of endogenous P production by, the placental JEG-3 cells leads to a decrease in promoter activity, which is reversed by the replacement of P. Further studies have identified a putative PRE, namely human GR-PRE (located between -535 and -521, related to translation start site), that may be responsible for the P action since the mutation of these motifs reversed the P-mediated effects. The binding of PR to this element is confirmed by antibody supershift assays. The physiological effects of P are mediated through two PR isoforms, namely PR-A and PR-B. In the present study, overexpression of human PR-A resulted in a decrease in human promoter activity in both pituitary and placental cells. Interestingly, overexpression of PR-B exhibits a cell-dependent transcriptional activity, whereby it functions as a transcription activator in the placenta but as a transcription repressor in the pituitary. In summary, our results demonstrated a differential usage of PR-A and PR-B in transcriptional regulation of human GnRHR gene expression by P at the pituitary and placenta levels.

PMID: 11731610 [PubMed - indexed for MEDLINE]

Mol Hum Reprod 2002 Apr;8(4):333-40

Effect of mifepristone and levonorgestrel on expression of steroid receptors in the human Fallopian tube.

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It is likely that mifepristone or levonorgestrel in the future will find extended use for contraceptive purposes. It is therefore essential to characterize the modes of action of these compounds. To assess the effect on the human Fallopian tube, 24 women with regular menstrual cycles and proven fertility, admitted to the hospital for voluntary sterilization by laparoscopic technique, were randomly allocated to a control or one of two treatment groups. Treatments were given with either a single dose of 200 mg mifepristone or 0.75 mg levonorgestrel in two doses 12 h apart, on day LH+2. Surgery was performed on day LH+4 to LH+6. Steroid receptor expression was analysed by immunohistochemistry, Western blot and RT-PCR. In the controls, there was a higher concentration of progesterone receptors in the stromal cells in the isthmic region than in those in the ampullar region. Treatment with mifepristone increased the progesterone receptor concentration in epithelial and stromal cells and increased the estrogen receptor concentration in epithelial cells. No effect on steroid receptor concentration was found following levonorgestrel. The contraceptive effect of post-ovulatory mifepristone has previously been considered to be dependent on an effect on the endometrium. However an effect on the Fallopian tube could contribute to alter the peri-implantation milieu influencing fertilization and embryo development.

PMID: 11912281 [PubMed - indexed for MEDLINE]

FASEB J 2002 Jun;16(8):761-70

Enhancement of p53 activity and inhibition of neural cell proliferation by glucocorticoid receptor activation.

Crochemore C, Michaelidis TM, Fischer D, Loeffler JP, Almeida OF.

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In analyzing the molecular mechanisms underlying glucocorticoid-induced apoptosis in neural cells, we observed that dexamethasone, by activating glucocorticoid receptors, causes arrest of HT-22 cells in the G1 phase of the cell cycle; upon withdrawal of the agonist, cells resume proliferation. Our investigations revealed that glucocorticoid treatment, although having no effects on endogenous p53 protein stability, induces rapid translocation of p53 to the nucleus and enhances its transcriptional activity. Consistently, transfection studies with p53-responsive promoters revealed a substantial stimulation of the trans-activation potential of exogenous p53 by dexamethasone. Cells arrested in G1 failed to show signs of apoptosis even after overexpression of p53. Although dexamethasone induced transcription of the proapoptotic gene bax, there was no increase of Bax protein levels. We conclude that glucocorticoid receptor-induced neural cell cycle arrest is associated with an increase in nuclear translocation and transcriptional activity of p53, and suggest that potentiation of p53 may serve as a brake on cell proliferation and may prime cells for differentiation or death induced by other signals.

PMID: 12039857 [PubMed - indexed for MEDLINE]

Br J Pharmacol 2002 Apr;135(7):1634-40

Inhibition by glucocorticoids of the interleukin-1beta-enhanced expression of the mast cell growth factor SCF.

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1. Stem cell factor (SCF) is a major mast cell growth factor that promotes differentiation and chemotaxis of mast cells and inhibits their apoptosis. 2. We evaluated the effect of interleukin (IL)-1beta, a major pro-inflammatory cytokine, on the constitutive expression of SCF and studied the effects of two glucocorticoids, budesonide and dexamethasone, on the IL-1beta-enhanced SCF expression. 3. Human lung fibroblasts in culture were serum-starved for 48 h and treated with IL-1beta, budesonide and/or RU486. SCF cDNA was quantified after total RNA reverse transcription by on-line fluorescent polymerase chain reaction. SCF protein was quantified by ELISA. 4. IL-1beta induced an increase in SCF mRNA (+91% at 2.5 h) and protein production (+32%) by human lung fibroblasts in culture ($P<0.001$). 5. Budesonide inhibited IL-1beta-induced SCF mRNA expression (-68%) at 2.5 h and even more so at 10 h (-192%) ($P<0.001$). The expression of SCF protein also decreased by 3.5-fold at 10 h. Results were similar with dexamethasone. The glucocorticoid antagonist RU486 cancelled the effects induced by the glucocorticoids. 6. Increased SCF mRNA levels were associated with increased stability of this mRNA as measured after treatment with actinomycin D (1.9-fold at 2.5 h). Budesonide decreased this IL-1beta-enhanced stability by about 1.5-fold ($P<0.001$). 7. We conclude that in 'inflammatory' conditions, mimicked in vitro by IL-1beta, glucocorticoid treatment inhibits expression of the mast cell growth factor SCF. The reduced number and activation of mast cells observed in the bronchi of asthmatic patients treated by glucocorticoids may be due in part to this effect.

PMID: 11934803 [PubMed - indexed for MEDLINE]

Best Pract Res Clin Obstet Gynaecol 2002 Apr;16(2):181-91

Emergency contraception.

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The last decade has seen a huge interest in emergency contraception (EC) because of the potential it has to reduce abortion rates. A variety of hormonal methods is available although mifepristone-arguably the best method-is only licensed in China. The intrauterine device is highly effective but its use is limited because of the technical skill required for successful insertion. The mechanism of action of both the Yuzpe regimen of EC and of levonorgestrel is poorly understood and for all methods there are serious methodological difficulties involved with calculating efficacy. Nevertheless the risks and side-effects of EC are negligible and the practicalities of prescribing it are extremely simple. Research and programmatic efforts should concentrate on improving availability if EC is to fulfil its promise as a public health intervention to reduce unwanted pregnancy.

Publication Types:

- Review
- Review, Tutorial

PMID: 12041961 [PubMed - indexed for MEDLINE]

Fertil Steril 2002 Feb;77(2):366-72

Administration of an antiprogesterone up-regulates estrogen receptors in the endometrium of women using Norplant: a pilot study.

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OBJECTIVE: To determine the effect of a single dose of mifepristone (200 mg) on endometrial estrogen and progesterone receptors in Norplant users. DESIGN: A prospective single-blind placebo-controlled pilot study. SETTING; Women were recruited from a large family planning clinic and were studied either at the clinic or in a clinical research unit attached to a teaching hospital gynecology department. PATIENT(S): Eight women using Norplant and experiencing vaginal bleeding more often than once every 24 days. All completed the study. INTERVENTION(S): Endometrial biopsies were taken after treatment with both placebo and 200 mg of mifepristone, both given at the start of a bleeding episode. MAIN OUTCOME MEASURE(S): Expression of endometrial progesterone (PR) and estrogen (ER) receptors, ovulation, and vaginal bleeding. RESULT(S): Mifepristone administration was associated with down-regulation of PR receptor subtype B and up-regulation of ER. Women treated with mifepristone showed a tendency to increased ovulation rates and reduced vaginal bleeding. CONCLUSION(S): The effect of mifepristone on endometrial steroid receptors was consistent with functional inhibition of progesterone. The findings warrant further investigation of this regimen as a strategy to reduce frequent bleeding.

Publication Types:

- Clinical Trial

PMID: 11821099 [PubMed - indexed for MEDLINE]

Ann Intern Med 2002 Aug 6;137(3):180-9

Emergency contraception.

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Emergency contraception is used to prevent pregnancy after a coital act not adequately protected by a regular method of contraception. In contrast to early medical abortion, emergency contraception prevents a pregnancy from starting and does not disrupt an established pregnancy. The most commonly used approaches consist of two oral doses of contraceptive steroids. The levonorgestrel-only regimen (levonorgestrel, 0.75 mg, repeated in 12 hours) appears to be more effective and better tolerated than the Yuzpe regimen (ethinyl estradiol, 100 microg, and levonorgestrel, 0.5 mg, repeated in 12 hours). In the largest randomized, controlled trial to date, levonorgestrel prevented about 85% of pregnancies that would have occurred without its use. Hormonal emergency contraception has no known medical contraindications, although it is not indicated for suspected or confirmed pregnancy. However, if hormonal emergency contraception is inadvertently taken in early pregnancy, neither the woman nor the fetus will be harmed. Nausea and vomiting associated with the Yuzpe regimen can be reduced by prophylactic use of meclizine. A strong medical and legal case exists for making hormonal emergency contraception available over the counter, as has happened in countries other than the United States. Easier access to and wider use of emergency contraception could dramatically lower the high rates of unintended pregnancy and induced abortion in the United States.

Publication Types:

- Review
- Review, Tutorial

PMID: 12160366 [PubMed - indexed for MEDLINE]

Fertil Steril 2001 Dec;76(6):1196-201

Noncompliance among a group of women using a novel method of contraception.

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OBJECTIVE: To compare the incidence of noncompliance measured objectively by a home use fertility monitor with the traditional self-reported incidence of compliance in a study of a new method of contraception. DESIGN: Prospective cohort study. SETTING: A large family planning clinic in Edinburgh. PATIENT(S): Thirty-two healthy women who took part in a trial assessing the efficacy of a novel method of contraception involving accurately timed administration of a single dose of mifepristone. INTERVENTION(S): Mifepristone was administered orally and a blood sample was collected on the same day. MAIN OUTCOME MEASURE(S): Percentage of missed tests detected by the monitor against the self-reported percentage during the critical period. RESULT(S): Women failed to perform 24.2% (95% confidence interval, 16.5-31.5) of the tests in the 162 cycles analyzed. They missed tests at an absolutely vital time for contraceptive efficacy in 42% of cycles according to the monitor while admitting to missing tests in 14.8%. Poor compliance was associated with younger women, those who discontinued the study before completion, and cycles in which women were not relying on the contraceptive method. CONCLUSION(S): The use of microelectronic monitoring systems may improve our understanding of the extent of patient noncompliance, providing objective information that no other monitoring technique can produce. This understanding provides the opportunity to make the optimum use of potentially effective treatments while validating research evidence.

PMID: 11730750 [PubMed - indexed for MEDLINE]

Circulation 2001 Dec 4;104(23):2826-31

Sex steroids used in hormonal treatment increase vascular procoagulant activity by inducing thrombin receptor (PAR-1) expression: role of the glucocorticoid receptor.

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BACKGROUND: The use of sex steroids in oral contraception or hormonal replacement therapy is associated with an increased risk of cardiovascular thromboembolic complications. Although both the estrogen and the progestin components have been involved, the underlying mechanisms responsible are unclear. METHODS AND RESULTS: This study examined whether sex steroids promote hemostasis indirectly by increasing the procoagulant activity of blood vessels. Treatment of vascular smooth muscle cells with several progestins (progesterone, 3-keto-desogestrel, gestodene, and medroxyprogesterone acetate) upregulated proteolytically activatable thrombin receptor (PAR-1) expression, resulting in a potentiated thrombin-induced tissue factor expression and surface procoagulant activity. In contrast, neither the progestins levonorgestrel, norethisterone, and norgestimate nor the synthetic estrogen 17alpha-ethinylestradiol had such effects. The effect of the stimulatory progestins, which induce glucocorticoid-like effects in several cell systems, was mimicked by dexamethasone and inhibited by the progesterone and glucocorticoid receptor antagonist RU-38486. In addition, long-term administration of progesterone, 3-keto-desogestrel, or medroxyprogesterone acetate to ovariectomized rats increased PAR-1 protein level in the arterial wall, resulting in an increased responsiveness of isolated aortic rings to thrombin. CONCLUSIONS: These data demonstrate that several progestins markedly potentiate the vascular procoagulant effects of thrombin by increasing the availability of membrane thrombin receptors in the smooth muscle, an effect that is most likely due to their glucocorticoid-like activity.

PMID: 11733402 [PubMed - indexed for MEDLINE]

Curr Opin Obstet Gynecol 2002 Jun;14(3):325-30

Mifepristone: contraceptive and non-contraceptive uses.

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Mifepristone is an orally active progesterone antagonist. It can be used for both contraceptive and non-contraceptive clinical indications. It is a very effective drug for emergency contraception with a low incidence of side effects. There is a potential for mifepristone to be used as a once-a-month pill. There is a need, however, for a simple, inexpensive and accurate method to identify the luteinizing hormone surge before this method can be used in clinical practice. The daily administration of mifepristone offers promise as an effective method of contraception but more studies need to be done. The combination of mifepristone with a prostaglandin analogue is a well-established method for termination of pregnancy of up to 9 weeks. Recent data suggest that this combination may also be used up to 9-13 weeks of pregnancy. Although mifepristone is effective in dilating the cervix before vacuum aspiration, misoprostol is probably the drug of choice in most situations. In the second trimester, mifepristone is effective in shortening the abortion process induced by prostaglandin analogues. The combination of mifepristone and prostaglandin also offers a medical method for management of miscarriages. Mifepristone has been used for a number of other indications, but further studies are needed before such treatment can be recommended.

Publication Types:

- Review
- Review, Tutorial

PMID: 12032390 [PubMed - indexed for MEDLINE]

J Midwifery Womens Health 2002 Mar-Apr;47(2):68-73

Adolescent emergency contraception: attitudes and practices of certified nurse-midwives.

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Teenage pregnancy has reached epidemic proportions in the United States with I million pregnancies and more than 500,000 live births occurring each year among women under the age of 20. The safety and efficacy of postcoital administration of oral contraceptives, commonly called "emergency contraception" (EC), have been well documented. However, EC is dramatically underused in the United States. Because low use of EC may be attributable, in part, to both lack of knowledge, as well as misinformation on the part of health care providers, further research in this area is warranted. Because midwives play a significant role in the provision of reproductive health care to adolescents, their attitudes about the use of EC among teens may impact the availability of emergency contraception options to these clients. This article presents results of a survey of certified nurse-midwives with respect to their attitudes, practices, and policies related to EC and provides recommendations specific to this provider population.

PMID: 12019988 [PubMed - indexed for MEDLINE]

Mol Cell Endocrinol 2001 Oct 25;183(1-2):165-70

Modulation of 11 beta-hydroxysteroid dehydrogenase type 2 activity in Ishikawa cells is associated with changes in cellular proliferation.

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An important determinant of the potency of steroid hormones is the presence of activating and inactivating enzymes in target cells. The 11 beta-hydroxysteroid dehydrogenase type 1 and type 2 enzymes (11 beta HSD1 and 11 beta HSD2) modulate glucocorticoid action and may be important in regulating cellular growth. In the present study we examined 11 beta-hydroxysteroid dehydrogenase in Ishikawa endometrial cancer cells to see if modulation of enzyme activity could potentiate the antiproliferative effects of glucocorticoids. Ishikawa cells contain an NAD dependent enzyme migrating at 41 kDa on Western blots, consistent with the presence of the glucocorticoid-inactivating enzyme 11 beta HSD2, while the NADP dependent 11 beta HSD1 is barely detectable. Given that glucocorticoids decrease cellular proliferation we asked whether inhibition of 11 beta HSD2 could further enhance this effect. Cultivation of cells in the presence of 1 microM cortisol resulted in an elevation of 11 beta HSD2 and this was associated with a decrease in cell number. Enzyme activity and cell proliferation showed a biphasic response to the synthetic anti-progestin and anti-glucocorticoid RU38486, with < or =10 nM exerting agonistic effects and > or =100 nM producing antagonist effects in the presence of 1 microM cortisol. Inhibition of 11 beta HSD2 activity by glycyrrhetinic acid did not enhance the anti-proliferative effects of 1 microM cortisol, but the inhibitor showed significant antiproliferative activity in the absence of added glucocorticoid, consistent with protection of the low levels of glucocorticoids present in culture medium. Interestingly, the commonly used 11 beta HSD inhibitor, Carbenoxolone, did not block 11 beta HSD2 activity in whole Ishikawa cells, and there was no effect on cell proliferation, however, complete inhibition of 11 beta HSD2 was achieved in cellular homogenates suggesting that a barrier exists to entry of the inhibitor into intact cells. This study suggests that inhibition of 11 beta HSD2 activity can enhance the antiproliferative effects of low, but not high concentrations of glucocorticoids, and that beneficial effects may be attained in vivo at the nadir of diurnal glucocorticoid levels.

PMID: 11604236 [PubMed - indexed for MEDLINE]

Endocrinology 2002 May;143(5):1889-900

A glucocorticoid-responsive mutant androgen receptor exhibits unique ligand specificity: therapeutic implications for androgen-independent prostate cancer.

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The cortisol/cortisone-responsive AR (AR(ccr)) has two mutations (L701H and T877A) that were found in the MDA PCa human prostate cancer cell lines established from a castrated patient whose metastatic tumor exhibited androgen-independent growth. Cortisol and cortisone bind to the AR(ccr) with high affinity. In the present study, we characterized the structural determinants for ligand binding to the AR(ccr). Our data revealed that many of the C17, C19, and C21 circulating steroids, at concentrations that are found in vivo, functioned as effective activators of the AR(ccr) but had little or no activity via the wild-type AR or GRalpha. Among the synthetic glucocorticoids tested, dexamethasone activated both GRalpha and AR(ccr), whereas triamcinolone was selective for GRalpha. In MDA PCa 2b cells, growth and prostate-specific antigen production were stimulated by potent AR(ccr) agonists such as cortisol or 9alpha-fluorocortisol but not by triamcinolone (which did not bind to or activate the AR(ccr)). Of the potential antagonists tested, bicalutamide (casodex) and GR antagonist RU38486 showed inhibitory activity. We postulate that corticosteroids provide a growth advantage to prostate cancer cells harboring the promiscuous AR(ccr) in androgen-ablated patients and contribute to their transition to androgen-independence. We predict that triamcinolone, a commonly prescribed glucocorticoid, would be a successful therapeutic agent for men with this form of cancer, perhaps in conjunction with the antagonist casodex. We hypothesize that triamcinolone administration would inhibit the hypothalamic-pituitary-adrenal axis, thus suppressing endogenous corticosteroids, which stimulate tumor growth. Triamcinolone, by itself, would not activate the AR(ccr) or promote tumor growth but would provide glucocorticoid activity essential for survival.

PMID: 11956172 [PubMed - indexed for MEDLINE]

Chung Hua Yen Ko Tsa Chih 2002 Jan;38(1):42-4

[Effect of RU38486 on fibronectin expression in cultured human trabecular cells]

[Article in Chinese]

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OBJECTIVE: To study the effect of RU38486 on fibronectin expression in human trabecular cells (HTCs) in vitro. METHODS: The trabecular specimens from human donors were primarily cultured and subcultured. Cultured cells were observed by light and electron microscopes. Fibronectin (FN), laminin (LN) and neuron-specific enolase (NSE) in extracellular matrix (ECM) of the cells were immunohistochemically stained with LSAB method. The quantities of FN [optical density (A) means] affected by different concentrations of dexamethasone (Dex) and RU38486 were measured through indirect immunochemical method associated with computer image analysis. RESULTS: According to the growing characteristics and morphological features, the cultured cells were identified as HTCs. Comparison of A means of FN induced by Dex and RU38486 was 10(-6) mol/L dex (12 days) > 10(-7) mol/L Dex (12 d) > 10(-7) mol/L Dex (5 d) > Control group = 10(-7) mol/L Dex (5 d) + 10(-8) mol/L RU38486 (7 d). CONCLUSION: Dex can stimulate HTCs in vitro to secrete more FN. Bit RU38486 can reverse this high level of FN expression induced by Dex on receptor level. The efficacy of RU 38486 [glucocorticoid receptor (GR)-antagonist] in reducing intraocular pressure in vivo should be confirmed by further studies.

PMID: 11955301 [PubMed - indexed for MEDLINE]

Br J Cancer 2001 Dec 14;85(12):1978-86

Demonstration of mixed properties of RU486 in progesterone receptor (PR)-transfected MDA-MB-231 cells: a model for studying the functions of progesterone analogues.

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Progesterone antagonist RU486 (mifepristone) has been implicated for many anti-neoplastic and obstetrical applications. But the compound has demonstrated undesired agonist-like effect depending on cell, tissue and species studied. Using PR-transfected breast cancer cells MDA-MB-231, this report describes the similarities and differences between progesterone- and RU486-mediated effects on cell growth, cell differentiation and, at the molecular level, on the activation of p44/p42 MAP kinases (MAPK). Like progesterone, RU486 inhibited cells growth by arresting the cells in G0/G1 phase of the cell cycle. In contrast to progesterone that induced cell spreading, RU486 induced a multipolar, stellate morphology. RU486-treated cells showed no increase of stress fibers, nor was there any increase of focal adhesions as progesterone-treated cells did. Furthermore, despite of the fact that both compounds inhibited cell growth, RU486 significantly stimulated the activation of p44/p42 MAP kinases whereas progesterone markedly inhibited the activation. Nonetheless, the effects of RU486 were PR-mediated and RU486 was able to antagonize the effect of progesterone on cell growth and focal adhesion. In conclusion, RU486 can act not only as a progesterone antagonist, a progesterone agonist but also induced morphological and molecular changes that were distinct from progesterone-mediated effects in PR-transfected MDA-MB-231 cells. The non-progesterone-like effect of RU486 may be mediated through a pathway that is different from the progesterone-mediated pathway, or it is the result of a blockade of certain critical step(s) in the progesterone-mediated pathway. In any case, undesired side effects of antiprogestin may create clinical complications. PR-transfected MDA-MB-231 breast cancer cells provide a model for studying the functions of progesterone analogues.

PMID: 11747343 [PubMed - indexed for MEDLINE]

Proc Natl Acad Sci U S A 2002 Jun 11;99(12):7940-4

Coactivator/corepressor ratios modulate PR-mediated transcription by the selective receptor modulator RU486.

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Selective receptor modulators, such as the antiprogestin RU486, are known to exhibit partial agonist activities in a cell-type-dependent manner. Employing an in vitro chromatin transcription system that recapitulates progesterone receptor (PR)-mediated transcription in vivo, we have investigated the molecular basis by which the antiprogestin RU486 regulates transcription in a cell-type-specific manner. We have compared the effects of RU486 on PR-dependent transcription in vitro using T47D and HeLa cell nuclear extracts. RU486 exhibits a differential ability to activate transcription within these two cell types. The differential effect on transcription correlates with different ratios of endogenous coactivators/corepressors in these cells. Unlike agonist-bound PR that interacts only with coactivators such as steroid receptor coactivator-1 (SRC-1), RU486-bound PR binds to both coactivator SRC-1 and corepressor silencing mediator for retinoid and thyroid hormone receptor (SMRT) in vitro. Both SRC-1 and SMRT have the capacity to modulate RU486-dependent activity. Moreover, a change in the relative levels of SRC-1 and SMRT contained in our chromatin transcription system modulates agonist/antagonist effects of RU486 on transcription by PR. Our data indicate that the ability of RU486 to activate transcription is modulated by the ratio of coactivators to corepressors and substantiate the important roles of coregulators in the regulation of steroid receptor mediated transactivation in response to selective receptor modulators.

PMID: 12048256 [PubMed - indexed for MEDLINE]

Obstet Gynecol 2002 Jul;100(1):65-71

Emergency contraception with mifepristone and levonorgestrel: mechanism of action.

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OBJECTIVE: To study the effect of mifepristone and levonorgestrel on ovarian function and endometrial development in doses effective as emergency contraception. METHODS: Twelve fertile women were treated with either 10 mg of mifepristone as a single dose (n = 6) or two doses of 0.75 mg of levonorgestrel, 12 hours apart (n = 6) before and after ovulation. An endometrial biopsy performed during the implantation period was analyzed for endometrial maturation and expression of markers of endometrial receptivity. The markers tested for were integrin alpha4 and beta3, cyclooxygenase-1 and -2, progesterone receptors, Dolichos biflorus agglutinin lectin binding, and pinopodes. Urinary excretion of luteinizing hormone, estrone, and pregnanediol were also determined. RESULTS: Treatment with mifepristone and levonorgestrel before ovulation inhibited the luteinizing hormone surge showing no significant differences between the means of luteinizing hormone measurements. When mifepristone was administered in the early luteal phase, downregulation of progesterone receptors was inhibited in five of six women. No significant alteration was found in any of the remaining markers of endometrial receptivity. CONCLUSION: The mode of action of emergency contraception with mifepristone or levonorgestrel is primarily due to inhibition of ovulation rather than inhibition of implantation.

Publication Types:

- Clinical Trial

PMID: 12100805 [PubMed - indexed for MEDLINE]

J Am Soc Nephrol 2001 Dec;12(12):2787-96

Glucose and prednisolone alter basic fibroblast growth factor expression in peritoneal mesothelial cells and fibroblasts.

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The mechanism of peritoneal fibrosis in patients on continuous ambulatory peritoneal dialysis is poorly understood. The production of basic fibroblast growth factor (bFGF) by human peritoneal mesothelial cells cultured in high glucose medium was investigated, and the behavior of peritoneal fibroblasts, as well as the inhibitory effect of prednisolone, was assessed. Reverse transcriptase-PCR and immunocytochemistry showed the expression of glucocorticoid receptors in mesothelial cells. The semiquantitative reverse transcriptase-PCR showed that high glucose medium (4.0%) increased bFGF mRNA by 2.5-fold relative to control medium (0.1% glucose), with 83% suppression of the increase by 1 microM prednisolone. The bFGF protein level in culture supernatant was also increased by 1.5-fold in high glucose medium, with this change showing 45% suppression by 1 microM prednisolone. These effects of prednisolone were prevented by a glucocorticoid receptor antagonist (RU486) in a concentration-dependent manner. The proliferation of peritoneal fibroblasts was increased 1.9-fold by the supernatant of mesothelial cells cultured in high glucose medium, with 85% suppression by 1 microM prednisolone and suppression to 16% below basal proliferation by an anti-bFGF neutralizing antibody (10 microg/ml), whereas proliferation showed a concentration-dependent increase on addition of an anti-transforming growth factor beta-neutralizing antibody. Recombinant bFGF (50 to 1000 pg/ml) likewise caused a concentration-dependent increase of peritoneal fibroblast proliferation and fibronectin release by these cells was also increased (at 50 to 5000 pg/ml). These results suggest the potential importance of bFGF for initiation of peritoneal fibrosis and the possible efficacy of glucocorticoids for preventing such fibrosis in patients receiving peritoneal dialysis.

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J Biol Chem 2002 Jan 11;277(2):1538-43

Allosteric effects of dexamethasone and RU486 on glucocorticoid receptor-DNA interactions.

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The glucocorticoid receptor (GR) is a DNA-binding protein that can regulate the transcription of a large number of genes in a ligand-dependent fashion. Although much progress has been made on the mechanism of transcriptional regulation by GR, a potential allosteric effect of GR-binding ligands on specific GR-DNA interactions is controversial. In this study, gel-shift methods are used to measure the effects of a classical agonist dexamethasone and a prototypical antagonist RU486 on the in vitro interactions of GR with DNA substrates, which contain glucocorticoid response elements (GREs) from promoters of GR-regulated genes. These studies show that cell extracts containing human GR bind specifically and with high affinity to GREs in the absence of ligand. An agonist dexamethasone and antagonist RU486 do not affect the affinity of GR for DNA but subtly alter the electrophoretic mobility of the GR-DNA complex. Importantly, the dissociation rate of GR from DNA increases as a function of the concentration of GRE-containing DNA. At a fixed DNA concentration, dexamethasone-bound GR dissociates from DNA significantly faster than does ligand-free GR or RU486-bound GR. These results are consistent with a model for transcriptional activation in which a dynamic complex is formed between agonist-bound GR and DNA.

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Neurology 2002 May 14;58(9):1436

Mifepristone (RU 486) for Alzheimer's disease.

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Mifepristone (RU 486) for Alzheimer's disease

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Prolonged exposure to high glucocorticoid levels during life has been linked to hippocampal pathology and cognitive impairment.[1] For example, excessive levels of endogenous or exogenous corticosteroids have been associated with impaired attention, concentration, and memory.[1,2] Longitudinal studies have correlated increased plasma cortisol with cognitive decline and hippocampal atrophy.[3] In rats, adrenalectomy at midlife attenuates subsequent hippocampal degeneration and cognitive decline.[4]

AD is associated with hippocampal atrophy and increased hypothalamo–pituitary–adrenal (HPA) axis activity, both of which may correlate with cognitive deficits.[3] If prolonged exposure to glucocorticoids also plays a role in AD, we hypothesized that countering such effects might have therapeutic potential. We evaluated mifepristone (RU 486, Roussel UCLAF, Romainville, Seine-St.-Davideins, France), a long-acting antagonist of progesterone and glucocorticoid receptors,[5] for the treatment of AD.

This was a pilot, single-site, randomized, placebo-controlled, double blind, 6-week trial in patients with mild to moderate AD. The study was reviewed by the Institutional Review Board of New York University School of Medicine, and participants were enrolled after providing written informed consent. Key inclusion criteria were diagnosis of probable AD (National Institute of Communicative Disorders and Stroke and AD and Related Disorders Association criteria), Mini-Mental State Examination (MMSE) score between 10 and 27, medically stable condition, and Global Deterioration Scale score of 3, 4, 5, or 6 (mild to severe). No participants were taking cholinesterase inhibitors. Eligible participants were randomized to mifepristone (200 mg) or placebo daily at bedtime. The AD Assessment Scale–Cognitive subscale (ADAS-Cog)[6] was administered at screening, at approximately 12 hours after the first dose and at postbaseline weeks 3, 5, and 6. Other assessments included the Hamilton Depression Rating Scale (HDRS) and safety evaluations. Before the intended enrollment of patients could be completed, Roussel UCLAF, the study sponsor, decided to withdraw mifepristone from the US and discontinued all studies, including this one. For the patients enrolled before study termination, efficacy variables were analyzed as a change from baseline by treatment both for completers and for the intent-to-treat population (last observation carried forward). Student's *t*-tests (one-tailed) were used to test the hypothesis that mifepristone was more effective than placebo.

Nine patients (6 men and 3 women, mean age = 72.0 ± 10.8 years; mean MMSE score = 20.8 ± 3.8; mean ADAS-Cog total score = 22.6 ± 5.3, mean HDRS score = 5.6 ± 1.9) were randomized—four to placebo and five to mifepristone. At baseline, the mifepristone group tended to be older but did not significantly differ from the placebo group in mean age ($p = 0.56$), baseline ADAS-Cog score ($p = 0.49$), HDRS score ($p = 0.80$), and MMSE ($p = 0.94$) score. Six patients completed the study. Two patientson active medication discontinued after 2 and 3 weeks, and one patient on placebo dropped out at week 6.

At 12 hours after first dose, the change from baseline in ADAS-Cog total scores was not statistically different between the two groups. However, patients treated with mifepristone performed better ($t = 2.83$, $p < 0.0128$) on the ADAS-Cog Word Recall subtest. At week 6, the mean change from baseline in ADAS-Cog total score among completers revealed that patients treated with mifepristone tended to improve (by 2.67 points) whereas patients treated with placebo tended to worsen (by 1.67 points). However, this difference of 4.3 points failed to reach substantial significance. There was also a trend for better performance by the mifepristone group on scores of specific ADAS-Cog subtests (Orientation, Word Recognition, and Word Recall) as shown in the table. There was no significant difference between the groups in HDRS scores. Intent-to-treat analyses revealed similar results.

Mifepristone was associated with the following adverse effects: One participant developed a generalized pruritic maculopapular rash after 2 weeks and was discontinued. Another individual developed a nonpruritic rash limited to the chest and the abdomen after 5 weeks of treatment and was treated with an antihistamine. A third participant developed asymptomatic hypokalemia (2.8 mmol/L) on his final visit and was treated with a potassium supplement. Two individuals also had increased fatigue and loss of appetite without weight change, and one individual experienced two episodes of severe headache after 3 weeks of treatment.

This is the first controlled trial to examine the effects of a central glucocorticoid receptor antagonist on cognition in AD. Although limitations such as small sample size, short treatment duration, and one-tailed tests do not allow any firm conclusions regarding efficacy, this pilot study provides new data on the safety and the feasibility of this approach. A longer study involving a better tolerated, second-generation glucocorticoid receptor antagonist is warranted to confirm efficacy in AD.

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Supported by a grant from Roussel to N.P. N.P. has also received grants or honoraria from Merck, Whitehouse Station, NJ; Pharmacia & Upjohn, Peapack, NJ; Eli Lilly, Indianapolis, IN; Forest, St. Louis, MO; Novartis, Summit, NJ; Mediolanum, Milan, Italy; Zeneca, Wilmington, DE; Janssen-Titusville, NJ; Fidia, Washington DC; and G.D. Searle, Skokie, IL. S.F. has received grants or honoraria from Pfizer, New York, NY; Eisai, Teaneck, NJ; Eli Lilly, Indianapolis, IN; Novartis, Summit, NJ; Merck, Whitehouse Sta-

Table *Cognitive outcomes of completers at week 6 in AD*

Measure	Placebo (n = 3)	RU486 (n = 3)	*t*-Test statistics	*p* Value*
ADAS-Cog total score	1.67 ± 8.9	−2.67 ± 6.7	0.67	$0.20 < p < 0.30$
Word Recall Item score	0.00 ± 1.0	−0.33 ± 0.6	0.50	$0.30 < p < 0.40$
Orientation Item score	1.00 ± 1.0	−1.67 ± 2.1	2.00	$0.05 < p < 0.10$
Word Recognition Item score	1.67 ± 2.1	−0.67 ± 3.1	1.09	$0.10 < p < 0.20$

Values are expressed as mean ± SD.
Data shown are change from baseline at week 6; a positive change indicates worsening and a negative change reflects improvement.

* One-tailed.

ADAS-Cog = AD Assessment Scale–Cognitive.

J Clin Endocrinol Metab 2002 Aug;87(8):3740-4

Transactivation assay for determination of glucocorticoid bioactivity in human serum.

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We have developed a mammalian cell (COS-1) bioassay, which measures glucocorticoid bioactivity (GBA) directly from a small amount of human serum. The assay is based on the expression of human glucocorticoid receptor (GR) together with a coactivator protein and reporter plasmid containing GR response elements upstream of the luciferase gene. Ten microliters of human serum, in duplicate, are added directly to the cell culture medium, and GBA is derived from reporter gene activity. The assay differentiates between biopotencies of synthetic steroids, and importantly, mifepristone (RU486) is able to block glucocorticoid-induced response. The assay is sensitive (<15.6 nM cortisol in fetal calf serum) and precise, with the within- and between-assay coefficients of variation less than 8% and 10%, respectively. We measured serum GBA (bioassay) and cortisol (RIA) levels in 34 asthmatic children (age range, 5.7-14.2 yr) at baseline and after treatment with either inhaled budesonide (800 microg/d, n = 14), fluticasone propionate (500 microg/d, n = 14), or cromones (control group, n = 6). Pretreatment serum GBA and cortisol levels correlated strongly ($r = 0.90$, $P < 0.0001$, $n = 34$). Two months of treatment with inhaled budesonide resulted in excess GBA in circulation, which was not attributable to endogenous cortisol ($P < 0.001$). In the fluticasone propionate group, the presence of serum excess GBA was at the borderline of statistical significance ($P < 0.08$) after 2 months of inhalation therapy, and no excess GBA was detected in the cromone group. In conclusion, our bioassay enables measurement of mammalian cell response to bioactive glucocorticoids in circulation and provides a novel means to investigate patients receiving drugs acting through the GR.

Publication Types:

- Clinical Trial

PMID: 12161504 [PubMed - indexed for MEDLINE]

EMBO J 2001 Nov 1;20(21):6071-83

Factor recruitment and TIF2/GRIP1 corepressor activity at a collagenase-3 response element that mediates regulation by phorbol esters and hormones.

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To investigate determinants of specific transcriptional regulation, we measured factor occupancy and function at a response element, col3A, associated with the collagenase-3 gene in human U2OS osteosarcoma cells; col3A confers activation by phorbol esters, and repression by glucocorticoid and thyroid hormones. The subunit composition and activity of AP-1, which binds col3A, paralleled the intracellular level of cFos, which is modulated by phorbol esters and glucocorticoids. In contrast, a similar AP-1 site at the collagenase-1 gene, not inducible in U2OS cells, was not bound by AP-1. The glucocorticoid receptor (GR) associated with col3A through protein-protein interactions with AP-1, regardless of AP-1 subunit composition, and repressed transcription. TIF2/GRIP1, reportedly a coactivator for GR and the thyroid hormone receptor (TR), was recruited to col3A and potentiated GR-mediated repression in the presence of a GR agonist but not antagonist. GRIP1 mutants deficient in GR binding and coactivator functions were also defective for corepression, and a GRIP1 fragment containing the GR-interacting region functioned as a dominant-negative for repression. In contrast, repression by TR was unaffected by GRIP1. Thus, the composition of regulatory complexes, and the biological activities of the bound factors, are dynamic and dependent on cell and response element contexts. Cofactors such as GRIP1 probably contain distinct surfaces for activation and repression that function in a context-dependent manner.

PMID: 11689447 [PubMed - indexed for MEDLINE]

Int J Clin Pract 2002 Mar;56(2):140-4

The potential of mifepristone (RU486) as a female contraceptive drug.

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This article reviews the development of mifepristone (RU486) as a female contraceptive drug. Mifepristone is an orally active compound with nearly 40% bioavailability after first pass effect. The steady plasma level of mifepristone ranges from 65 nmol/l with 1 mg/day to 1 micromol/l with 10 mg/day and reaches 2.5 micromol/l, 4.5 micromol/l and 5.4 micromol/l with mifepristone 50 mg, 100 mg and 200 mg daily, respectively, over the treatment period. Inhibition of ovulation may be achieved at serum mifepristone concentration of 232.7 nmol/l. Mifepristone appears to antagonise progesterone at the pituitary level to suppress gonadotropin and steroid hormone secretion rather than to act primarily on the hypothalamus to delay or inhibit ovulation. In fact, the endometrium is most sensitive to mifepristone. Low-dose mifepristone impairs luteal phase endometrial development and receptivity by altering endometrial parakine, cytokine and enzyme activity. Thus, low-dose mifepristone can significantly reduce the rate of conception without inhibiting ovulation. However, further research is needed to standardise the dose and dose-schedule to achieve the desired efficacy of low-dose mifepristone for routine clinical use with minimal or no side-effects.

Publication Types:

- Review
- Review Literature

PMID: 11926701 [PubMed - indexed for MEDLINE]

Endocrinology 2002 Aug;143(8):3071-82

Identification and characterization of novel estrogen receptor-beta-sparing antiprogestins.

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The steroid hormones estrogen and progesterone together regulate the development and maintenance of the female reproductive system. The actions of these two hormones are mediated by their respective nuclear receptors located within overlapping cell populations in target organs. The molecular mechanism of action of these two hormones has been defined to a large extent using estrogen receptor (ER) and progesterone receptor (PR) antagonists. In the case of ER, the available antagonists are highly receptor selective. With respect to PR, however, the available antiprogestins also interact with the receptors for glucocorticoids, mineralocorticoids, and androgens. Whereas these cross-reactivities can usually be managed in studies of female reproductive function, it is the recent demonstration that RU486 is an effective antagonist of the beta-isoform of ER that suggested the need for more selective antiprogestins. In this study, we used cell-based transcriptional assays combined with screens using coactivator peptide analogs to identify two novel classes of antiprogestins that distinguish themselves from the antiprogestin RU486 in the manner they interact with PR. One class exhibits the characteristics of a pure antiprogestin in that its members bind to the receptor and induce a conformational change that prevents the presentation of two potential coactivator binding surfaces on the protein. The second class of compounds distinguish themselves from RU486 in that they are ERbeta sparing. When tested in vivo the ER-sparing antiprogestins were as effective as RU486 in suppressing superovulation. It is anticipated that the availability of these new antiprogestins will advance the studies of PR pharmacology in a manner similar to how the availability of selective ER modulators has helped the study of ER action.

PMID: 12130573 [PubMed - indexed for MEDLINE]

J Biol Chem 2002 Jul 19;277(29):26238-43

RU486-induced glucocorticoid receptor agonism is controlled by the receptor N terminus and by corepressor binding.

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Glucocorticoid-induced gene transcription has been shown to be mediated by coactivators bound to the glucocorticoid receptor (GR). The glucocorticoid antagonist RU486 interferes with the steroid-mediated activation and can also exhibit partial agonist activity, a response in which corepressors have been implicated. Here we have shown that deletion of the N terminus of GR totally abolishes the agonist activity of RU486. Furthermore, we have demonstrated that corepressors bind directly to the RU486-bound GR as determined by glutathione S-transferase pull-down, mammalian two-hybrid assay, and coimmunoprecipitation. Fine mapping of the interaction regions within GR and the corepressor NCoR reveals a complex interaction profile that involves a number of domains in each protein. Notably, the N and the C termini of GR are both involved in corepressor binding. Thus, the N terminus of GR is a major determinant for RU486-dependent NCoR interaction as well as for RU486-mediated agonist activity.

PMID: 12011091 [PubMed - indexed for MEDLINE]

Crit Care 2002 Aug;6(4):330-4

Bench-to-bedside review: a possible resolution of the glucose paradox of cerebral ischemia.

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The glucose paradox of cerebral ischemia (namely, the aggravation of delayed ischemic neuronal damage by preischemic hyperglycemia) has been promoted as proof that lactic acidosis is a detrimental factor in this brain disorder. Recent studies, both in vitro and in vivo, have demonstrated lactate as an excellent aerobic energy substrate in the brain, and possibly a crucial one immediately postischemia. Moreover, evidence has been presented that refutes the lactic acidosis hypothesis of cerebral ischemia and thus has questioned the traditional explanation given for the glucose paradox. An alternative explanation for the aggravating effect of preischemic hyperglycemia on the postischemic outcome has consequently been offered, according to which glucose loading induces a short-lived elevation in the release of glucocorticoids. When an episode of cerebral ischemia in the rat coincided with glucose-induced elevated levels of corticosterone (CT), the main rodent glucocorticoid, an aggravation of the ischemic outcome was observed. Both the blockade of CT elevation by chemical adrenalectomy with metyrapone or the blockade of CT receptors in the brain with mifepristone (RU486) negated the aggravating effect of preischemic hyperglycemia on the postischemic outcome.

Publication Types:

- Review
- Review, Tutorial

PMID: 12225609 [PubMed - indexed for MEDLINE]

J Biol Chem 2002 Jan 25;277(4):2525-33

The activated glucocorticoid receptor modulates presumptive autoregulation of ribosomal protein S6 protein kinase, p70 S6K.

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Protein metabolism in eukaryotic organisms is defined by a synthesis-degradation equilibrium that is subject to regulation by hormonal and nutritional signals. In mammalian tissues such as skeletal muscle, glucocorticoid hormones specify a catabolic response that influences both protein synthetic and protein degradative pathways. With regard to the former, glucocorticoids attenuate mRNA translation at two levels: translational efficiency, i.e. translation initiation, and translational capacity, i.e. ribosome biogenesis. Glucocorticoids may impair translational capacity through the ribosomal S6 protein kinase (p70 S6K), a recognized glucocorticoid target and an effector of ribosomal protein synthesis. We demonstrate here that the reduction in growth factor-activated p70 S6K activity by glucocorticoids depends upon a functional glucocorticoid receptor (GR) and that the GR is both necessary and sufficient to render p70 S6K subject to glucocorticoid regulation. Furthermore, the DNA binding and transcriptional activation but not repression properties of the GR are indispensable for p70 S6K regulation. Finally, a mutational analysis of the p70 S6K carboxyl terminus indicates that this region confers glucocorticoid sensitivity, and thus glucocorticoids may facilitate autoinhibition of the enzyme ultimately reducing the efficiency with which T389 is phosphorylated.

PMID: 11705993 [PubMed - indexed for MEDLINE]

Invest Ophthalmol Vis Sci 2001 Dec;42(13):3173-81

Delayed secondary glucocorticoid responsiveness of MYOC in human trabecular meshwork cells.

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PURPOSE: To characterize the glucocorticoid responsiveness of the glaucoma gene MYOC (myocilin/TIGR) in cultured human trabecular meshwork (TM) cells. METHODS: MYOC expression in two independently derived human TM cell lines was quantified by Western immunoblot analysis of protein levels and quantitative PCR analysis of mRNA levels. Promoter activity was measured indirectly with the luciferase reporter gene in a dual luciferase reporter assay. RESULTS: Application of the synthetic glucocorticoid dexamethasone (Dex) to cultured TM cells at 100 nM resulted in a delayed (8-16 hours) induction of myocilin. The concentration dependence (median effective concentration [EC(50)], approximately 10 nM) and reversal by the glucocorticoid antagonist, RU486, implicates the glucocorticoid receptor (GR). In an interesting observation, RU486 alone acted as a partial agonist to MYOC expression. Treatment of TM cells with the protein synthesis inhibitor cycloheximide abolished the Dex induction, suggesting an indirect effect of the GR on MYOC expression. In addition, the RNA synthesis inhibitor actinomycin D also blocked Dex induction, indicating that the Dex effect was due to increased MYOC transcription. Analysis of up to 2700 nucleotides (nt) of the MYOC gene 5'-flanking region in luciferase reporter constructs showed no Dex induction, despite the presence of multiple putative glucocorticoid response element (GRE)-like half-sites in the MYOC promoter and the presence of an intact cellular GR-mediated signaling system. CONCLUSIONS: MYOC is a delayed secondary glucocorticoid-responsive gene. Characterization of the transcription factors that mediate the secondary response will shed new light on the pathophysiology of steroid-induced ocular hypertension and glaucoma.

PMID: 11726619 [PubMed - indexed for MEDLINE]

Ann N Y Acad Sci 2002 Mar;955:159-73; discussion 199-200, 396-406

Regulation and modulation of abnormal immune responses in endometriosis.

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There is ample evidence demonstrating that endometriosis is accompanied by inflammatory reactions in the peritoneum, resulting in abnormal levels of a variety of cytokines and chemokines in the peritoneal fluid. Among the immunological parameters that have been shown to be altered in the peritoneal cavity of women with endometriosis, an increase in the number of activated nonadherent macrophages that show reduced surface expression of scavenger receptors has been observed. The cause-and-effect relationship between aberrant peritoneal macrophage activity and endometriosis is still unknown. We have demonstrated that steroid hormone receptor agonists and antagonists [e.g., retinoids, antiglucocorticoids, ligands to peroxisome proliferator activated receptors (PPARs)] can regulate macrophage functions in ways that could either suppress or stimulate the growth of ectopic endometrial lesions. Our studies include a number of relevant findings: (1) RU486, acting as an antioxidant, can suppress activation of NFkappaB, a nuclear transcription factor that affects the expression of several inflammatory genes such as those for MCP-1, GM-CSF, CSF-1, and various adhesion molecules; (2) IL-6 secretion from a variety of cell types including endometrial cells is inhibited by retinoic acid; and (3) retinoids and PPARgamma ligands can upregulate the expression of scavenger receptors in cells of the monocyte/macrophage lineage. These observations, combined with the possibility that macrophage activity may play a fundamental role in endometriosis, suggest that pharmacologic manipulation of macrophage function may provide a novel mechanism for treating this disease.

Publication Types:

- Review
- Review, Tutorial

PMID: 11949945 [PubMed - indexed for MEDLINE]

Cancer Res 2001 Oct 1;61(19):7179-83

Differential expression of members of the tumor necrosis factor alpha-related apoptosis-inducing ligand pathway in prostate cancer cells.

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Androgen ablation therapy induces apoptosis only in androgen-sensitive prostate cancer cells; therefore, other cytotoxic drugs are being used to induce apoptosis in androgen-refractory cells. Mifepristone, an antiprogestin used individually or together with the antiestrogen Tamoxifen, has been recommended for induction of cell death and treatment of several hormonal cancers. However, little is known about the mechanism of action of these drugs in prostate cancer. Therefore, we investigated the effect of Mifepristone on the tumor necrosis factor alpha-related apoptosis-inducing ligand (TRAIL) pathway, a newly identified and very effective member of tumor necrosis factor-alpha family. Mifepristone and Tamoxifen induced significant expression of death receptors in prostate cancer cells in vitro and in xenografts. However, Mifepristone in combination with Tamoxifen did not increase prostate cancer cell death compared with their individual values. The involvement of the TRAIL pathway was further confirmed by the activation of caspase-8 in Mifepristone-treated cells. This was followed by truncation of Bid, confirming that Mifepristone activates the TRAIL pathway. This knowledge is being used to design a combination treatment of TRAIL and Mifepristone to induce significant apoptosis in prostate cancer cells.

PMID: 11585752 [PubMed - indexed for MEDLINE]

Biochem Pharmacol 2002 Mar 1;63(5):945-9

Pharmacological characterization of the ATP-dependent low K(m) guanosine 3',5'-cyclic monophosphate (cGMP) transporter in human erythrocytes.

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The efflux pump for cGMP has been shown to be an ATP-energized multiorganic anion transporter. The present study was performed to extend the knowledge of the pharmacological characteristics of this efflux pump. Inside-out vesicles prepared from fresh blood were incubated with [3H]-cGMP (1 microM) with or without various concentrations of competitors for 120min at 37 degrees. The tested compounds could be divided in four groups: one with high affinity (K(i) < 5 microM), a second with moderate affinity (K(i): 5-50 microM), a third with low affinity (K(i): 0.1-5mM) and the fourth with extremely low or no affinity at all. With the mean K(i)-values given in parenthesis, the high affinity group consisted of mifepristone (0.2 microM), zaprinast (0.35 microM), dipyridamole (0.35 microM), estradiol 3-beta-glucuronide (0.42 microM), genistein (0.43 microM), estradiol 17-beta-glucuronide (0.47 microM), onapristone (1.3 microM), progesterone (1.7 microM) and sildenafil (3.6 microM). The inhibitors with medium affinity were estradiol (8 microM), sulfinpyrazone (13 microM), daunorubicin (23 microM), megestrol acetate (26 microM), doxorubicin (28 microM), 6-thioguanine (28 microM) and 6-thioguanosine-5'-monophosphate (32 microM). The low affinity group comprised 6-TIMP (220 microM), 6-methylmercaptopurine (MMP) (220 microM), vincristine (270 microM), medroxyprogesterone (680 microM), para-aminohippurate (PAH) (1.9mM) and taurocholate (2.2mM). No or minimal effect was seen in the presence of 6-mercaptopurine (6-MP), methotrexate, 9-(2-phosphonylmethoxyethyl)adenine and mitoxantrone. The cGMP transporter had a unique pharmacological profile, different from that of MRP1, but with some characteristics in common with MRP4 and MRP5.

PMID: 11911846 [PubMed - indexed for MEDLINE]

Fertil Steril 2001 Dec;76(6):1225-31

Progesterone receptor antagonists Org 31710 and RU 486 increase apoptosis in human periovulatory granulosa cells.

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OBJECTIVE: To investigate if progesterone receptor (PR)-mediated effects are involved in regulating the susceptibility to apoptosis in LH receptor-stimulated human luteinizing granulosa cells. DESIGN: Laboratory study. SETTING: Goteborg University and an in vitro fertilization laboratory of a university hospital. PATIENT(S): Women undergoing oocyte retrieval for in vitro fertilization after ovulation induction with gonadotropins. INTERVENTION(S): Luteinizing granulosa cells were isolated from follicular aspirates after oocyte removal. The cells were treated with or without RU 486 (1 microM-100 microM), Org 31710 (1 microM-100 microM), progesterone (1 nM-10 microM), dexamethasone (0.5 microM-100 microM), dihydrotestosterone (1 nM-25 microM), RU 486 (10 microM-100 microM) + dexamethasone (50 microM), and picrotoxin (1 microM-100 microM) and were cultured under serum-free conditions. MAIN OUTCOME MEASURE(S): Measurement of caspase-3 activity; detection of internucleosomal DNA fragmentation using gel electrophoresis and fluorospectrophotometry; progesterone analysis of spent medium. RESULT(S): Addition of the PR antagonists RU 486 or Org 31710 in vitro to human luteinizing granulosa cells caused an increase in caspase-3 activity and a dose-dependent increase in internucleosomal DNA fragmentation. No effect on DNA fragmentation was seen after addition of dexamethasone, dihydrotestosterone, or picrotoxin. CONCLUSION(S): Nuclear PR-mediated effects are involved in regulating the susceptibility to apoptosis in LH receptor-stimulated human luteinizing granulosa cells.

PMID: 11730755 [PubMed - indexed for MEDLINE]

Maturitas 2002 Aug 30;42(4):287-94

Lack of stimulatory effect of dienogest on the expression of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 by endothelial cell as compared with other synthetic progestins.

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OBJECTIVES: Monocyte adhesion to endothelial cells is an important initial event at the onset of atherosclerosis. It is partially mediated by the expression of adhesion molecules on the endothelial cell surface. While estrogens inhibit the development of atherosclerosis, the effect of co-administered progestin remains controversial. We examined the effect of progestins on cytokine-stimulated human umbilical venous endothelial cell (HUVEC) expression of adhesion molecules. METHODS: In HUVECs, mRNA expression of progesterone receptors (PRs) and androgen receptors (AR) was determined by RT-PCR. HUVECs were stimulated by interleukin-1beta (IL-1beta) for 24 h with or without various steroids, and then the cell-surface expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) was semiquantified by ELISA. RESULTS: In all preparations of HUVECs used in this study, RT-PCR confirmed mRNA expression of both isoforms of PR, PR-A and PR-B, as well as AR. Addition of progesterone (10(-10)-10(-7) M) or dienogest (DNG) (10(-10)-10(-8) M) did not affect IL-1beta-stimulated ICAM-1 or VCAM-1 expression. In contrast, medroxyprogesterone acetate, norethindrone acetate and levonorgestrel (10(-10)-10(-8) M) dose-dependently increased cell adhesion molecules. The progestin-induced increase was blocked by the concomitant addition of mifepristone, a PR antagonist, but not by hydroxyflutamide, an AR antagonist, indicating that the progestin stimulation was mediated predominantly via PR. CONCLUSIONS: These results suggest that DNG, unlike other synthetic progestins, lacks stimulation of cell adhesion molecules. For the prevention of atherosclerosis, estrogen in combination with DNG may be a suitable regimen in hormone replacement therapy in postmenopausal women.

PMID: 12191851 [PubMed - indexed for MEDLINE]

Cancer Res 2002 Jun 1;62(11):3298-307

Stromal cells promote angiogenesis and growth of human prostate tumors in a differential reactive stroma (DRS) xenograft model.

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Reactive stroma has been reported in many cancers, including breast, colon,and prostate. Although changes in stromal cell phenotype and extracellular matrix have been reported, specific mechanisms of how reactive stroma affects tumor progression are not understood. To address the role of stromal cells in differential regulation of tumor incidence, growth rate, and angiogenesis, LNCaP xenograft tumors were constructed in nude mice with five different human prostate stromal cell lines as well as GeneSwitch-3T3 cells engineered to express lacZ under mifepristone regulation. Alone, LNCaP prostate carcinoma cells were essentially nontumorigenic, whereas combinations of LNCaP cells with three different human prostate stromal cell lines (L/S tumors) resulted in a tumor incidence (50-63%) similar to that of control LNCaP plus Matrigel (L/M) tumors over a 9-week period. In contrast, LNCaP combinations with two other human prostate stromal cell lines were nontumorigenic, illustrating that stromal cell effects are differential. L/S tumors exhibited well-developed blood vessels at 2 weeks, whereas control L/M tumors were avascular at 2 weeks and exhibited blood lakes in lieu of extensive vessels at later time points. Xenografts constructed under three-way conditions (LNCaP, Matrigel, and stromal cells; L/M/S tumors) exhibited a 100% tumor incidence and showed rapid blood vessel formation as early as day 7 with mature vessels formed by day 10. L/M/S tumors exhibited a 10.3-fold increase in microvessel density, and the corresponding hemoglobin:tumor weight ratio was increased 2-fold relative to L/M control tumors at day 10. L/M/S tumor wet weight and volume increased by 1.6- and 2.4-fold, respectively, by day 21, compared with control L/M tumors. L/M/S tumors made with LNCaP cells plus GeneSwitch-3T3-pGene/lacZ stromal cells showed similar results. Mifepristone-regulated gene expression was observed in stromal cells immediately adjacent to clusters of carcinoma cells and in vessel walls in a mural cell (pericyte) position. This study shows that regulation of angiogenesis is one mechanism through which stromal cells affect LNCaP tumor incidence and growth rate. This regulation may be mediated through direct recruitment and interactions of stromal cells with endothelial cells. Furthermore, this study describes for the first time a model system with regulated transgene expression in the stromal compartment of an experimental carcinoma. These findings point to the stromal compartment as a potential source of new prognostic markers and therapeutic targets and show the utility of the carcinoma-stromal xenograft model system in dissecting specific mechanisms of reactive stroma.

PMID: 12036948 [PubMed - indexed for MEDLINE]

Int J Obes Relat Metab Disord 2002 Jul;26(7):905-11

Hormonal regulation of interleukin-6 production in human adipocytes.

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OBJECTIVE: To elucidate the hormonal regulation of interleukin-6 (IL-6) production by human adipose tissue and its relation to leptin. DESIGN: In vitro study. Human adipocytes were incubated with dexamethasone (with or without RU486), norepinephrine and epinephrine (with or without propranolol), or insulin. MEASUREMENTS: IL-6 and leptin secretion by human adipocytes. RESULTS: A gradual increase in IL-6 secretion by adipocytes during differentiation was observed. A positive correlation was found between basal IL-6 release and both glycerol 3-phosphate dehydrogenase activity--a marker of adipocyte differentiation-and leptin release. Dexamethasone decreased IL-6 secretion and increased leptin secretion in a dose-dependent manner. Both catecholamines increased IL-6 and leptin secretion. The effects of dexamethasone and catecholamines on IL-6 and leptin were abrogated by RU486 and propranolol, respectively. Incubation with insulin resulted in a dose-dependent stimulation of IL-6 and leptin secretion. CONCLUSIONS: IL-6 is produced by human adipocytes and is a potential marker of adipocyte differentiation. Furthermore it is a hormonally regulated cytokine, suppressed by glucocorticoids, and stimulated by catecholamines and insulin in physiological concentrations.

PMID: 12080442 [PubMed - indexed for MEDLINE]

J Biol Chem 2002 Jul 19;277(29):26573-80

Deciphering the phosphorylation "code" of the glucocorticoid receptor in vivo.

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The glucocorticoid receptor (GR) is phosphorylated at multiple serine residues in a hormone-dependent manner, yet progress on elucidating the function of GR phosphorylation has been hindered by the lack of a simple assay to detect receptor phosphorylation in vivo. We have produced antibodies that specifically recognize phosphorylation sites within human GR at Ser(203) and Ser(211). In the absence of hormone, the level of GR phosphorylation at Ser(211) was low compared with phosphorylation at Ser(203). Phosphorylation of both residues increased upon treatment with the GR agonist dexamethasone. Using a battery of agonists and antagonists, we found that the transcriptional activity of GR correlated with the amount of phosphorylation at Ser(211), suggesting that Ser(211) phosphorylation is a biomarker for activated GR in vivo. Mechanistically, the kinetics of Ser(203) and Ser(211) phosphorylation in response to hormone differed, with Ser(211) displaying a more robust and sustained phosphorylation relative to Ser(203). Analysis of GR immunoprecipitates with phospho-GR-specific antibodies indicated that the receptor was phosphorylated heterogeneously at Ser(203) in the absence of hormone, whereas in the presence of hormone, a subpopulation of receptors was phosphorylated at both Ser(203) and Ser(211). Interestingly, biochemical fractionation studies following hormone treatment indicated that the Ser(203)-phosphorylated form of the receptor was predominantly cytoplasmic, whereas Ser(211)-phosphorylated GR was found in the nucleus. Likewise, by immunofluorescence, Ser(203)-phosphorylated GR was located in the cytoplasm and perinuclear regions of the cell, but not in the nucleoplasm, whereas strong phospho-Ser(211) staining was evident in the nucleoplasm of hormone-treated cells. Our results suggest that differentially phosphorylated receptor species are located in unique subcellular compartments, likely modulating distinct aspects of receptor function.

PMID: 12000743 [PubMed - indexed for MEDLINE]

Pharmacotherapy 2002 Jan;22(1):43-53

Hormonal emergency contraception.

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In the 1960s, high-dose estrogen was identified as a highly effective emergency contraceptive but was associated with a high frequency of nausea and vomiting. The combination of low-dose estrogen and a progestin (the Yuzpe regimen) is highly effective and much better tolerated. Recently, a progestin-only regimen containing levonorgestrel was found to be more effective than the Yuzpe regimen and caused significantly less nausea and vomiting. Danazol, an antigonadotropin, is well tolerated but has questionable efficacy Mifepristone has several pharmacologic actions that make it highly effective with an adverse-effect profile similar to that of the Yuzpe regimen. Progress has been made in the last 3 years toward increasing the number of emergency contraceptives that are accessible to women in the United States, and several highly effective options are available. The most effective and well-tolerated regimen available is levonorgestrel. However, the barriers to access and low patient and provider awareness limit the impact of emergency contraception on the rate of unintended pregnancies.

Publication Types:

- Review
- Review, Tutorial

PMID: 11794429 [PubMed - indexed for MEDLINE]

J Steroid Biochem Mol Biol 2002 Jun;81(2):141-6

RU486 antagonizes the inhibitory effect of peroxisome proliferator-activated receptor alpha on interleukin-6 production in vascular endothelial cells.

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Peroxisome proliferator-acitivated receptor alpha (PPARalpha) is a member of nuclear receptor superfamily. Recent studies have shown that the activators for PPARalpha inhibit the expression of some inflammatory molecules in vascular endothelial cells (ECs) and vascular smooth muscle cells, indicating the anti-inflammatory roles of PPARalpha on vascular walls. In this investigation, we showed that RU486, already proved to be an active anti-glucocorticoid and anti-progesterone agent, blocked the inhibition of tumor necrosis factor (TNF)-alpha-stimulated interleukin-6 (IL-6) production by the PPARalpha activator fenofibrate in human umbilical vein ECs. Transient transfection of bovine aortic ECs with an IL-6 promoter construct demonstrated that RU486 blocked the inhibitory effect of fenofibrate on TNF-alpha-induced IL-6 promoter activity. By fluorescence microscopy, RU486 was found to prevent fenofibrate-induced nuclear translocation of PPARalpha. Thus, RU486 has an antagonizing effect on PPARalpha-mediated down-regulation of IL-6 in vascular ECs. This effect may be exerted by its interference with the nuclear translocation of PPARalpha.

PMID: 12137803 [PubMed - indexed for MEDLINE]

Methods Enzymol 2002;346:551-61

Ligand-inducible transgene regulation for gene therapy.

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A synthetic ligand regulable system for gene transfer and expression has been developed in our laboratory based on mechanistic studies of steriod hormone receptor and transcriptional regulation. This gene switch system possesses most of the important features that are required for application of the system in biological research and clinical gene therapy in the future. As the primary ligand tested in this system, mifepristone can effectively turn on the regulatory circuit at doses much lower than those used in the clinic. By modification of the chimeric regulator and its feedback regulatory mode, this system has been optimized to produce very low basal activity with high inducibility in the presence of mifepristone. Also, improvements in regulator composition have been made to minimize immunogenicity and make the system more amenable to human gene therapy. Moreover, incorporation of this gene switch system into the HC-Ad vector system has further enhanced the efficiency of gene transfer and the long-term inducible expression of transgenes. However, for each application within a different biological system, the gene switch needs to be optimized to achieve appropriate inductions. In particular, the method used to deliver the transgenes and adjustment of ligand dosage are critical for in vivo gene expression.

PMID: 11883090 [PubMed - indexed for MEDLINE]

Pharmacology 2002 Apr;64(4):169-75

Regulation of endothelin-1 production in deoxycorticosterone acetate- salt-treated endothelial cells.

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The aim of this study was to investigate the direct effect of deoxycorticosterone acetate (DOCA) on the expression of endothelin-1 (ET-1) mRNA and production of ET-1 peptides in cultured bovine carotid endothelial cells (BCEC) and human umbilical vein endothelial cells (HUVEC). The mineralocorticoid, DOCA, was administered to BCEC and HUVEC with or without additional salt (200 mmol/l). The ET-1 mRNA was elevated to 150% and 180% after a 24-hour incubation with DOCA (5 micromol/l) in BCEC and HUVEC, respectively. Intracellular content of ET-1 peptides of BCEC and HUVEC was increased from 21.66 +/- 0.3 to 23.64 +/- 0.19 fmol/10(5) cells and from 8.38 +/- 0.82 to 11.26 +/- 0.91 fmol/10(5) cells, respectively, in the DOCA-conditioned medium. Also, DOCA treatment for 24 h increased the secretion of ET-1 peptide from 1.62 +/- 0.17 to 5.33 +/- 0.67 fmol/10(5) cells in BCEC and from 0.95 +/- 0.08 to 3.56 +/- 0.36 fmol/10(5) cells in HUVEC. In DOCA-salt-treated endothelium, regulation of ET-1 gene was similar to that with DOCA alone. The DOCA-induced increase in expression of ET-1 mRNA and the ET-1 peptide level were both diminished in dexamethasone (DEX, 10 nmol/l)- or mifepristone (RU486, 0.5 micromol/l)-treated endothelium. These results suggest that DOCA directly increased the ET-1 mRNA expression in endothelium and could be mediated in part by a glucocorticoid receptor pathway which was independent of salt and hyperosmolarity.

PMID: 11893896 [PubMed - indexed for MEDLINE]

Eur J Obstet Gynecol Reprod Biol 2001 Oct;98(2):152-9

Progesterone and ovulation.

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The role of progesterone (P) in the mechanism of ovulation is controversial at best. The contraceptive application of P was established in rodents in 1936 and with orally absorbed progestogenes was put to human use. There were hints on the proovulatory actions of P administered before the time of ovulation in rats by 1948. Similarly, in 1954 the observation of high P level in the preovulatory follicle pointed to a role in ovulation. Neither of these two observations was further investigated and the positive feedback effect of P exerted on gonadotropins was described in 1968. Still the positive feedback between P and gonadotropins were not recognized as a physiologic mechanism, much less utilized pharmacologically. The apparent contradiction between these two different actions of P continues upto now. The paper sets out to expose this controversy and tries to resolve it using extensive literary data and the author's experiences with synthetic progestogenes in contraception, in the treatment of infertility and with the antigestagen mifepristone in blocking ovulation. The precise mechanisms lying behind these applications are explored and discussed in detail. The putative role of oestradiol (E2) in the mechanism of eliciting the gonadotropin surge is extensively discussed but refuted as the ovulatory signal. The time sequence between the rise of P and gonadotropins contradicts the common wisdom of LH causing luteinization. The positive feedback effect of P on the E2 sensitized ovulatory axis on the hypothalamic and pituitary level is discussed and its local role in the mechanism of follicular rupture is also taken into account. The final proof seems to be the antiovulatory effect of mifepristone, which blocked both GnRH pulsatility, pituitary sensitivity to GnRH and follicular rupture in several experiments. Thus, the dogma of LH peak causing follicular rupture and subsequent luteinization seems questionable, the putative role of E2 to initiate the ovulatory cascade has to be discarded and P's role as a trigger of the physiological mechanisms leading to ovulation should be firmly recognized.

Publication Types:

- Review
- Review, Tutorial

PMID: 11574124 [PubMed - indexed for MEDLINE]

J Med Chem 2002 Sep 26;45(20):4379-82

6-Aryl-1,4-dihydro-benzo[d][1,3]oxazin- 2-ones: a novel class of potent, selective, and orally active nonsteroidal progesterone receptor antagonists.

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Novel 6-aryl-1,4-dihydro-benzo[d][1,3]oxazin-2-ones were synthesized and tested as progesterone receptor (PR) antagonists. These compounds were potent and showed good selectivity for PR over other steroid receptors such as the glucocorticoid and androgen receptors (e.g., greater than 80-fold selectivity at PR for 4h). Numerous 6-aryl benzoxazinones (e.g., 4h-j) were active orally in the uterine decidualization and component C3 assays in the rats. In these in vivo models,4h had potencies comparable to mifepristone.

PMID: 12238914 [PubMed - indexed for MEDLINE]

Eur J Pharmacol 2001 Nov 23;431(3):365-71

Beclomethasone, budesonide and fluticasone propionate inhibit human neutrophil apoptosis.

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Inhaled glucocorticoids are widely used to treat chronic obstructive pulmonary disease without much evidence of efficiency in this disease where neutrophils may contribute to the pathophysiology. This prompted us to test the effects of several currently used inhaled and systemic glucocorticoids on human neutrophil apoptosis. Beclomethasone, budesonide, dexamethasone, fluticasone propionate, hydrocortisone and prednisolone inhibited apoptosis in a concentration-dependent manner as assessed by flow cytometric analysis, annexin-V binding and morphological analysis. The maximal inhibition of apoptosis was 50-60%. The order of potency was fluticasone propionate (EC(50) 0.6+/-0.2 nM) approximately equal to budesonide (EC(50) 0.8+/-0.2 nM)> dexamethasone approximately equal to prednisolone approximately equal to beclomethasone approximately equal to hydrocortisone. The inhibitory effects of glucocorticoids were reversed by mifepristone. Moreover, glucocorticoids slightly enhanced the inhibitory effect of granulocyte-macrophage colony-stimulating factor (GM-CSF) on neutrophil apoptosis. The present data suggests that budesonide and fluticasone propionate prolong human neutrophil survival by inhibiting apoptosis at clinically relevant drug concentrations via an effect on glucocorticoid receptor.

PMID: 11730731 [PubMed - indexed for MEDLINE]

Life Sci 2002 Aug 16;71(13):1523-34

Divergent effect of mometasone on human eosinophil and neutrophil apoptosis.

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Mometasone is a potent synthetic glucocorticoid, which is under development as an inhaled preparation for the treatment of asthma. Previous studies have suggested that glucocorticoids have direct effects on human eosinophil and neutrophil apoptosis. The present study was designed to characterize the effects of mometasone on constitutive apoptosis and cytokine-afforded survival in isolated human eosinophils and neutrophils. The isolated eosinophils or neutrophils were cultured in vitro, and apoptosis was assessed by flow cytometric analysis of relative DNA content, by annexin-V binding and morphological analysis. Mometasone enhanced constitutive human eosinophil apoptosis in a concentration-dependent manner. The maximal enhancement of eosinophil apoptosis was 2.1-fold with an EC(50) value of 5.63 +/- 2.33 nM. This enhancing effect was reversed by the glucocorticoid receptor antagonist, mifepristone. In the presence of added cytokines, mometasone reversed tumor necrosis factor -alpha-induced eosinophil survival but not that afforded by interleukin -5. In contrast, mometasone inhibited human neutrophil apoptosis in a concentration-dependent manner. The maximal inhibition of neutrophil apoptosis was 50% with an EC(50) value of 0.17 +/- 0.03 nM. The inhibitory effect was partly reversed by mifepristone. In the presence of added cytokines, mometasone further enhanced neutrophil survival induced by the granulocyte-macrophage colony-stimulating factor and leukotriene B(4). The present data suggests that mometasone has opposite effects on apoptosis of human eosinophils and neutrophils at clinically relevant drug concentrations via an effect on glucocorticoid receptor.

PMID: 12127907 [PubMed - indexed for MEDLINE]

Zhonghua Fu Chan Ke Za Zhi 2002 Apr;37(4):220-2

[Apoptosis and expression of relative genes in early pregnant chorionic villi and decidua]

[Article in Chinese]

Zhang Y, Chen G, Liu Y, Fu G.

Department of Obstetrics and Gynecology, The Third Medical School, Peking University, Beijing 100083, China.

OBJECTIVE: To investigate the effects of mifepristone on apoptosis and expression of relative genes in early pregnant chorionic villi and decidua. METHODS: The specimen of early pregnant chorionic villi and decidua obtained from 10 cases of requesting termination of pregnancy by curettage, 20 cases of mifepriston contragestation. The paraffin sections were used to determine apoptotic cells by TdT-mediated dUTP-biotin nick end labeling method, to identify bcl-2, bax, fas, fasL and proliferating cell nuclear antigen (PCNA) by immunohistochemistry, to demonstrate fas and fasL mRNA by in situ hybridization. RESULTS: In normal early pregnant specimens, apoptotic cells were mainly observed in syncytiotrophoblast, but not in cytotrophoblast cells, occasionally seen in decidua cells. The antigen of bax, fas, fasL were present in syncytiotrophoblast cells and decidua with lower amount. While bcl-2 antigen staining was strong in cytotrophoblastic cells and in decidua. PCNA protein was present in cytotrophoblastic and decidual cells only. In the specimens treated with mifepristone, apoptotic cells were increased in syncytiotrophoblastic cells of villi and visualized in decidua cells. The expression of fas, fasL and bax was also higher than that of normal. CONCLUSIONS: Mifepristone increased apoptosis in syncytiotrophoblastic and decidua cells, but had no effect on the expression of bcl-2 and PCNA.

PMID: 12133415 [PubMed - indexed for MEDLINE]

J Clin Endocrinol Metab 2002 Jun;87(6):2514-9

Long-term progestin treatment inhibits RANTES (regulated on activation, normal T cell expressed and secreted) gene expression in human endometrial stromal cells.

Zhao D, Lebovic DI, Taylor RN.

Center for Reproductive Science, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California-San Francisco, Box 0556, San Francisco, CA 94143-0556, USA.

RANTES (regulated on activation, normal T cell expressed and secreted) is synthesized by endometrial and endometriotic stromal cells and circulates in peritoneal fluid. Reports indicate that medroxyprogesterone acetate (MPA) is clinically effective in alleviating pelvic pain in the majority of endometriosis patients, which leads us to hypothesize that MPA may be antiinflammatory. Prolonged treatment (8 d) with MPA resulted in 36% and 50% decreases in luciferase activity and RANTES protein production, respectively, whereas shorter treatment (2 or 4 d) with MPA had no significant effect. We also observed that 8 d of MPA increased PR expression. Both effects were blocked by RU486. Cotransfection of endometrial stromal cells with PR enhanced the effects mediated by endogenous PR. In addition, its action via progesterone response element cis-elements, PR appeared to inhibit trans-activation of a nuclear factor-kappaB-responsive element, further suppressing RANTES expression. These studies indicate that prolonged progestin exposure down-regulates endometrial RANTES gene transcription in vitro. The effect is PR dependent and mediated in part through a nuclear factor-kappaB pathway. The clinical effectiveness of chronic progestin treatment in endometriosis-associated pelvic pain may be attributed to its inhibition of RANTES production and its suppression of inflammatory responses in the pelvis.

PMID: 12050207 [PubMed - indexed for MEDLINE]

ATTACHMENT 12

Not For Public Release
Status Report
Post Marketing Study Commitment

Date of Report:	December 2002
Applicant Name:	Population Council
Product Name:	Mifeprex® (mifepristone) Tablets (Oral), 200 mg
Application Number:	NDA 20-687
Date of Application Approval:	September 28, 2000
Date of Post Marketing Study Commitment:	September 28, 2000
Description of Post Marketing Study Commitment:	Two studies are to be conducted. ***Study 1*** – A cohort-based study of safety outcomes of patients having medical abortions under the care of physicians who provide surgical intervention compared to physicians who refer their patients for surgical intervention. 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. ***Study 2*** – A surveillance study on outcomes of ongoing pregnancies.
Original Schedule for Post Marketing Study Commitment:	Final protocols for both studies to be submitted within six months of NDA approval.

Current Status of Post Marketing Study Commitment: *PENDING*

Explanation of Status Of Studies: ***Study 1 -***

Study Status – *Pending*
Explanation of Status – Protocol was resubmitted to FDA on January 25, 2002. The final protocol was submitted to FDA on November 8, 2002. Enrollment will begin when national sales of mifepristone support selection of the study sample.

As in the first year, the majority of the sales in the second year of distribution have been to (b) (4) (b) (4) (b) (4) almost all of which provide their own surgical services. Currently, sales volume of mifepristone is too small to allow for the selection of a cohort of providers of mifepristone medical abortion who would refer their patients when surgical intervention is required.

In order to establish the referring/non-referring status of providers, we will be sending a letter to all Mifeprex® providers. We anticipate that the number of referring providers may be too small to support selection of the study sample this year.

Study 2 –

Study Status – *Pending*
Explanation of Status – We are currently revising the protocol in response to comments sent to us by FDA on April 1, 2002.

We are also in the process of making final revisions on study forms. We anticipate that the study will begin in the first quarter of 2003.

ATTACHMENT 13

For Public Release
Status Report
Post Marketing Study Commitment

Date of Report: December 2002

Applicant Name: Population Council

Product Name: Mifeprex® (mifepristone) Tablets (Oral), 200 mg

Application Number: NDA 20-687

Date of Application Approval: September 28, 2000

Commitment #1:

Commitment Date: September 28, 2000

Commitment: A cohort-based study of safety outcomes of patients having medical abortions under the care of physicians who provide surgical intervention compared to physicians who refer their patients for surgical intervention. 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.

Current Status: Pending

Explanation of Status: Discussion between the FDA and the Population Council on the final protocol are in process. Enrollment will begin when national sales of mifepristone support selection of the study sample.

Commitment #2

Commitment Date: September 28, 2000

Commitment: A surveillance study on outcomes of ongoing pregnancies.

Current Status: Pending

Explanation of Status: The final protocol has been submitted to the FDA. It is anticipated that the study will begin in the first quarter of 2003.

ATTACHMENT 14

STATUS REPORT OF OTHER POST MARKETING STUDIES – ONGOING STUDIES

STUDY STATUS SUMMARY (I) – SEPTEMBER 27, 2002

Study Title: Mifepristone-misoprostol medical abortion: Simplifying the regimen

Protocol Number: 205-US

Study Phase:

Date of Study Initiation: February 1, 2001

Study Status (Ongoing/Completed/Discontinued): Ongoing

Investigator(s)/Study Center(s):

1) (b) (4), (b) (6)
2)
3)
4)
5)

Objective: To investigate the safety, efficacy and acceptability of a simplified regimen of mifepristone-misoprostol medical abortion, including home administration of misoprostol and a lower dose of mifepristone (200 mg).

Study Design: Prospective, non-comparative trial

Drugs:

Investigational Drug: Mifepristone + Misoprostol

Control Drug: None

Dosage: 200 mg oral mifepristone, 400 µg oral misoprostol (2 days later)

Description of Patients: Pregnant women with gestations under 49 days LMP

STUDY STATUS SUMMARY (I) – SEPTEMBER 27, 2002 (CONT.)

Number of Patients

Planned:	370
Enrolled:	361
Age Range:	18 - 45
Gender:	female
Race:	n/a
Dropped:	0
Completed:	361

Safety Variables: Frequency of blood transfusion, administration of IV fluids and hospitalization

Efficacy Variables: Success, complete abortion without a surgical intervention

Safety Results:

Blood transfusion	= 0
Administration IV fluids	= 2
Hospitalization	= 1

Efficacy Results: Success = 92.8% (284/306)

Results still preliminary. Final results to be calculated in coming months.

STATUS REPORT OF OTHER POST MARKETING STUDIES – ONGOING STUDIES

STUDY STATUS SUMMARY (II) – SEPTEMBER 27, 2002

Study Title: Mifepristone-misoprostol medical abortion: Simplifying the regimen

Protocol Number: 205-Eastern Europe

Study Phase:

Date of Study Initiation: December 2001

Study Status (Ongoing/Completed/Discontinued): Ongoing

Investigator(s)/Study Center(s):

(b) (4), (b) (6)

Objective: To investigate the safety, efficacy and acceptability of a simplified regimen of mifepristone-misoprostol medical abortion, including home administration of misoprostol and a lower dose of mifepristone (200 mg).

Study Design: Prospective, non-comparative trial

Drugs:

Investigational Drug: Mifepristone + Misoprostol

Control Drug: None

Dosage: 200 mg oral mifepristone, 400 µg oral misoprostol (2 days later)

Description of Patients: Pregnant women with gestations under 56 days LMP

STUDY STATUS SUMMARY (II) – SEPTEMBER 27, 2002 (CONT.)

Number of Patients

Planned:	500 (200, Albania; 100, Latvia; 100, Lithuania; 100, Slovakia)
Enrolled:	200 (200, Albania)
Age Range:	18 - 45
Gender:	female
Race:	n/a
Dropped:	0
Completed:	200

Safety Variables: Frequency of blood transfusion, administration of IV fluids and hospitalization

Efficacy Variables: Success, complete abortion without a surgical intervention

Safety Results:

Blood transfusion	= 0
Administration IV fluids	= 0
Hospitalization	= 0

Efficacy Results: Success = 98.0% (196/200)

Results still preliminary.

STATUS REPORT OF OTHER POST MARKETING STUDIES – ONGOING STUDIES

STUDY STATUS SUMMARY (III) – SEPTEMBER 27, 2002

Study Title: Mifepristone-misoprostol medical abortion: Simplifying the regimen

Protocol Number: 205-India

Study Phase:

Date of Study Initiation: July 2002

Study Status (Ongoing/Completed/Discontinued): Ongoing

Investigator(s)/Study Center(s):

(b) (4), (b) (6)

Objective: To investigate the safety, efficacy and acceptability of a simplified regimen of mifepristone-misoprostol medical abortion, including home administration of misoprostol and a lower dose of mifepristone (200 mg).

Study Design: Prospective, non-comparative trial

Drugs:

Investigational Drug: Mifepristone + Misoprostol

Control Drug: None

Dosage: 200 mg oral mifepristone, 400 µg oral misoprostol (2 days later)

Description of Patients: Pregnant women with gestations under 56 days LMP.

Number of Patients

Planned: 400
Enrolled: 50
Age Range: 18 - 45
Gender: female
Race: n/a

STUDY STATUS SUMMARY (III) – SEPTEMBER 27, 2002 (CONT.)

Dropped:	0
Completed:	50

Safety Variables: Frequency of blood transfusion, administration of IV fluids and hospitalization

Efficacy Variables: Success, complete abortion without a surgical intervention

Safety Results:

Blood transfusion	= 0
Administration IV fluids	= 0
Hospitalization	= 0

Efficacy Results: Success = 80%

Results preliminary.

STATUS REPORT OF OTHER POST MARKETING STUDIES – ONGOING STUDIES

STUDY STATUS SUMMARY (IV) – SEPTEMBER 27, 2002

Study Title: Mifepristone-misoprostol medical abortion: Expanding access and increasing autonomy

Protocol Number: 283

Study Phase:

Date of Study Initiation: June 2001, France
December 2001, Sweden

Study Status (Ongoing/Completed/Discontinued): Ongoing

Investigator(s)/Study Center(s):

(b) (4), (b) (6)

Objective: To investigate the safety, efficacy and acceptability of a regimen of mifepristone-misoprostol medical abortion which includes 200 mg mifepristone (600 mg in Sweden) and two doses of 400 µg misoprostol given 2 days apart (1 and 3 days following administration of mifepristone).

Study Design: Prospective, non-comparative trial

Drugs:

Investigational Drug: Mifepristone + Misoprostol

Control Drug: None

Dosage: 200 mg oral mifepristone, 2 doses 400 µg oral misoprostol (1 and 3 days later)

Description of Patients: Pregnant women with gestations under 56 days LMP

Number of Patients

Planned: 250 (100, Austria; 100, Sweden; 50, France)
Enrolled: 102 (52, Sweden; 50, France)

STUDY STATUS SUMMARY (IV) – SEPTEMBER 27, 2002 (CONT.)

Age Range:	18 - 45
Gender:	female
Race:	n/a
Dropped:	0
Completed:	102

Safety Variables: Frequency of blood transfusion, administration of IV fluids and hospitalization

Efficacy Variables: Success, complete abortion without a surgical intervention

Safety Results:

Blood transfusion	= 0
Administration IV fluids	= 0
Hospitalization	= 0

Efficacy Results: Success = 100.0% (102/102)

Results still preliminary.

STATUS REPORT OF OTHER POST MARKETING STUDIES – ONGOING STUDIES

STUDY STATUS SUMMARY (V) – SEPTEMBER 27, 2002

Study Title: Mifepristone-Induced Cervical Softening Prior to Hysteroscopy

Protocol Number: 290 (The Population Council is the sponsor of this study. The investigational drug was provided by Exelgyn, Paris, France)

Study Phase:

Date of Study Initiation: December 25, 2001

Study Status (Ongoing/Completed/Discontinued): **Ongoing**

Investigator(s)/Study Center(s):

1) (b) (4), (b) (6)

Objective: The objective of this study is to determine whether mifepristone produces cervical softening and dilation in non-pregnant women who require hysteroscopy for a medical indication.

Study Design: Randomized double blind placebo controlled study

Drugs:

Investigational Drug: Mifegyne® from Exelgyn

Control Drug: Placebo

Dosage: 200 mg oral mifepristone or placebo

Description of Patients: Normal non-pregnant women who are scheduled to undergo hysteroscopy for a medical indication.

Number of Patients

Planned:	60 (30 treated and 30 placebos)
Enrolled:	56
Age Range:	18 - 50
Gender:	female
Race:	n/a
Dropped:	0
Completed:	56

STUDY STATUS SUMMARY (V) – SEPTEMBER 27, 2002 (CONT.)

Safety Variables:	Follow normal safety evaluation. (The double blind code will be broken in case of an adverse event, which might threaten the women's health.)
Efficacy Variables:	As a result of the study treatment there may be a reduction in pain which normally occurs with a hysteroscopy procedure.
Safety Results:	No adverse events were reported.
Efficacy Results:	Since this is a double blind study its premature to determine the effectiveness of this study until the study is completed and the code is broken.

STATUS REPORT OF OTHER POST MARKETING STUDIES – ONGOING STUDIES

STUDY STATUS SUMMARY (VI) – SEPTEMBER 27, 2002

Study Title: A randomized study of buccal versus vaginal misoprostol administration 24 to 48 hours after mifepristone (200 mg) for abortion up to 56 days LMP

Protocol Number: 302

Study Phase:

Date of Study Initiation: December 31, 2001

Study Status (Ongoing/Completed/Discontinued): Ongoing

Investigator(s)/Study Center(s):

1) [redacted] (b) (4), (b) (6)

Objective: To compare the safety, efficacy and acceptability of two regimens of mifepristone-misoprostol medical abortion, 800 µg buccal misoprostol and 800 µg vaginal misoprostol given 24 to 48 hours following administration of 200 mg mifepristone.

Study Design: Randomized, comparative trial

Drugs:

Investigational Drug: Mifepristone + Misoprostol

Control Drug: None

Dosage: 200 mg oral mifepristone, 800 µg buccal or vaginal misoprostol (1 to 2 days later)

Description of Patients: Pregnant women with gestations under 56 days LMP

Number of Patients

Planned:	442
Enrolled:	141
Age Range:	18 - 45
Gender:	female
Race:	n/a

STUDY STATUS SUMMARY (VI) – SEPTEMBER 27, 2002 (CONT.)

Dropped:	0
Completed:	141
Safety Variables:	Frequency of blood transfusion, administration of IV fluids and hospitalization
Efficacy Variables:	Success, complete abortion without a surgical intervention
Safety Results:	Blood transfusion = 0 Administration IV fluids = 1 Hospitalization = 0
Efficacy Results:	Success = 95.5 (800 µg buccal misoprostol, n = 66) 90.0 (800 µg vaginal misoprostol, n = 67) Results still preliminary.

STATUS REPORT OF OTHER POST MARKETING STUDIES – ONGOING STUDIES

STUDY STATUS SUMMARY (VII) – SEPTEMBER 27, 2002

Study Title: Mifepristone followed in 24 to 48 hours by misoprostol for late first trimester abortion (between 9 and 12 weeks LMP)

Protocol Number: 313

Study Phase:

Date of Study Initiation: May 31, 2002

Study Status (Ongoing/Completed/Discontinued): Ongoing

Investigator(s)/Study Center(s):

1) (b) (4), (b) (6)
2)

Objective: To examine the safety, efficacy and acceptability of a regimen of 200 mg mifepristone and 800 µg misoprostol (and up to two additional doses of 400 µg oral misoprostol every 3 to 4 hours following the initial dose, where necessary) for termination of gestations 64 to 84 days LMP.

Study Design: Prospective, non-comparative trial

Drugs:

Investigational Drug: Mifepristone + Misoprostol

Control Drug: None

Dosage: 200 mg oral mifepristone, 800 µg vaginal misoprostol 1 to 2 days later. Up to 2 additional doses of 400 µg oral misoprostol every 3 to 4 hours following initial dose, where necessary.

Description of Patients: Pregnant women with gestations under 64 to 84 days LMP

Number of Patients

Planned: 250
Enrolled: 18
Age Range: 18 - 45
Gender: female
Race: n/a

STUDY STATUS SUMMARY (VII) – SEPTEMBER 27, 2002 (CONT.)

Dropped:	0
Completed:	18 (15, Rochester; 3, India)
Safety Variables:	Frequency of blood transfusion, administration of IV fluids and hospitalization
Efficacy Variables:	Success, complete abortion without a surgical intervention
Safety Results:	Blood transfusion = 0 Administration IV fluids = 0 Hospitalization = 0
Efficacy Results:	Success = 88.9% (16/18)

Results still preliminary.

ATTACHMENT 15

STATUS REPORT OF OTHER POST MARKETING STUDIES – COMPLETED STUDIES

STUDY STATUS SUMMARY (I) – SEPTEMBER 27, 2002

Study Title: Mifepristone-misoprostol medical abortion: Simplifying the regimen

Protocol Number: 205-Vietnam

Study Phase:

Date of Study Initiation: January 1, 2001

Study Status (Ongoing/Completed/Discontinued): Completed

Investigator(s)/Study Center(s):

(b) (4), (b) (6)

Objective: To investigate the safety, efficacy and acceptability of a simplified regimen of mifepristone-misoprostol medical abortion, including home administration of misoprostol and a lower dose of mifepristone (200 mg).

Study Design: Prospective, non-comparative trial

Drugs:

Investigational Drug: Mifepristone + Misoprostol

Control Drug: None

STUDY STATUS SUMMARY (I) – SEPTEMBER 27, 2002 (CONT.)

Dosage: 200 mg oral mifepristone, 400 µg oral misoprostol (2 days later)

Description of Patients: Pregnant women with gestations under 56 days LMP

Number of Patients

Planned:	1600
Enrolled:	1560
Age Range:	18 - 45
Gender:	female
Race:	n/a
Dropped:	0
Completed:	1560

Safety Variables: Frequency of blood transfusion, administration of IV fluids and hospitalization

Efficacy Variables: Success, complete abortion without a surgical intervention

Safety Results:

Blood transfusion	= 0
Administration IV fluids	= 0
Hospitalization	= 0

Efficacy Results: Success

Home users: 88.3 (1178)
Clinic users: 93.3 (167)

Results still preliminary. Final results to be calculated in coming months.

STATUS REPORT OF OTHER POST MARKETING STUDIES – COMPLETED STUDIES

STUDY STATUS SUMMARY (II) – SEPTEMBER 27, 2002

Study Title: Comparison of abortions induced by mifepristone followed by vaginal versus oral misoprostol up to 56 days gestation

Protocol Number: 298

Study Phase:

Date of Study Initiation: February 27, 2001

Date of IND Submission: June 19, 2001 (Submission Serial Number 216)

Study Status (Ongoing/Completed/Discontinued): Completed

Investigator(s)/Study Center(s):

(b) (4), (b) (6)

1)
2)
3)
4)
5)

Objective: To compare the safety, efficacy and acceptability of three regimens of mifepristone-misoprostol medical abortion, 400 µg oral misoprostol, 600 µg oral misoprostol and 800 µg vaginal misoprostol given 24 to 48 hours following administration of 200 mg mifepristone.

Study Design: Randomized, comparative trial

Drugs:

Investigational Drug: Mifepristone + Misoprostol

Control Drug: None

Dosage: 200 mg oral mifepristone, 400 µg oral misoprostol or 600 µg oral misoprostol or 800 µg vaginal misoprostol (1 to 2 days later)

Description of Patients: Pregnant women with gestations under 56 days LMP

STUDY STATUS SUMMARY (II) – SEPTEMBER 27, 2002 (CONT.)

Number of Patients

Planned:	1500
Enrolled:	971*
Age Range:	18 - 45
Gender:	female
Race:	n/a
Dropped:	0
Completed:	971

Safety Variables: Frequency of blood transfusion, administration of IV fluids and hospitalization

Efficacy Variables: Success, complete abortion without a surgical intervention

Safety Results:

Blood transfusion	= 1
Administration IV fluids	= 2
Hospitalization	= 1
Death	= 1

Efficacy Results: Success =

94.7 ± 2.5 (400 µg oral misoprostol, n =302)

92.7 ± 3.0 (600 µg oral misoprostol, n=294)

94.1 ± 2.6 (800 µg vaginal misoprostol, n=301)

Results still preliminary.

* Please note the enrollment figure of 940 as reported in the last annual report for NDA 20-687 dated December 14, 2001 was a preliminary enrollment figure.

POPULATION COUNCIL/DANCO LABORATORIES, LLC

ANNUAL REPORT FOR MIFEPRISTONE TABLETS, 200 mg

NDA # 20-687

TIME PERIOD COVERED: SEPTEMBER 28, 2001 –SEPTEMBER 27, 2002

TABLE OF CONTENTS

9(a) SUMMARY OF SIGNIFICANT NEW INFORMATION

A "Dear Health Care Provider" letter, developed with the FDA was sent to all current Mifeprex® providers and to new providers thereafter. See Attachment 1.

During the reporting period, Supplement S-001 was filed to extend the expiration dating of Mifeprex from 18 months to 24 months. This Supplement was approved on March 29, 2002.

The approval letter for this product waived the pediatric requirement so no information on that subject is reported.

Danco has received information, from Laboratoires Exelgyn and from certain clinical investigators conducting studies under their own INDs, which, although not required to be reported as periodic or 15-day reports, may constitute "significant new information...that might affect the safety...of the drug product." That information is included as Attachment 2 and Attachment 3 respectively.

9(b) DISTRIBUTION DATA

During the period of this report, a total of (b) (4) batches were released for distribution. The standard theoretical batch size is (b) (4) tablets (equivalent to (b) (4) patient packs containing three tablets each). The NDC number for Mifepristone Tablets, 200 mg is 64875-001-03. A summary of the commercial distribution data for the reporting period is tabulated below.

DISTRIBUTION DATA FOR MIFEPRISTONE TABLETS, 200 mg

NDC 64875-001-03	# of patient packs (3 tablets/pack)
# patient packs shipped	(b) (4)
# patient packs returned (short dating)	
Net # shipped	(b) (4)

9(c) LABELING

There were no changes in the labeling during the reporting period.

Immediately following are samples of the printed foil, package insert, package carton, patient brochure and medication guide.

NDA 20-687
Sample of Aluminum Foil
September 2002

MIFEPREX™

(mifepristone) Tablets, 200 mg

For Oral Administration Only

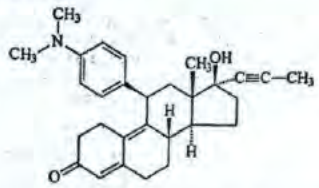
If Mifeprex* results in incomplete abortion, surgical intervention may be necessary. Prescribers should determine in advance whether they will provide such care themselves or through other providers. Prescribers should also give patients clear instructions on whom to call and what to do in the event of an emergency following administration of Mifeprex.

Prescribers should make sure that patients receive and have an opportunity to discuss the Medication Guide and the PATIENT AGREEMENT.

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 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);
- 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
(see CONTRAINDICATIONS)

1. Bleeding

Vaginal bleeding occurs in almost all patients during the treatment procedure. According to data from the U.S. and French trials, women should expect to experience 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.

In some cases, excessive bleeding may require treatment by 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. Confirmation of Pregnancy Termination

Patients should be scheduled for and return for a follow-up visit at approximately 14 days after administration of mifepristone to confirm that the pregnancy is completely terminated and to assess the degree of bleeding. Vaginal bleeding is not evidence of the termination of pregnancy. Termination can be confirmed by clinical examination or ultrasonographic scan. Lack of bleeding following treatment, however, usually indicates failure. Medical abortion failures should be managed with surgical termination.

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. 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 or heavy vaginal bleeding is not proof of a complete expulsion;
- 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

Over 620,000 women in Europe have taken mifepristone in combination with a prostaglandin to terminate pregnancy. Among these 620,000 women, about 415,000 have received mifepristone together with misoprostol. As of May 2000 a total of 82 cases have 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

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 retardation, 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 anti-progestational 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 1% in the U.S. and French trials are shown in Table 3.

Bleeding and 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, Bleeding for additional information). Women also typically experience abdominal pain, including uterine cramping. Other commonly reported side effects were nausea, vomiting and diarrhea. Pelvic pain, fainting, headache, dizziness, and asthenia occurred rarely. 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
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.

OVERDOSAGE

No serious adverse reactions were reported in tolerance studies in [illegible] where mifepris- overdose, she should be observed closely for signs of adrenal failure.

The oral acute LD50 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 healthcare 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 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 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 the most important information I should know about Mifeprex?

Mifeprex is used to end an early pregnancy. 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. By using Mifeprex, you probably will not need a surgical procedure to end your pregnancy.

When you use Mifeprex, you also need to take another medicine called misoprostol. You take misoprostol 2 days after you take Mifeprex.

You need to sign a statement (PATIENT AGREEMENT). Before you get Mifeprex, you will need to read and understand the information in this Medication Guide. Then you will need to sign a statement that you have decided to end your pregnancy.

You must visit your provider on Day 1, Day 3, and about Day 14. See the section called "How should I take Mifeprex?" for information about what happens at each visit. If you do not follow all the steps in "How should I take Mifeprex?" you will not know if your pregnancy has ended.

What to do if you are still pregnant after Mifeprex or 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.

Symptoms to expect. This treatment causes cramping and bleeding. 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.

If you are not already bleeding after taking Mifeprex, you probably will begin to bleed once you take misoprostol. This is a 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 that come from your uterus. This is an expected part of ending the pregnancy.

Heavy bleeding and the need for surgery. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (curettage) to stop it. This is why you must talk with your provider about what to do if you need emergency care to stop heavy and possibly dangerous bleeding.

Before you take Mifeprex. Your provider will give you a telephone number to call if you have any questions, concerns, or problems. Your provider will also give you the name and phone number of who will handle emergencies.

Talk with your provider. You and your provider should discuss the benefits and risks for you of using Mifeprex.

What is Mifeprex?

Mifeprex blocks a hormone needed for your pregnancy to continue. When used together with another medicine called misoprostol, Mifeprex ends your pregnancy. About 5-8 out of 100 women taking Mifeprex will need a surgical procedure to end the pregnancy or to stop too much bleeding.

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:**
  - Your provider will check to see if you are still pregnant.
  - If you are still pregnant, take 2 misoprostol tablets.
  - Misoprostol may cause cramps, nausea, diarrhea, and other symptoms. Your health care 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 2 weeks after you took 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?

You should not take certain other medicines, because they may interfere with the treatment. Ask your provider about what medicines you can take for pain. 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.

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

What are the possible side effects of using Mifeprex?

See the section "What is the most important information I should know about Mifeprex?" for symptoms to expect.

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

Other side effects of the 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.

If you are worried about any side effects you have, talk with your provider about them. Your provider will give you a telephone number to call if you have any questions, concerns, or problems. Your provider's telephone number is _____.

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 US Food and Drug Administration.

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.
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 the 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:

- 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: _____

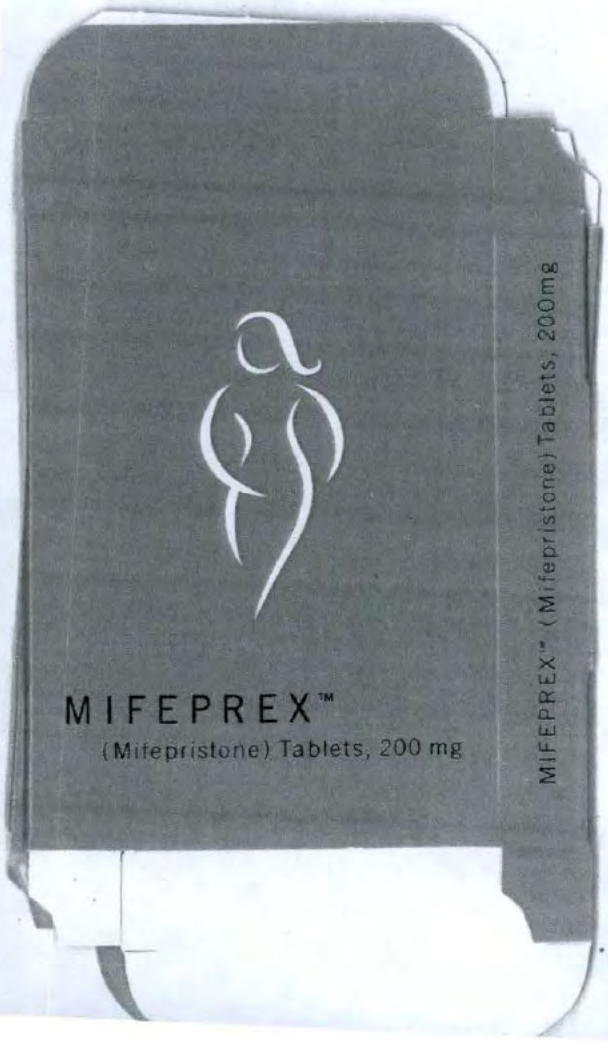
Name of Provider print: _____

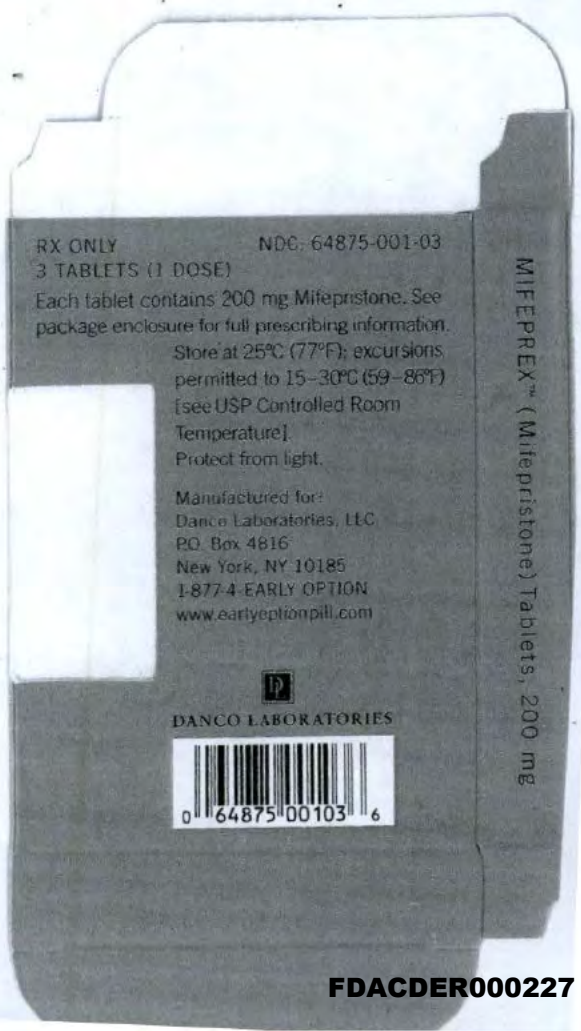
Date: _____

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.

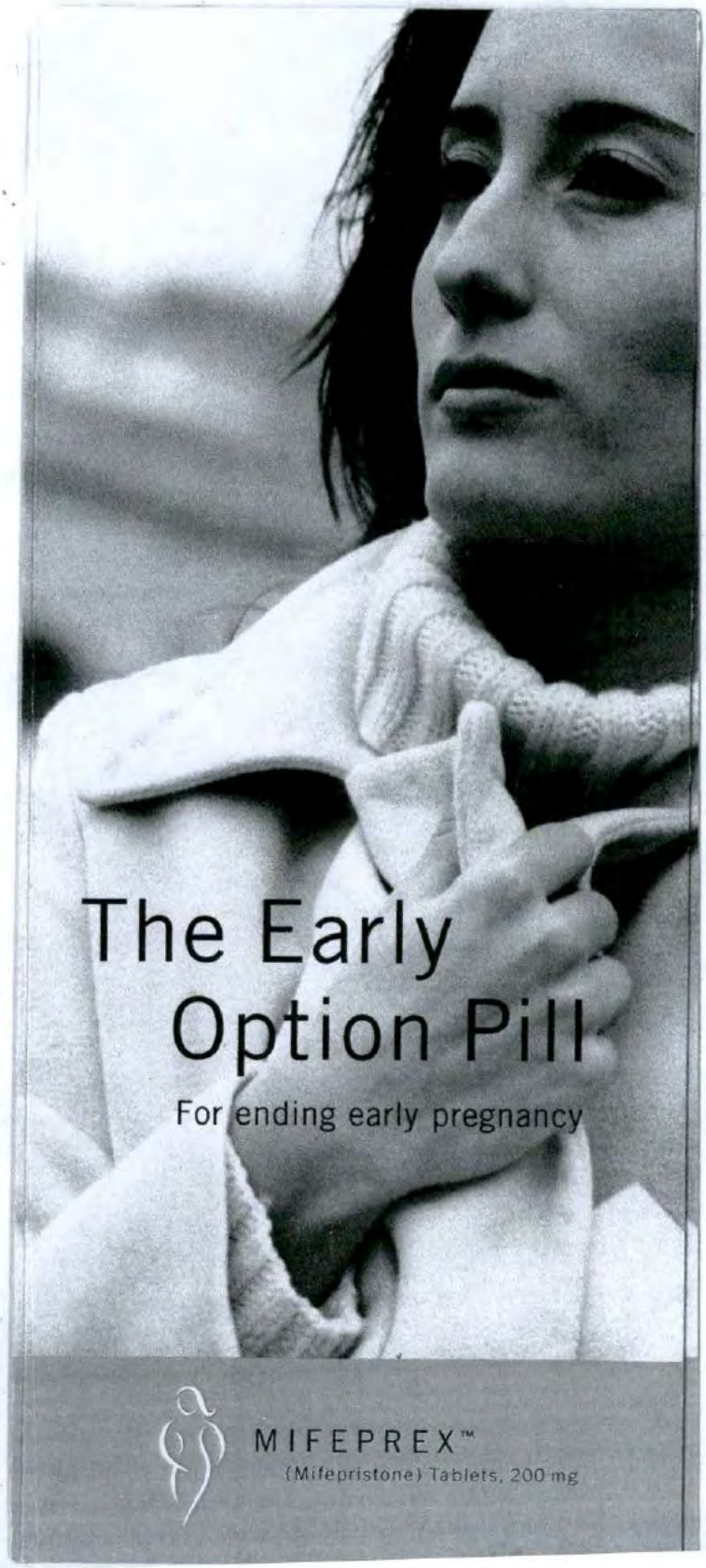
12/08/00 Rev. 1

NDA 20-687
Sample of Package Carton
September 2002





NDA 20-687
Sample of Patient Brochure
September 2002



PRIVATE OPTION

How is Mifeprex provided?

Mifeprex is provided through a doctor's office or clinic. The early option pill can be taken only during the first seven weeks of pregnancy. You make three visits over a two-week period. At the first visit, you receive the Medication Guide (to help you understand how the early option works), counseling and sign a statement that you have decided to end your pregnancy. You then take three tablets, each containing 200 milligrams of Mifeprex.

Two days later, you return and take two tablets each containing 200 micrograms of misoprostol. A follow-up visit approximately 12 days later is very important to check that the pregnancy has ended because if it has not ended, there is a chance that there may be birth defects. A few women who take Mifeprex will need a surgical procedure to end the pregnancy or to stop heavy bleeding. Your health care provider will communicate to you how s/he has planned to handle this possibility.

Mifeprex offers you a more private option, with support and counseling readily available throughout the process. Your provider will give you a name and number to call if you have any questions and, if different, a name and number to call in an emergency.

Where do I get more information?

For more information on Mifeprex*,
please contact the Mifeprex hotline by phone at:
1-877-4 Early Option (1-877-432-7596)

Or find us on the Internet at: www.earlyoptionpill.com

The Early Option Pill

For ending early pregnancy

* Mifeprex is a trademark of Danco Laboratories, LLC.

DANCO LABORATORIES

MIFEPREX™
(Mifepristone) Tablets, 200 mg

FDACDER000229

The Early Option Pill

What is Mifeprex ?

Mifeprex is a new option for American women. It is the first Food and Drug Administration (FDA) approved early option pill for ending early pregnancy. Mifeprex followed by misoprostol is a safe and effective non-surgical method for ending early pregnancy. Women in Europe have used this option for more than a decade.

Why choose Mifeprex?

Mifeprex is a non-invasive early option for ending pregnancy. Mifeprex is taken orally, allowing you to avoid anesthesia or surgery in most cases. Some women feel it is a more private option. When you choose the early option pill, you will receive counseling and support throughout the process.

A PROVEN REGIMEN

What experience has there been with Mifeprex?

Mifeprex has gone through the rigorous Food and Drug Administration (FDA) approval process for safety and effectiveness. Mifeprex is the only FDA approved pill for ending early pregnancy. You should tell your provider about any medications you are taking. You should discuss with your health care provider whether or not Mifeprex is right for you.

In Europe, over half a million women have used this drug. Worldwide, this early option has now been approved for use in eighteen countries.

How effective is Mifeprex?

Mifeprex followed by misoprostol is approximately 92–95 percent effective in ending pregnancy.

MIFEPREX AND YOU

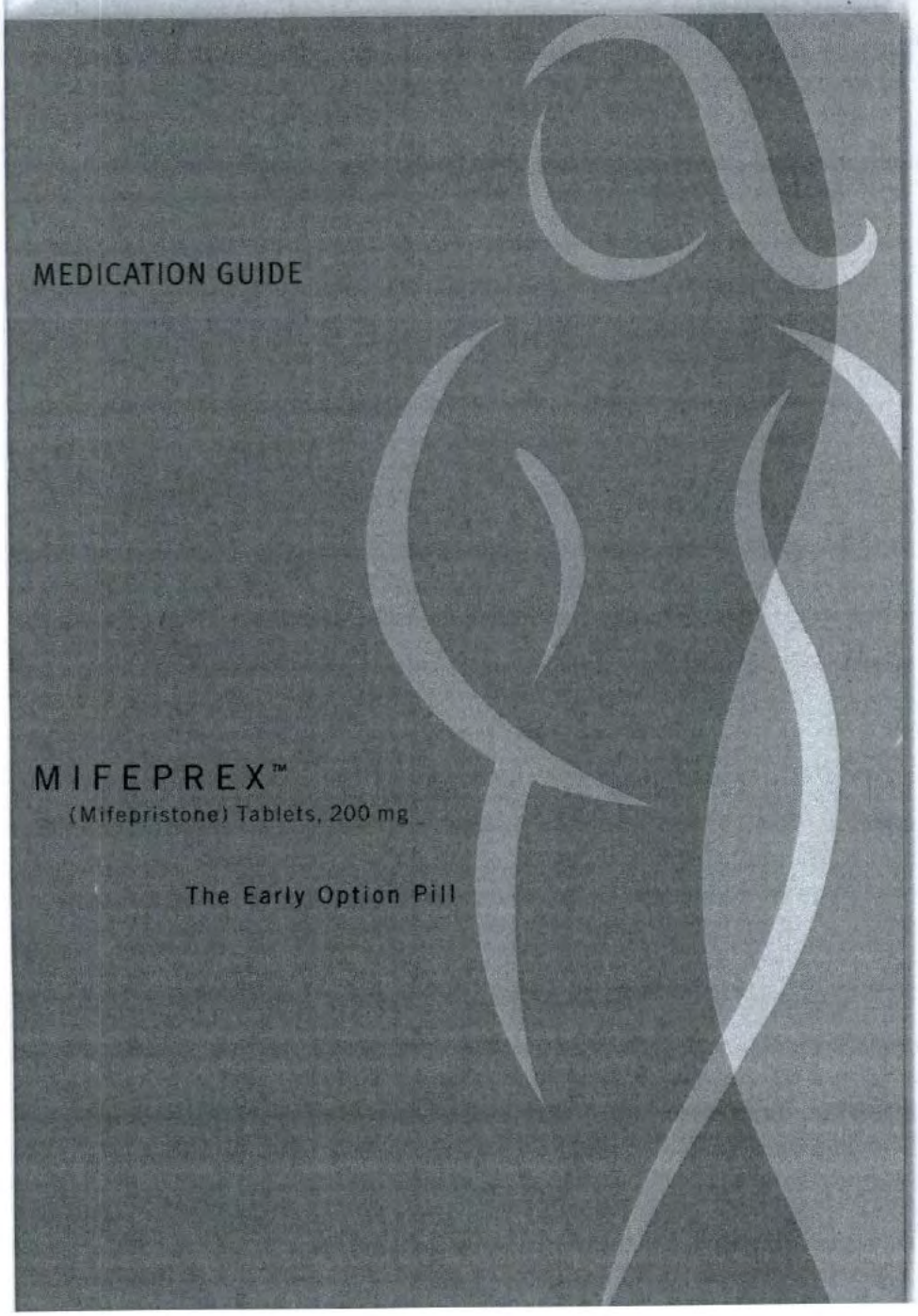
How does Mifeprex work?

Mifeprex blocks a hormone needed to maintain pregnancy. When followed by another medicine, misoprostol, Mifeprex ends the pregnancy.

What are the side effects of Mifeprex?

Bleeding and cramping are a normal part of the process. You may experience bleeding similar to or greater than a heavy period and can expect bleeding or spotting for an average of 9–16 days. In some cases, women may have severe bleeding and need to contact their doctor right away. Side effects of the combined regimen that may occur include nausea, headache, vomiting, diarrhea, dizziness, fatigue and back pain. You can take a pain reliever to help alleviate discomfort.

NDA 20-687
Sample of Medication Guide
September 2002



DANCO LABORATORIES

P.O. Box 4816
New York, NY 10185

1.877.4 EARLY OPTION
(1.877.432.7596)

www.earlyoptionpill.com

MEDICATION GUIDE

MIFEPREX™

(Mifepristone) Tablets, 200 mg

The Early Option Pill

CONTACT INFORMATION

Danco Laboratories
P.O. Box 4816
New York, NY 10185

1.877.4 EARLY OPTION
(1.877.432.7596)
www.earlyoptionpill.com

MEDICATION GUIDE

MIFEPREX™ (Mifepristone) Tablets, 200 mg
For Oral Administration Only

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 the most important information I should know about Mifeprex?

Mifeprex is used to end an early pregnancy. 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. By using Mifeprex, you probably will not need a surgical procedure to end your pregnancy.

When you use Mifeprex, you also need to take another medicine called misoprostol. You take misoprostol 2 days after you take Mifeprex.

You need to sign a statement (PATIENT AGREEMENT). Before you get Mifeprex, you will need to read and understand the information in this Medication Guide. Then you will need to sign a statement that you have decided to end your pregnancy.

You must visit your provider on Day 1, Day 3, and about Day 14. See the section called "How should I take Mifeprex?" for information about what happens at each visit. If you do not follow all the steps in "How should I take Mifeprex?" you will not know if your pregnancy has ended.

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

* Mifeprex is a trademark of Danco Laboratories, LLC.

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

Symptoms to expect. This treatment causes cramping and bleeding. 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.

If you are not already bleeding after taking Mifeprex, you probably will begin to bleed once you take misoprostol. This is a 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 that come from your uterus. This is an expected part of ending the pregnancy.

Heavy bleeding and the need for surgery. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (curettage) to stop it. This is why you must talk with your provider about what to do if you need emergency care to stop heavy and possibly dangerous bleeding.

Before you take Mifeprex. Your provider will give you a telephone number to call if you have any questions, concerns, or problems. Your provider will also give you the name and phone number of who will handle emergencies.

Talk with your provider. You and your provider should discuss the benefits and risks for you of using Mifeprex.

What is Mifeprex?

Mifeprex blocks a hormone needed for your pregnancy to continue. When used together with another medicine called misoprostol, Mifeprex ends

your pregnancy. About 5-8 out of 100 women taking Mifeprex will need a surgical procedure to end the pregnancy or to stop too much bleeding.

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:**
  - Your provider will check to see if you are still pregnant.
  - If you are still pregnant, take 2 misoprostol tablets.
  - Misoprostol may cause cramps, nausea, diarrhea, and other symptoms. Your health care 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 2 weeks after you took 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?

You should not take certain other medicines, because they may interfere with the treatment. Ask your provider about what medicines you can take for pain. 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.

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

What are the possible side effects of using Mifeprex?

See the section "What is the most important information I should know about Mifeprex?" for symptoms to expect.

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

Other side effects of the 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.

If you are worried about any side effects you have, talk with your provider about them. Your provider will give you a telephone number to call if you have any questions, concerns, or problems. Your provider's telephone number is _____.

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.

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.
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 the 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:
    - 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.

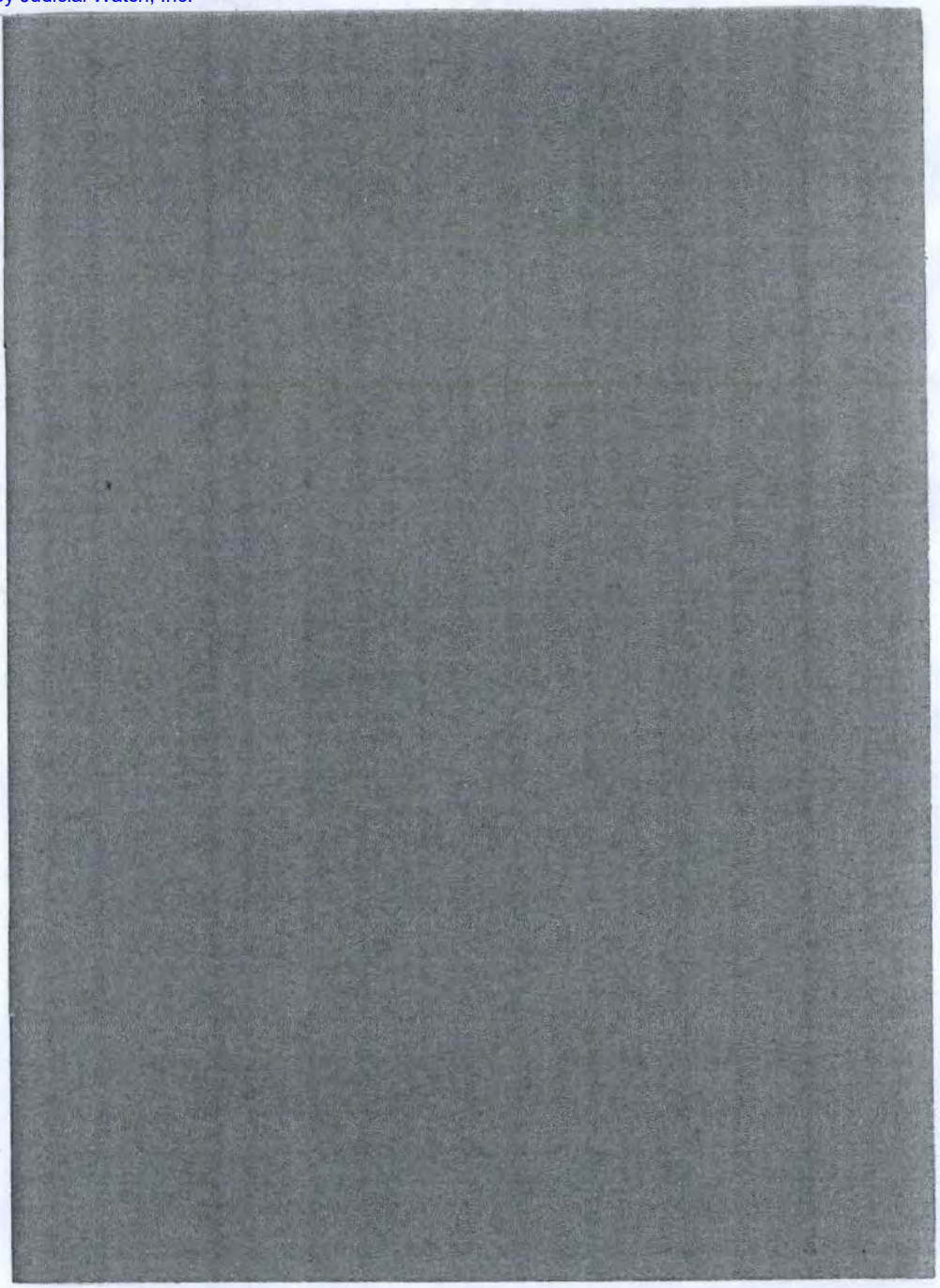
Provider's Signature: _____

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.

9/28/00



9(d) CHEMISTRY MANUFACTURING AND CONTROLS CHANGES

9(d) 1. Drug Substance

9(d) 1.1. Specifications and Test Methods

There were no changes in test methods or specifications during the reporting period. However, the retest period for Drug Substance was extended to (b) (4) months based on (b) (4) month long term data on three lots of Drug Substance.

9(d) 1.2. Manufacturing Procedure

There were no changes in manufacturing procedures during the reporting period. Batches of (b) (4) kg of Drug Substance remain the standard.

The Auxiliary Raw Materials and Suppliers pages 146 and 147 in **Section 1.6.2** of the CMC section for the drug substance have been revised to include new, qualified suppliers of raw materials. The new suppliers have been highlighted, in bold print. See Attachment 4.

9(d) 1.3. Packaging Procedure

There were no changes in the packaging materials or procedures during the reporting period.

9(d) 1.4. Stability Data

The three batches of Drug Substance submitted in the original Drug Substance CMC, lot numbers (b) (4), have attained (b) (4) months of long-term stability. Based on these data the retest dating was extended to (b) (4) months.

Additionally, lot numbers, (b) (4), (b) (4) reported on last year remain on long term stability. Finally, three batches from 2002; lot numbers (b) (4) and (b) (4) have been put on long-term stability. Data on all those batches described above are included in Attachment 5.

All data to date on all batches continue to demonstrate the stability of the Drug Substance.

9(d) 2. Drug Product

9(d). 2.1 Specifications and Test Methods

There were no changes in test methods or specifications during the reporting period. A copy of the specifications is included as Attachment 6. The test methods were previously submitted in Amendment 069, dated January 2001.

Regarding our previous commitment to review the specification for residual (b) (4) (NMT (b) (4) %) in the drug product after (b) (4) batches were manufactured, we have since manufactured (b) (4) batches of Mifepristone Tablets, 200 mg and have submitted a proposed change in the specification as Supplement S-004.

The results for the residual (b) (4) for the (b) (4) batches were non-detectable because the levels were below the limit of quantification for the method (LOQ is (b) (4) %).

9(d) 2.2 Formulation

There were no changes in the formulation of the product.

9(d) 2.3 Manufacturers of Drug Substance and Inactive Ingredients

There were no changes in the manufacturer of any of the inactive ingredients.

9(d) 2.4 Manufacturing Procedure

There were no changes in the manufacturing procedure. The current manufacturing procedure is designated as MPR # 100101 Rev # 03, dated 11/11/1999. This was previously submitted in Amendment 038, dated December 7, 1999 as Attachment 1.

9(d) 2.5 Packaging Procedure

There were no changes in the packaging materials (types or manufacturers) used to produce the blister cards.

A new (b) (4) blister packaging machine, model (b) (4), was purchased, installed in January 2002 and qualified for use with mifepristone tablets, 200 mg. The functionality of the machine and

performance is essentially the same as the previous blister packaging machine.

The blister packaging procedure was revised to reflect the use of the (b) (4) blister packaging machine. The current procedure is designated as MPR P000101 Rev # 5 dated 12/7/2001.

A copy of the revised procedure is included as Attachment 7.

9(d) 2.6 Stability Data

The batches that are in the current stability program are batch #s (b) (4) . The first five batches were placed in both controlled room temperature and accelerated stability programs. The most recent annual stability batch ((b) (4)) was placed in the controlled room temperature stability program. All batches were manufactured by our approved contract manufacturer for the finished product and tested by our approved contract testing laboratory. The stability data for each of the six batches are summarized in Attachment 8. The batches met all stability specifications at each time interval. The stability data supports the current expiration period of 24 months.

9(e) NON-CLINICAL LABORATORY STUDIES

9(e) 1. Unpublished Reports

During the reporting period, there were no unpublished reports of non-clinical studies conducted with mifepristone of which we are aware.

9(e) 2. Published Reports

Appended in Attachment 9 is an updated bibliography of non-clinical publications on mifepristone. Copies of listed references will be provided upon request.

9(f) CLINICAL DATA

9(f) 1. Published Clinical Trials of the Drug

Appended in Attachment 10 is an updated bibliography of clinical references for Mifepristone. In Attachment 11 abstracts of clinical publications on mifepristone are provided. Copies of these references will be provided upon request.

9(f) 2. Summaries of Completed Unpublished Clinical Trials

No information regarding completed unpublished clinical trials not performed by us or on our behalf has come to our attention in the period covered by this report.

Summary information regarding clinical studies performed by us or on our behalf and for which there is no postmarketing study commitment is provided in section 9(g) 2. of this report.

9(f) 3. Other Clinical Trials

Below is a tabulation of institutions to which Danco has provided Drug Product or Drug Substance. Investigational use of the drug is described in IND's held by the individual investigators working with those institutions.

Drug Product:

(b) (4)

Drug Substance:

(b) (4)

9(g) STATUS REPORTS - POST MARKETING STUDIES

9(g) 1. Status Reports – Post Marketing Study Commitments [21CFR 314.81(b)(2)(vii)]

Study Commitment Status Report Not for Public Release

Appended in Attachment 12 is a confidential status report of the postmarketing study commitments not for public release.

Study Commitment Status Report for Public Release

Appended in Attachment 13 is a status report of the postmarketing study commitments for public release.

9(g) 2. Other Post Marketing Studies [21CFR 313.81 (b)(2)(viii)]

Ongoing Clinical Studies

Status reports of other ongoing postmarketing studies are provided in Attachment 14.

Completed Clinical Studies

Other post marketing studies completed during this reporting period are provided in Attachment 15.

Stability Issues

Status reports for all product stability studies are provided in Section 9(d) 2.6.

ATTACHMENT 1

PO Box 4816
New York, NY 10185

DANCO LABORATORIES

infoline
1.877.4.EARLY OPTION
www.earlyoptionpill.com

April 19, 2002

Dear Health Care Provider:

This letter is to inform you of new safety information with regard to prescribing Mifeprex® and to remind you of your responsibility to report certain events and provide patient counseling, as stated in your Prescriber's Agreement.

New Safety Information

We have received a small number of reports of ruptured ectopic pregnancies (including one death from hemorrhage due to a ruptured ectopic pregnancy). As you will recall, Mifeprex* and misoprostol are not an effective treatment of ectopic pregnancy. Confirmed or suspected ectopic pregnancy is a contraindication for the use of Mifeprex and should be ruled out prior to initiating Mifeprex treatment. Because ectopic pregnancy may be present despite your best efforts to rule it out before starting Mifeprex treatment, you should be mindful of the possibility of an ectopic pregnancy throughout the treatment period and have a plan for its management.

Two cases of serious systemic bacterial infection (one fatal) following treatment with Mifeprex and misoprostol have been reported. While it is known that menstruation, childbirth and abortion (whether spontaneous, surgical or medical) create conditions that can result in infection, we do not believe that Mifeprex and misoprostol present a special risk of infection. Although serious infection in medical abortion is rare, we ask that you be alert to this possibility if your patients report symptoms or have signs of infection.

We have also received a report of myocardial infarction occurring in a 21 year old woman three days following use of Mifeprex and misoprostol.

No causal relationship between any of these events and use of Mifeprex and misoprostol has been established.

Approved Regimen

As a reminder, the Food and Drug Administration (FDA) approved regimen for administration of Mifeprex is:

- 600 mg Mifeprex taken orally in the office or clinic
- 400 mcg of misoprostol taken orally in the office or clinic 48 hours after the Mifeprex.

The FDA has not reviewed or approved other dosing regimens for early termination of pregnancy.

ifeprex is a registered trademark of Danco Laboratories, LLC

Reporting Adverse Events and On-going Pregnancy

We would like to remind you to report any Serious Adverse Events (SAEs) associated with Mifeprex use to the address below. Serious adverse events include death, hospitalization, blood transfusion, and other major events. In the case of on-going pregnancy following treatment with the Mifeprex regimen (approximately 1%), you should also notify us if the patient chooses to proceed with her pregnancy.

Please provide a brief clinical synopsis by writing, calling, or emailing:

Medical Director
Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
Medicaldirector@earlyoptionpill.com
Toll free at 1-877-4 Early Option (1-877-432-7596)

We may need to contact you to obtain additional information, so please include your contact information. The following information is helpful when you report adverse events: age of patient; gestational age; dosages and means of administration of all medications, including concomitant medications; clinical information on the patient, including relevant past medical history, laboratory results, and health care course; and final outcome of the patient.

Patient Counseling

We would like to remind you of the importance of helping your patients understand the benefits and risks of the Mifeprex regimen. During the first of three office visits, please give the patient a Medication Guide to read, as well as a Patient Agreement to read and sign. (These materials are included with each Mifeprex order. If you need additional copies, please contact our authorized distributor.)

As you are aware, bleeding and cramping are a normal part of the process; women can expect bleeding or spotting for an average of 9 to 16 days. Women may experience bleeding that is similar to, or greater than, a heavy period. In the U.S. clinical trials, about 1 out of 100 women required a surgical procedure, identical to the procedure for miscarriage, to stop heavy bleeding. If you do not plan to provide this procedure yourself, you must have made arrangements with someone who will and provide this contact information to your patient. Other side effects that may occur include nausea, headache, vomiting, diarrhea, dizziness, fatigue and back pain.

For more information about Mifeprex, visit www.earlyoptionpill.com or call the 24-hour hotline, toll-free at 1-877-4 Early Option (1-877-432-7596). If you have an emergent question, a physician will usually return your call within the hour. For general questions, our Medical Director typically returns calls within 24 hours.

Sincerely,
Danco Laboratories, LLC

ATTACHMENT 2

PERIODIC SAFETY UPDATE REPORT FOR:

MIFEGYNE®

MIFEPRISTONE

EXELGYN LABORATORY
6 rue Christophe COLOMB
F- 75008 Paris

June 1st, 2001 until May 31st, 2002

PSUR n° 13 \ JUNE 2002

June 30th, 2002

(b) (4), (b) (6)

(b) (4), (b) (6)

TABLE OF CONTENTS

Page

1 - INTRODUCTION

This is the thirteenth Periodic Safety Update Report (PSUR N°13) on *Mifepristone*, compiled for regulatory authorities since January 1991.
It summarises safety data received by the Medical Department of Exelgyn from worldwide sources, during the period from June 1, 2001 to May 31, 2002.

Mifepristone (RU 486) is a potent antiprogestin, available as 200mg tablets for oral administration. Mifepristone is marketed by Exelgyn and was developed by Roussel Uclaf. The Population Council (USA) also has rights to mifepristone under a special agreement.

The initial and main indication for *Mifepristone* is medical termination of early intra-uterine pregnancy (first approval in France in December 1988), in combination with a prostaglandin analogue (misoprostol or gemeprost). This combination leads to successful pregnancy termination in more than 95% of cases.

Mifepristone is also approved for therapeutic termination of pregnancy beyond the first trimester in combination with prostaglandin analogues, softening and dilatation of the cervix uteri prior to surgical pregnancy termination and induction of labour for fœtal death in utero.

This report is compiled in the format proposed by ICH3 Topic E2C (Step 4 Document issued in November 1996).

2 - WORLDWIDE MARKET AUTHORISATION STATUS

The cumulative worldwide market authorisation status of *Mifepristone*, specifying the respective dates of approval and dates of launch is presented in Appendix 11.1.

During the period covered by the PSUR:

- New marketing authorisations were obtained through national procedure in the following countries: Azerbaijan, New Zealand and Uzbekistan.

3 - UPDATE OF REGULATORY OR MANUFACTURER ACTIONS TAKEN FOR SAFETY REASONS

3.1. Action taken by the Marketing Authorisation Holder (MAH)

The action taken for safety reasons during the covered period are described hereunder

- In Sweden, a type II variation was submitted on December 4th, 2001 in order to harmonise the section "4.1. Therapeutic indication" of the Swedish SmPC, with the European SmPC. In this context, the following new indications were submitted and are still outstanding :
  - Softening and dilatation of the cervix uteri prior to surgical termination of pregnancy during the first trimester.
  - Preparation for the action of prostaglandin analogues in the termination of pregnancy for second trimester.
  - Labour induction in foetal death in utero, in patients where prostaglandin and oxytocin cannot be used.

- In UK, type II variations mentioned in the previous report was approved and all amendments concerning the indication is now in the SmPC.

3.2. Action taken by the Regulatory Authorities

During the period of review, there was no specific action taken for safety reasons by the regulatory authorities.

There was no marketing authorisation rejection, no suspension or withdrawal, no restriction of distribution, no clinical trial suspension, no dosage or formulation modification, and no change in target population or indications.

4 – CHANGES TO REFERENCE SAFETY INFORMATION

The Master Data Sheet (MDS) which includes the Core Safety Information has been used as a reference document for the preparation of the present PSUR (see Appendix 11.2.1).

Although there is no major change, the Master Data Sheet was revised in 1998 to be in line with the document proposed in the mutual recognition procedure. Since the last report, there is no major modification in the MDS and in the SmPC.

However in Sweden harmonisation of SmPC in section "4.1. Therapeutic indication" was submitted to be in line with the European SmPC

In UK, the type II variation concerning two modifications in the indications are now mentioned in the SmPC.

5 - PATIENT EXPOSURE

A crude estimate of the number of patients treated with *Mifepristone* has been calculated from the sales volumes, in units, of drug sold in the period from June 1, 2001 to May 31, 2002. It has been assumed that each patient has received the standard dose of 600mg (3 tablets). This may underestimate the number of patients exposed to the drug. Indeed, in the UK, many physicians use a lower dose of 200mg. Also, since the approval of the indication "Softening and dilatation of the cervix" at the dose of 200mg in France, a number of patients received only one tablet.

5.1. CLINICAL TRIALS

From information obtained by Exelgyn Laboratories, it is estimated that (b) (4) patients, included in ongoing clinical trials during the period of review, received *Mifepristone*.

For all these trials, the medication is provided by Exelgyn only.

Information regarding these studies is presented in Appendix 11.3.1 and 11.3.2.

5.2. MARKET EXPERIENCE

During the period covered by this review (from June 1, 2001 to May 31, 2002), *Mifepristone* sales amount to (b) (4) units (on May 2002). Assuming one unit represents one treatment course, this would correspond to (b) (4) women who received mifepristone.

5.3. TOTAL EXPOSURE

(b) (4)

Clinical trials
Worldwide sales
Total

Thus it is estimated that over (b) (4) patients received *Mifepristone* in the period covered by this safety update report.

6 - INDIVIDUAL CASE HISTORIES

All spontaneous and clinical trial reports, published and unpublished, meeting the criteria defined below, and received by the Medical Department of Exelgyn, from worldwide sources during the review period, are presented in Appendix 11.4.
The cases have been classified by body system and the details tabulated in a line-listing format. When reports of events affecting more than one body system were received, the most clinically serious event has been assigned to the corresponding body system and the other events listed with it.

6.1. SPONTANEOUS REPORTS

All serious (irrespective of labelling), and non serious, spontaneous reports received by Exelgyn, and medically unsubstantiated consumer reports mentioned in this section, are presented in a line-listing format in the attached documents: Appendix 11.4. is a listing with information on each individual case as recommended in the ICH guidelines.

During the period of review, the Medical Department of Exelgyn recorded from health professionals and authorities **23 spontaneous reports** (of which **12 cases of serious adverse events, 11 non serious adverse events** and **no case from clinical trials**) in association with *Mifepristone*.

- The 12 cases of serious adverse events reported during the period of review are classified as follows:
  - 3 serious unlabelled, in which 1 case of unintended pregnancy with fetal malformation, 1 case of death and 1 case of thoracic pain (ischaemic accident).
  - 9 serious labelled with 5 cases of unintended pregnancy, 2 cases of allergic reaction, 1 excessive bleeding and 1 septicaemia to *Streptococcus*.
- Among the 11 non serious cases, 9 cases of unintended pregnancy and 2 cases of rash were reported.

The outcome of the cases **S20000024S/MIF2** (previously reported as case S20000024S/MIF1 in PSUR n°11) and **S2000017UK/MIF1** (from PSUR n°12), are normal pregnancy with healthy baby (date of birth: (b) (6) and spontaneous abortion in the second case.

6.2. STUDY REPORTS

Unlabelled, serious, attributable adverse event reports are included. An unlabelled event is defined, as any particular untoward medical happening experienced by a patient that is not described in the Master Data Sheet. A serious event is one that is fatal, life-threatening, disabling, incapacitating, results in hospitalisation or prolongs hospitalisation, overdose, cancer or congenital anomaly. For the purpose of this report an event is considered to be attributable if the investigator or the company has rated the causality relationship with mifepristone as possible or more than possible.

No case was reported from clinical trials during the period of review.

Other studies are conducted by independent investigators or organisations and are listed in Appendix 11.3.1, the products used in these trials are provided by Exelgyn.

7 – STUDIES

7.1. NEWLY ANALYSED AND PUBLISHED STUDIES (References list Appendix 11.5.)

There is no newly analysed study.

7.2. TARGETED NEW STUDIES

There are no targeted new studies during the period of review.

7.3. PUBLISHED SAFETY STUDIES

SETTING UP A ONE-STOP MIFEPRISTONE-MISOPROSTOL MEDICAL TERMINATION OF PREGNANCY SERVICE FOR ALL GESTATION FROM 5 TO 23 WEEKS – A REVIEW OF 482 CASES.
J. I. Ojidu, S. D. Sabharwal.
J. Obstet. Gynaecol., 2001, Vol/Iss/Pg.21/4 (386-388)

Mifepristone–misoprostol combination is increasingly being utilised for medical termination of pregnancy on account of its reported efficacy, safety and lower cost. Experience with this modality of effecting termination of pregnancy from 9 to 13 weeks' gestation is scanty. At the Scunthorpe General Hospital in the United Kingdom, we established a nurse-led, one-stop medical termination of pregnancy service using ***mifepristone*** and misoprostol for all gestations from 5 to 23 weeks. A review of the case records of 482 women who had medical termination of pregnancy at all gestations from 5 to 23 weeks from December 1997 to May 1999 was undertaken in order to assess the effectiveness and complication associated with the ***mifepristone***-misoprostol protocol. Complete abortion was achieved in 406 (84 %) women. Surgical evacuation was required to complete the abortion in 74 (16 %) women. The complete abortion rate was similar across the spectrum, i.e. 87 % in the 5-8-weeks group; 79 % in the 9-13-weeks group; and 87 % in those of greater-than or equal to 14 weeks. Two failures occurred: one of them proceeded to surgical evacuation after three courses of misoprostol, while the over continued with her pregnancy after one course. Three women (0.6 %) required blood transfusion for haemorrhage, while two others were treated for infection. Oral ***mifepristone*** with or without vaginal misoprostol is an effective and safe regimen for termination of all pregnancies from 5 to 23 weeks' gestation.

FIRST TRIMESTER ABORTION WITH MIFEPRISTONE AND VAGINAL MISOPROSTOL.

U. B. Knudsen
Contraception 2001; 63/5: 247-250.

This study assessed the efficacy and side effects of first trimester medical abortion using ***mifepristone*** and vaginally administered misoprostol. Medical abortion was first in Denmark in December 1997, and the acceptability of this new approach in a Danish population was evaluated. This study included the first 100 women seeking medical abortion. The gestational age was from 33 to 56 days. All received 600 mg ***mifepristone (RU 486)*** orally followed 2 days later by vaginally administered misoprostol 400 µg. Success was defined as achieving complete abortion without the need for surgical evacuation. Ninety-three percent achieved a successful medical termination of pregnancy. Side effects were few, and the acceptability was high. Ninety percent of the women would prefer medical abortion in case of a new unwanted pregnancy. The combination of ***mifepristone*** and vaginally administered misoprostol is effective, safe, has few side effects and in well accepted by Danish women.

SECOND TRIMESTER MEDICAL ABORTION WITH MIFEPRISTONE AND GEMEPROST.

O. S. Tang, K. J. Thong, D. T. Baird
Contraception 2001; 64/1: 29-32

The treatment outcomes of 956 women undergoing second trimester termination of pregnancy with ***mifepristone*** and gemeprost were studied. The median gestational age was 16 weeks (range: 12-24 weeks). All women were treated with 200 mg ***mifepristone*** orally, followed 36 h later with 1 mg vaginal gemeprost administered every 6 h to maximum of 4 doses in the first 24 h. A second course of 1 mg vaginal gemeprost was given 3-hourly in the next 12 h, if abortion had not occurred. Overall, 96.4 % and 98.8 % of the women aborted within 24 and 36 h, respectively. The median induction-to-abortion interval was 7.8 h (range: 0.5-109.9h). The induction-abortion interval was longer in nulliparous women (7.3%; $p<0.001$). Ten (0.1%) women failed to abort with gemeprost and required other methods for abortion. In conclusion, a combination of ***mifepristone*** and gemeprost is a safe, effective, and non-invasive method of medical abortion for second trimester pregnancy.

A RANDOMIZED COMPARISON OF MEDICAL ABORTION AND SURGICAL VACUUM ASPIRATION AT 10-13 WEEKS GESTATION

P. W. Ashok, A. Kidd, G. M.M.Flett, A. Fitzmaurice, W. Graham and A. Templeton
Human Reproduction, 2002, Vol.17/1: 92-98

A patient-centred, partially randomised, controlled trial was carried out. Those who expressed a strong preference for either medical (n = 15) or surgical (n = 62) abortion were allocated to that method. The remainder agreed to be randomized.

The medical method (n = 188) was mifepristone 200 mg followed by misoprostol up to 3 doses, and surgery (n = 180) was by vacuum aspiration under general anaesthesia. Outcome measures included efficacy rates, medical complications within 8 weeks of the procedure, patient preferences and acceptability.
Among women who underwent medical abortion, 5.4% required a second procedure compared with 2.1% who had surgery, although this difference was not statistically significant. Side effects experienced were higher in women who underwent medical abortion compared with those who underwent surgery. There were no significant differences in the rates of major complications up to 8 weeks. Prior to termination, 80% of women had a preference for a method, with 72% preferring medical and 28% preferring surgical abortion. Following abortion, 70% of those who underwent medical termination and 79% who underwent surgery would opt for the same method in the future.
Medical abortion is safe and effective at 10-13 weeks gestation and should be considered an option for those women who wish to avoid surgery and anaesthesia.

8 - OTHER INFORMATION

8.1. EFFICACY-RELATED INFORMATION

No information was received during the period of review involving relevant lack of efficacy, which might represent a significant hazard to the treated population.

8.2. LATE-BREAKING INFORMATION

There is no information received since the data lock point, which might alter the risk benefit profile of mifepristone.

9 - OVERALL SAFETY EVALUATION

9.1.OVERVIEW

From the data presented in this safety update and cumulative experience to date, it is considered that no further amendment to the Master Data Sheet is required at present, with respect to the reported listed adverse reactions, and especially those qualified as serious. No significant increase in the frequency of reports for any category of known toxicity was identified.

From the cumulative experience on mifepristone, it is considered that the statements given in the Core Safety Information of the last version of the Master Data Sheet are adequate with respect to mifepristone use in all its approved indications.

However type II variation for harmonisation of Swedish SmPC (section 4.1. Therapeutic indication) was submitted on December 4th, 2001 to be on line with the European SmPC.

9.2. DRUG INTERACTIONS

No information concerning interaction has been identified during the period of review.

9.3. OVERDOSE OR MISUSE

One case of misuse was reported. This case from France (S2001020F/MIF1) concerns a 22-year-old female patient who received 200 mg of mifepristone (instead of 600 mg as mentioned in SmPC) for medical termination of pregnancy at 12 weeks gestation. The patient experienced incomplete abortion with excessive bleeding.

9.4. DRUG ABUSE

There is no potential of drug abuse with mifepristone, as prescription is restricted to hospital (only one dose).

9.5. EXPERIENCE IN PREGNANCY

Twelve new cases of developing pregnancy were recorded during the period of review. In the majority of these cases of continuing pregnancies, women changed their mind either after mifepristone intake, before prostaglandin administration, or after exposure to both drugs.
Some cases were reported prospectively. The outcome was the following:

- seven cases of surgical termination of pregnancy,
- continuing pregnancy in five patients.

All cases are presented in the consecutive PSURs. The tables have been updated since PSUR n° 12 and are presented in Appendix 11.6.

The outcome of two previous pregnancies (case # S2000024S/MIF1 from PSUR n°11 and S2000017UK/MIF1 from PSUR n°12) were reported, normal birth in one patient and spontaneous abortion in the other patient.

Since the first marketing in 1989, **146** cases of ongoing pregnancies were identified either as spontaneous cases reported to or solicited by the company, or included in the listing even if the case was insufficiently documented. Ten of these cases were reported with various malformations.

The manufacturer recommends in the Master Data Sheet, "the woman must be informed that in the event of the failure of the method, the pregnancy is liable to continue to develop. The foetus may then be exposed to a risk of malformation".

9.6. EXPERIENCE DURING LACTATION

No new information concerning experience during lactation has emerged during the period of review.

9.7. LONG-TERM TREATMENT

The currently approved indications of mifepristone require one single dose, or two doses in case of foetal death in utero.

However some patients have received long-term daily treatment with mifepristone in non-registered indication such as unresectable meningiomas, leiomyosarcomas, Cushing syndrome. The two main adverse reactions identified during long-term use are reversible amenorrhea in premenopausal women and sub-acute adrenal failure symptoms. In addition, endometrial hyperplasia might be a potential adverse reaction of long-term mifepristone administration, possibly related to continued unopposed estrogen action.

9.8.EXPERIENCE IN SPECIAL PATIENT GROUPS

There is no information concerning the experience in special patient groups.

10 - CONCLUSION

No area of safety concern has been identified during the period of review. The data presented in this report are consistent with the cumulative experience to date and provide no information, which could alter the risk-benefit ratio of mifepristone.

Exelgyn Medical Department will continue to monitor reports of adverse experiences received worldwide and will revise the SmPC when an evaluation of surveillance data yields significant new information.

11. APPENDICES

APPENDIX 11.1

CUMULATIVE REGULATORY APPROVAL / DECISION DATES

APPENDIX 11.1.1.

REGISTRATION STATUS UP TO 1998

MIFEGYNE®
REGISTRATION STATUS AS OF NOVEMBER 1998

COUNTRY	DOSAGE PER TABLET	DATE OF			INDICATIONS (and POSOLOGY)
		APPROVAL	LAUNCH	TRANSFER OF MARKETING AUTHORIZATION	
FRANCE	200mg	December 28th, 1988 July 17th, 1992 November 6th, 1998	September 1989	8/8/97 CIP N°556 473.0	• Medical alternative to surgical termination of intra-uterine pregnancy of up to 49 days amenorrhea (600mg single dose) • Preparation for the prostaglandin action in therapeutic pregnancy termination (600mg single dose) • Fœtal death in utero (600mg x 2 days) • Softening and dilatation of the cervix uteri prior to voluntary pregnancy termination by vacuum aspiration during the first quarter (200mg single dose)
U.K.	200mg	July 1st, 1991 August 4th, 1995	July 1991	24/09/97 PL 16152/0001	• Medical alternative to surgical termination of intra-uterine pregnancy of up to 63 days amenorrhea (600mg single dose) • Softening and dilatation of the cervix uteri prior to mechanical cervical dilatation for pregnancy termination (600mg single dose) • Termination of pregnancy between 13 and 20 weeks gestation in combination with gemeprost (600mg single dose)
SWEDEN	200mg 600mg	September 4th, 1992 August 2nd, 1995	October 1992	1/10/97 ASP 91-0246 ASP95-0005	• Medical alternative to surgical termination of intra-uterine pregnancy of up to 63 days amenorrhea (600mg single dose) • Termination of pregnancy in the second trimester (600mg single dose) Same indications as for 200mg tablets

APPENDIX 11.1.2.

NEW REGISTRATION AND LAUNCH DATES

MIFEGYNE® REGISTRATION STATUS AS OF MAY 31, 2002

COUNTRY	DATE OF SUBMISSION	DATE OF APPROVAL	PLANNED / ACTUAL DATE OF LAUNCH	LICENSE NUMBER
		E U R O P E		
Mutual Recognition Procedure	**April 6th, 1999**	**July 6th, 1999**		**FR/H/137/01**
AUSTRIA	**April 6th, 1999**	September 21st, 1999	Marketed December 1999	1-23220
BELGIUM	**April 6th, 1999**	November 22nd, 1999	July 3rd, 2000	2 532 IE 1 F3
DENMARK	**April 6th, 1999**	August 27th, 1999	Marketed Q_1 2000	30 741
FINLAND	**April 6th, 1999**	December 20th, 1999	Marketed Q_1 2000	MTnr 14064 FIN
FRANCE	-	December 28th, 1988 Update December 15th, 1999	Marketed 1989	556 473.0
GERMANY	**April 6th, 1999**	August 19th, 1999	Marketed November 1999	46 038 .00.00
GREECE	**April 6th, 1999**	October 10th,1999	Q_4 2001	2455001
LUXEMBOURG	**November 26th, 1999**	December 11th, 2000	January, 2001	1181/00/11/0052
NETHERLANDS	**April 6th, 1999**	August 25th, 1999	Marketed January 2000	RVG 24 206
SPAIN	**April 6th, 1999**	October 21st, 1999	Marketed February 2000	62.278
SWEDEN	—	September 4th,1992	Marketed Q_3 1992	11642
UK	—	July 1st, 1991 Updated August 4th, 1999 Updated August 8th, 2001	Marketed Q_3 1991	PL 16152 / 0001
		O T H E R S		
AZERBAIJAN		April 20th, 2001	**2002**	SN-004 00254
GEORGIA	**September 13th, 2000**	December 11th, 2000	**March, 2001**	R-0000075
ISRAEL	**February 7th, 1999**	August 10th, 1999	Marketed September 1999	115 52 29641 00
NEW ZEALAND	**2000**	August 30th, 2001	September 2001	-
NORWAY	**March 29th, 1999**	December, 2000	May 1st, 2001	99.1943
OUZBEKISTAN		June 8th ,2001	**2002**	6-250-95
RUSSIA	**November 22nd, 1998**	April 14th, 1999	Marketed September 1999	P-8-242 N°01 1033
SOUTH AFRICA	**April 9th, 1999**	**Pending**	**Q_3 2001**	NA
SWITZERLAND	**February 10th, 1999**	July 14th, 1999	Marketed October 99	55205
TAIWAN	**1999**	**Pending**	**Q_3 2001**	NA
TUNISIA	**August 8th, 1999**	November 15th, 2000	**2002?**	4303011H
UKRAINIA	**May, 1999**	June 23rd, 2000	**January, 2001**	P.0600/01921

APPENDIX 11.1.3.

DIFFERENCES IN THE LABELING OF THE EUROPEAN SMPC AND OTHERS COUNTRIES

APPROVED EUROPEAN SPC
JULY 6, 1999

* * * * *

Therapeutic indications & Posology

The European SPC has used the following wording. Consequently, the initial wording used in France and referred to in Appendix 11.1.1. has been modified to reflect the harmonized EU SmPC.

The following countries have been included in the procedure of Mutual Recognition: Austria, Belgium, Denmark, Finland, France (Reference Member State), Germany, Greece, the Netherlands, Spain.

- **Medical termination of developing intra-uterine pregnancy.**
  In sequential use with a prostaglandin analogue, up to 49 days of amenorrhea.

  600mg of mifepristone (i.e. 3 tablets of 200mg each) is taken in a single oral dose, followed by 36 to 48 hours later, the administration of a prostaglandin analogue; misoprostol 400µg orally, or gemeprost 1mg per vaginum.

- **Softening and dilatation of the cervix uteri prior to surgical termination of pregnancy during the first trimester.**

  200mg of mifepristone (one tablet), followed 36 to 48 hours later (but not beyond) by surgical termination of pregnancy.

- **Preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons *(beyond the first trimester)*.**

  600mg of mifepristone (i.e. 3 tablets of 200mg each) taken in a single oral dose, 36 to 48 hours prior to scheduled prostaglandin administration which will be repeated as often as indicated.

4- Labour induction in foetal death in utero.

In patients where prostaglandin or oxytocin cannot be used.
600mg of mifepristone (e.g. 3 tablets of 200mg each) in a single oral daily dose, for two consecutive days.

In the other countries where the product has been approved the wording is the following:

Israel

- **Medical alternative to uterine suction for termination of intra-uterine pregnancy:**
  - up-to-and no later than 49 days of amenorrhea (seven weeks).
  - In sequential use with a prostaglandin analogue, misoprostol 400µg per os administered 36 to 48 hours after mifegyne® intake.

  Only this indication has been approved at the moment.

Russia

- **Medical termination of pregnancy up to 42 days of amenorrhea:**
- 600mg of mifepristone in a single dose.
- **Medical termination of pregnancy up to 63 days of amenorrhea in association with a prostaglandin analogue (misoprostol, gemeprost):**
- 600mg of mifepristone followed 36 to 48hours later by gemeprost 1mg per vaginum.
- **Dilatation of the cervix uteri prior to a surgical termination of pregnancy up to 12 weeks:**
- 600mg of mifepristone in a single dose.
- **Preparation to the action of prostaglandin for termination of pregnancy between 13 and 20 weeks gestation for medical or social reasons:**

  600mg of mifepristone followed 36 to 48hours later by gemeprost 1mg p.v., repeated every three hours until complete expulsion.

The indication Labour induction for foetal death in utero has not been approved in Russia.

Sweden

- **Medical alternative to surgical termination of intra-uterine pregnancy of up to 63 days amenorrhea** (600 mg single dose).
- **Termination of pregnancy in the second trimester** (600 mg single dose).

Switzerland

The same text as in the EU has been approved for indications and posology with a slight difference in the wording of one indication: **Medical termination of intra-uterine pregnancy.**

UK

- **Medical termination of intra-uterine pregnancy** of up to 63 days gestation.
- **Softening and dilatation of the cervix uteri prior to mechanical cervical dilatation for pregnancy termination.**
- **For use in combination with gemeprost for termination of pregnancy between 13 and 24 weeks gestation.**
- **Labour induction in fetal death in utero.**

Contra-indications

For the above-mentioned countries the section Contra-Indications include the following:

In all indications:

- chronic adrenal failure
- known allergy to mifepristone or to any component of the product
- severe asthma uncontrolled by therapy

For countries included in the Mutual Recognition Procedure and for the UK, the following contra-indication has been added in all indications:

- **Inherited porphyria**

In the indication: medical termination of developing intra-uterine pregnancy:

- pregnancy not confirmed by ultrasound scan or biological tests
- pregnancy of 50 days' amenorrhea and beyond
- suspected extra-uterine pregnancy
- contra-indication to the prostaglandin analogue selected

In the indication: softening and dilatation of the cervix uteri prior to surgical termination of pregnancy:

- pregnancy not confirmed by ultrasound scan or biological test
- pregnancy of 84 days of amenorrhea and beyond (according to legal requirements)
- suspected extra-uterine pregnancy

Preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons *(beyond the first trimester):*

- contra-indication to the prostaglandin analogue selected

Labour induction in foetal death in utero:

Should prostaglandin combination be required, refer to Contra-Indications to the selected prostaglandin analogue.

In Israel, the section on Contra-Indications is different and include the following items:

1. Known allergy to mifepristone or to any component of the product.
2. Suspected extra-uterine pregnancy.
3. Pregnancy not confirmed by ultrasound scan.
4. Chronic adrenal failure.
5. Hemorrhagic disorders.
6. Long-term corticosteroid therapy.
7. Severe asthma uncontrolled by corticosteroid therapy.
8. Cardiac disease.
9. Hyperlipidemia.
10. Diabetes.
11. Patients with antipsychotic drug therapy.
12. Pregnancy beyond 49 days of amenorrhea.
13. As a special precaution, the medical method is not recommended for use in women over 35 years of age or who smoke more than 10 cigarettes/ day.
14. Know allergy to prostaglandins.
15. Patients with or history of cardiovascular disease.

In the UK, the following items are included in the Contra-Indication section of the UK data sheet:

1. Known allergy to mifepristone or to any component of the product.
2. Suspected extra-uterine pregnancy.
3. Pregnancy not confirmed by ultrasound scan or biological tests.
4. Chronic adrenal failure.
7. Severe asthma uncontrolled by corticosteroid therapy.
16. Inherited porphyria

Items 5, 6, 13 have been moved into the precautions section of the EU SmPC and item 13 is worded "... women over 35 years of age **and** who smoke more than 10 cigarettes/day". Item 9 and 11 do not exist in any of the master data sheet, EU, UK of Swedish information. Item 10 is included in the Precaution for use of the Master Data Sheet.

In addition, the following conditions have been considered in the warnings section: hepatic failure, renal failure, and malnutrition.

APPENDIX 11.2.

UPDATED LABELINGS

APPENDIX 11.2.1.

MASTER DATA SHEET

Exelgyn Laboratories
6, rue Christophe Colomb
F-75008 Paris

MIFEGYNE®
200mg
Mifepristone

Master Data Sheet

November 2001

SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT

- MIFEGYNE® 200mg, tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

(b) (4)

[redacted]

3. PHARMACEUTICAL FORM

- Light yellow, cylindrical, bi-convex tablets, for oral administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- **Medical alternative to surgical termination of intra-uterine pregnancy.**

  In sequential use with a prostaglandin analogue, administered 36 to 48 hours after MIFEGYNE® intake (see Posology and Method of Administration):
  - misoprostol 400µg orally (for pregnancies up to 49 days of amenorrhea),
  - or gemeprost 1mg, vaginal pessary (for pregnancies up to 63 days of amenorrhea).

  Under these conditions, the association of mifepristone and prostaglandins leads to a success rate of about 95 per cent of the attempted pregnancy terminations.
  (See Warnings and Precautions for use)

- **Softening and dilatation of the cervix uteri prior to surgical pregnancy termination.**

  Pre-treatment with mifepristone facilitates the surgical step of the mechanical dilatation.

- **Preparation for the action of prostaglandins analogues in the termination of pregnancy for medical reasons.**

  The use of MIFEGYNE® allows a significant reduction of the prostaglandins doses required for the expulsion.

- **Labour induction in fetal death in utero.**

  MIFEGYNE® administered alone leads to expulsion in about 60%, allowing avoidance, or reduction in the dose of prostaglandins. Therefore, it is indicated especially when prostaglandins are contra-indicated.

4.2 Posology and method of administration

1) **Medical alternative to surgical termination of intra-uterine pregnancy.**

MIFEGYNE® must not be administered if there is doubt as to the existence and age of the pregnancy, or in case of extra-uterine pregnancy. The prescribing doctor should in any case perform an ultrasound scan and/or measure ß-hCG before administration.

The method of administration which will be prescribed by the physician and applied in the presence of the practitioner or of a health professional will be as follows:

- 600mg of mifepristone (i.e. 3 tablets of 200mg each) is taken in a single oral dose, followed by

- 36 to 48 hours later, the administration of a prostaglandin analogue; misoprostol 400µg orally (pregnancies up to 49 days of amenorrhea), or gemeprost 1mg vaginally (pregnancies up to 63 days of amenorrhea).

2) **Softening and dilatation of the cervix uteri prior to surgical pregnancy termination.**

- 200mg of mifepristone (one tablet) in the presence of the physician or of a health professional, followed 36 to 48 hours later (but not beyond) by surgical termination of pregnancy.

3) Preparation for the action of prostaglandin analogs in the termination of pregnancy for medical reasons.

600mg of mifepristone (i.e. 3 tablets of 200mg each) taken in a single oral dose, in the presence of the physician or of a health professional, 36 to 48 hours prior to scheduled prostaglandin administration which will be repeated as often as indicated.

4) Labour induction for expulsion of a dead fetus (fetal death in utero).

- 600mg of mifepristone, e.g. 3 tablets of 200mg each, in a single oral daily dose, for two consecutive days

Labour should be induced by the usual methods if it has not started within 72 hours following the first administration of mifepristone.

4.3 Contra-Indications

This product SHOULD NEVER be prescribed in the following situations.

- Chronic adrenal failure.
- Known allergy to mifepristone or to any component of the product.
- Severe asthma uncontrolled by corticosteroid therapy.
- Inherited porphyria.

In the indication: medical alternative to surgical termination of intra-uterine pregnancy.

- Pregnancy not confirmed by ultrasound scan or biological tests.
- Pregnancy beyond 49 days of amenorrhea with misoprostol or beyond 63 days of amenorrhea with gemeprost.
- Suspected extra-uterine pregnancy.
- Contra-Indications due to the prostaglandins:
  - Known allergy to prostaglandins.
  - Patients with or history of cardiovascular disease (angina, Raynaud's syndrome or disease, cardiac arrhythmias, cardiac failure, severe hypertension).
    (See Precautions for use)

Preparation for the action of prostaglandins analogues in the termination of pregnancy for medical reasons.

- Contra-indications to prostaglandins where relevant.

Labour induction for expulsion of a dead fetus (fetal death in utero).

- Should prostaglandins combination be required, refer to contra-indications to the selected prostaglandin analogue.

4.4 Warnings and Precautions for use

Warnings

Specific national legal requirements

MIFEGYNE® and the prostaglandin analogues can only be prescribed and administered in accordance with the national legal requirements.

As a consequence, they can only be prescribed by a medical doctor and in a public or private hospital or centre (having approval to undertake terminations of pregnancies) in accordance with the national legal requirements.

The signature of an informed consent letter by the patient would certify that she has been fully informed about the method and its risks, except in the cases of preparation to the action of prostaglandins for pregnancy termination for medical reasons as well as for the labour induction for expulsion of a dead fetus (Fetal Death in Utero).

1) **Medical alternative to surgical pregnancy termination of intra-uterine pregnancy**

Failures

Unless abortion has already been completed, the use of MIFEGYNE® must be followed, 36 to 48 hours later, by a prostaglandin analogue administered either vaginally or orally, as mifepristone alone given without prostaglandins would lead to a failure rate of the method of at least 20 per cent.

According to the clinical trials and to the type of prostaglandin used, the failure rate varies. Failures occur in 1.3 to 7.5% of the cases receiving sequentially MIFEGYNE® followed by a prostaglandin analogue, of which:

- 0 to 1.5% of ongoing pregnancies
- 1.3 to 4.6% of partial abortion, with incomplete expulsion
- 0 to 1.4% of hemostatic curettage

Bleeding

The patient must be informed of the occurrence of prolonged vaginal bleeding (about 9 days after MIFEGYNE® intake) which may be heavy.

Bleeding occurs in almost all cases and is not in anyway a proof of complete expulsion.

The patient should be informed not to travel far away from the prescribing centre as long as complete expulsion has not been recorded. She will receive precise instructions as to whom she should contact and where to go, in the event of any problems emerging, particularly in the case of very heavy vaginal bleeding.

A follow-up visit must take place mandatorily within a period of **10 to 14 days** after administration of MIFEGYNE® to verify by the appropriate means (clinical examination, Beta-hCG measurement, ultrasound scan, etc...) that expulsion has been completed and that vaginal bleeding has stopped (apart from light bleeding the disappearance of which should be checked within a few days).

Persistence of vaginal bleeding at this point could indicate incomplete abortion, or an unnoticed extra-uterine pregnancy, and an appropriate treatment should be considered.

Since heavy bleeding requiring hemostatic curettage occurs in up to 1.4% of the cases during the medical method of pregnancy termination, special care should be given to patients with hemorrhagic disorders with hypocoagulability, or with anemia.

The decision to use the medical or the surgical method should be decided with specialised consultants according to the type of hemostatic disorder and the level of anemia.

2) **Softening and dilatation of the cervix uteri prior to surgical pregnancy termination**

For the full efficacy of therapy, the use of MIFEGYNE® must mandatorily be followed, 36 to 48 hours later and not beyond, by surgical termination.

The woman must be informed of the risk of bleeding, which may be heavy, following mifepristone intake. She will be informed of the rare occurrence (0.9%) of expulsion prior to the surgical termination.

She will receive precise instructions as to whom she should contact and where to go, in the event of any problems emerging, particularly in the case of very heavy vaginal bleeding.

3) **Preparation for the action of prostaglandin analogs for termination of pregnancy for medical reasons**

The administration of prostaglandins carries some risks; however pre-treatment with MIFEGYNE® has been shown to reduce the total dose of prostaglandins required. Moreover, the risks of other (mechanical) methods of termination for advanced pregnancies, beyond 12 weeks, have to be considered.

Precautions for use

1) **In all instances**

- The use of MIFEGYNE® requires blood group and rhesus determination and hence the prevention of rhesus allo-immunisation as well as other general measures taken usually during any pregnancy termination.

- In case of suspected acute adrenal failure, dexamethasone administration is recommended.

- Due to the antiglucocorticoid activity of mifepristone, the efficacy of long-term corticosteroid therapy may be decreased during the 3 to 4 days following MIFEGYNE® 's intake. Therapy should be adjusted.

  In the event of inhaled corticosteroid therapy, particularly in patients with asthma, it is recommended to adjust the treatment by doubling the dose during the 48 hours preceeding mifepristone's administration and for about one week duration.

- In patients with insulin-dependent diabetes, the occurrence of gastro-intestinal disorders induced by the pregnancy itself or by the treatment, would require an adjustment of insulin therapy.

- During clinical trials, pregnancies occurred between fetal expulsion and the resumption of menses. To avoid potential exposure of a subsequent pregnancy to mifepristone, it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after mifepristone administration.

- As a precaution and in the absence of specific studies, mifepristone should not be used in patients with:
  - Renal failure
  - Liver failure
  - Malnutrition

2) **Medical alternative to surgical termination of intra-uterine pregnancy.**

In any case of a pregnancy occurring on an intra-uterine device, this device must be removed before administration of MIFEGYNE®.

During the initial clinical trials, rare serious cardiovascular accidents similar to coronary spasms have been reported following the administration of a PGE_2 analogue (intra-muscular sulprostone). These events were reported in women over 30 years of age and smoking more than 10 cigarettes a day.

No such cases have been reported, since analogues of PGE_1 (gemeprost or misoprostol) have been used. The present experience is based upon (b) (4) treatments of which about (b) (4) used misoprostol and about (b) (4) used gemeprost.

Therefore, as a special precaution, the medical method is not recommended for use in women over 35 years of age and who smoke more than 10 cigarettes a day.

In any case, the risk of cardiovascular events must be taken into consideration when prostaglandins are used in association with mifepristone.

Method of prostaglandins administration

During intake and for three hours following the intake, the patients should be monitored in the treatment centre, which must be fitted with the appropriate cardiovascular monitoring and resuscitation equipment.

3) **For the sequential use of MIFEGYNE® - Prostaglandins, whatever the indication.**

The precautions related to the prostaglandins used should be followed if relevant.

4.5 Interaction with other drugs and other types of interactions.

Associations to be avoided

- Non steroidal anti-inflammatory drugs (NSAIDs) including aspirin. A decrease of the efficacy of the method can theoretically occur due to the antiprostaglandin properties of NSAIDs. Use preferably non-NSAIDs analgesics.

4.6 Pregnancy and lactation

Patients must be informed that in the event of failure of the methods, the pregnancy is liable to continue to develop. The fetus may then be exposed to a risk of malformation.

In studies performed in animals, fetal anomalies have been observed in rabbits (skull lesions), but not in rats and mice. No teratogenicity was observed after in vitro exposure of monkey embryos to mifepristone. When the pregnancy continued after mifepristone alone or with prostaglandins, uncommon cases of malformations have been reported in the fetus or the infant. Malformations have also been reported after the use of prostaglandins alone.

The exact role of mifepristone, prostaglandin analogue, or coincidental event cannot be established.

It is essential that termination of pregnancy by another method be undertaken at a follow-up visit, in the event of such failure.

Mifepristone is a lipophilic compound and may theoretically be excreted in the mother's breast milk. However, no data is available. Consequently, mifepristone use should be avoided during breast-feeding.

4.7 Effects or ability to drive and to use machines

Unknown.

4.8 Undesirable effects

Very common			>1/10
Common	>1/100	and	<1/10
Uncommon	>1/1000	and	<1/100
Rare	>1/10,000	and	<1/1000
Very rare	<1/10,000		

– Urogenital

- Bleeding

  Bleeding occurs in almost all women and increases with the age of pregnancy at the time of termination.

  Heavy bleeding occurs in about 5% of the cases and may require hemostatic curettage in up to 1.4% of the cases.

- Very common uterine contractions or cramping (10 to 45%) in the hours following prostaglandin intake.
- Uterine rupture has been uncommonly reported after prostaglandin intake for induction of second trimester termination of pregnancy of labour induction for fetal death in utero during the third trimester.

  The reports occurred particularly in multiparous women or in women with a cesarean section scar.

– Gastrointestinal

Nausea, vomiting, diarrhea, are very common after prostaglandin intake.

– Cardiovascular

Uncommon hypotension (0.25%).

– Hypersensitivity and skin

Uncommon skin rashes (0.2%). Single cases of urticaria, of erythroderma, erythema nodosum, epidermal necrolysis have also been reported.

– Other systems

Rare cases of headaches, malaise, common vagal symptoms (hot flushes, dizziness, chills), and uncommon fever have been reported .

4.9 Overdose

Dose-ranging studies have shown that administration of single doses of mifepristone up to 2 g caused no unwanted reaction.

In the event of accidental massive ingestion, signs of adrenal failure might occur. Any suggestion of acute intoxication, therefore, requires treatment in a specific environment, and with dexamethasone administration if relevant.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

OTHER SEX HORMONE AND MODULATOR OF THE REPRODUCTIVE FUNCTION/
ANTIPROGESTOGEN (GO3 X B01: Urogenital System and Sex Hormones).

Mifepristone is a synthetic steroid with an antiprogestational action as a result of competition with progesterone at the progesterone receptors.

At doses ranging from 3 to 10mg/kg orally, it inhibits the action of endogenous or exogenous progesterone in different animal species (rat, mouse, rabbit and monkey). This action is manifested in the form of pregnancy termination in rodents.

In women at doses greater than or equal to 1mg/kg, mifepristone antagonises the endometrial and myometrial effects of progesterone. During pregnancy it sensitises the myometrium to the contraction- inducing action of prostaglandins. During the first trimester, pre-treatment with mifepristone allows the dilatation and opening of the cervix uteri. While clinical data have demonstrated that mifepristone facilitates dilatation of the cervix, no data are available to indicate that this results in a lowering of the rate of early or late complications to the dilatation procedure.

In the event of an early termination of pregnancy, the combination of a prostaglandin analogue used in a sequential regimen after mifepristone leads to an increase in the success rate to about 95 % of the cases and accelerates the expulsion of the conceptus.

In clinical trials, according to the prostaglandin used and the time of application, the results slightly vary.

The success rate is up to 95.7% when misoprostol is used orally up to 49 days of amenorrhea, and with gemeprost applied vaginally, it reaches to 98.7% up to 49 days of amenorrhea and to 94.8% up to 63 days of amenorrhea.

According to the clinical trials and to the type of prostaglandin used, the failure rate may vary. Failures occur in 1.3 to 7.5% of the cases receiving sequentially MIFEGYNE® followed by a prostaglandin analog, of which:

- 0 to 1.5% of ongoing pregnancies
- 1.3 to 4.6% of partial abortion, with incomplete expulsion
- 0 to 1.4% of hemostatic curettage

Combinations of mifepristone with other prostaglandin analogues have not been studied.

During the termination of pregnancy for medical reasons *beyond the first trimester*, mifepristone administered at a 600-mg dose, 36 to 48 hours prior to the first administration of prostaglandins, reduces the induction-abortion interval, and also decreases the prostaglandin doses required for the expulsion.

When used for labour induction of fetal death in utero, mifepristone alone induces expulsion in about 60% of cases within 72 hours following the first intake. In that event, the administration of prostaglandin or ocytocics would not be required.

Mifepristone binds to the glucocorticoid receptor. It doesn't bind to mineralocorticoid receptors; therefore, the risk of acute adrenal failure during mifepristone intake is negligible. In animals at doses of 10 to 25mg/kg it inhibits the action of dexamethasone. In man the antiglucocorticoid action is manifested at a dose equal to or greater than 4.5mg/kg by a compensatory elevation of ACTH and cortisol.

Mifepristone has a weak anti-androgenic action which only appears in animals during prolonged administration of very high doses.

5.2 Pharmacokinetic properties

After oral administration of a single dose of 600mg mifepristone is rapidly absorbed. The peak concentration of 1.98mg/l is reached after 1:30 hours (means of 10 subjects).

There is a non-linear dose response. After a distribution phase, elimination is at first slow, the concentration decreasing by a half between about 12 and 72 hours, and then more rapid, giving an elimination half-life of 18 hours. With radio receptor assay techniques, the terminal half-life is of up to 90 hours, including all metabolites of mifepristone able to bind to progesterone receptors.

After administration of low doses of mifepristone (20mg orally or intravenously), the absolute bioavailability is 69%.

In plasma mifepristone is 98% bound to plasma proteins: albumin and principally alpha-1-acid glycoprotein (AAG), to which binding is saturable. Due to this specific binding, volume of distribution and plasma clearance of mifepristone are inversely proportional to the plasma concentration of AAG.

N-Demethylation and terminal hydroxylation of the 17-propynyl chain are primary metabolic pathways of hepatic oxidative metabolism.

Mifepristone is mainly excreted in faeces. After administration of a 600mg labelled dose, 10% of the total radioactivity is eliminated in the urine and 90% in the faeces.

5.3 Preclinical safety data

In toxicological studies in rats and monkeys up to a duration of 6 months, mifepristone produced effects related to its antihormonal (antiprogesterone, antiglucocorticoid and antiandrogenic) activity.

In reproduction toxicology studies, mifepristone acts as a potent abortifacient. No teratogenic effect of mifepristone was observed in rats and mice surviving foetal exposure. In rabbits surviving foetal exposure, however, isolated cases of severe abnormalities occurred (cranial vault, brain and spinal cord). The number of foetal anomalies was not statistically significant and no dose-effect was observed. In monkeys, the number of foetuses surviving the abortifacient action of mifepristone was insufficient for a conclusive assessment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous colloidal silica, maize starch, povidone, microcrystalline cellulose, magnesium stearate.

6.2 Incompatibilities

None known.

6.3 Shelf-life

3 years.

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

Blister pack (PVC and Aluminium foil and carton) containing 3 tablets.

6.6 Instructions for Use/Handling

The treatment procedure should be fully explained and completely understood by the patient.

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTORISATION NUMBER

9. DATE OF FIRST AUTHORISATION

10. DATE OF REVISION OF THE TEXT

November 2001.

APPENDIX 11.2.2.

EUROPEAN SMPC APPROVED JULY 6TH, 1999
UPDATED NOVEMBER, 2000

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MIFEGYNE® 200mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200-mg mifepristone.

3. PHARMACEUTICAL FORM

Tablet.
Light yellow, cylindrical, biconvex tablets marked "167 B" on one side.

4. CLINICAL PARTICULARS

For termination of pregnancy, MIFEGYNE® and the prostaglandin can only be prescribed and administered in accordance with the countries laws and regulations.

As a consequence, they can only be prescribed by a medical doctor and in public or private hospital or centre (having approval to undertake termination of pregnancy). The product will be administered in the presence of the medical practitioner or of a delegated health professional.

If required by the afore mentioned laws and regulations, the patient should sign a letter of informed consent to certify that she has been fully informed about the method and its risks.

This timing of the first visit should take into account the requirement of some countries for a period of reflection prior to the abortion procedure.

4.1 Therapeutic indications

1- Medical termination of developing intra-uterine pregnancy.

In sequential use with a prostaglandin analogue, up to 49 days of amenorrhea.

2- Softening and dilatation of the cervix uteri prior to surgical termination of pregnancy during the first trimester.

3- Preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons *(beyond the first trimester).*

4- Labour induction in foetal death in utero.

In patients where prostaglandin or oxytocin cannot be used.

4.2 Posology and Method of Administration

1- Medical termination of developing intra-uterine pregnancy

The method of administration will be as follows:

600mg of mifepristone (i.e. 3 tablets of 200mg each) is taken in a single oral dose, followed by 36 to 48 hours later, the administration of a prostaglandin analogue; misoprostol 400µg orally, or gemeprost 1mg per vaginum.

2- Softening and dilatation of the cervix uteri prior to surgical termination of pregnancy during the first trimester

200mg of mifepristone (one tablet), followed 36 to 48 hours later (but not beyond) by surgical termination of pregnancy.

3- Preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons

600mg of mifepristone (i.e. 3 tablets of 200mg each) taken in a single oral dose, 36 to 48 hours prior to scheduled prostaglandin administration which will be repeated as often as indicated.

4- Labour induction in foetal death in utero

600mg of mifepristone (e.g. 3 tablets of 200mg each) in a single oral daily dose, for two consecutive days.

Labour should be induced by the usual methods if it has not started within 72 hours following the first administration of mifepristone.

4.3 Contra-indications

This product SHOULD NEVER be prescribed in the following situations.

In all indications

- Chronic adrenal failure
- Known allergy to mifepristone or to any component of the product
- Severe asthma uncontrolled by therapy
- **Inherited porphyria**

In the indication: medical termination of developing intra-uterine pregnancy

- pregnancy not confirmed by ultrasound scan or biological tests
- pregnancy of 50 days' amenorrhea and beyond
- suspected extra-uterine pregnancy
- contra-indication to the prostaglandin analogue selected

In the indication: softening and dilatation of the cervix uteri prior to surgical termination of pregnancy:

- pregnancy not confirmed by ultrasound scan or biological test
- pregnancy of 84 days of amenorrhea and beyond (according to legal requirements)
- suspected extra-uterine pregnancy

Preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons *(beyond the first trimester)*

- contra-indications to the prostaglandin analogue selected

Labour induction in foetal death in utero

Should prostaglandin combination be required, refer to contra-indications to the prostaglandin analogue selected.

4.4 Special warnings and special precautions for use

Warnings

In the absence of specific studies, MIFEGYNE® is not recommended in patients with:

- *Renal failure*
- *Hepatic failure*
- *Malnutrition*

1- Medical termination of developing intra-uterine pregnancy

This method requires an active involvement of the woman who should be informed of the method's requirements:

- the necessity to combine treatment with prostaglandin to be administered at a second visit,
- the need for a control visit (3rd visit) within 10 to 14 days after MIFEGYNE's intake in order to check for complete expulsion,
- The possible failure of the method, leading to a pregnancy termination by another method.

In the case of a pregnancy occurring with an intra-uterine device in situ, this device must be removed before administration of MIFEGYNE®.

The expulsion may take place before prostaglandin administration (in about 3% of cases). This does not preclude the control visit in order to check for the complete expulsion and the uterine vacuity.

- Risks related to the method

  - Failures

    The non-negligible risk of failure, which occurs in 1.3 to 7.5 % of the cases, makes the control visit mandatory in order to check that the expulsion is completed.

  - Bleeding

    The patient must be informed of the occurrence of prolonged vaginal bleeding (up to 12 days after MIFEGYNE® intake) which may be heavy. Bleeding occurs in almost all cases and is not in anyway a proof of complete expulsion.

The patient should be informed not to travel far away from the prescribing centre as long as complete expulsion has not been recorded. She will receive precise instructions as to whom she should contact and where to go, in the event of any problems emerging, particularly in the case of very heavy vaginal bleeding.

A follow-up visit must take place within a period of 10 to 14 days after administration of MIFEGYNE® to verify by the appropriate means (clinical examination, ultrasound scan, and Beta-HCG measurement) that expulsion has been completed and that vaginal bleeding has stopped. In case of persistent bleeding (even light) beyond the control visit, its disappearance should be checked within a few days.

If an ongoing pregnancy is suspected, a further ultrasound scan may be required to evaluate its viability.

Persistence of vaginal bleeding at this point could signify incomplete abortion, or an unnoticed extra-uterine pregnancy, and appropriate treatment should be considered.

In the event of an ongoing pregnancy diagnosed after the control visit, termination by another method will be proposed to the woman.

Since heavy bleeding requiring hemostatic curettage occurs in 0 to 1.4% of the cases during the medical method of pregnancy termination, special care should be given to patients with hemostatic disorders with hypocoagulability, or with anemia. The decision to use the medical or the surgical method should be decided with specialised consultants according to the type of hemostatic disorder and the level of anaemia.

2- Softening and dilatation of the cervix uteri prior to surgical pregnancy termination

For the full efficacy of therapy, the use of MIFEGYNE® must be followed,
36 to 48 hours later and not beyond, by surgical termination.

- Risks related to the method

  - Bleeding

    The woman will be informed of the risk of vaginal bleeding which may be heavy, following MIFEGYNE's intake. She should be informed of the risk of abortion prior to surgery (although minimal): she will be informed on where to go in order to check for the completeness of expulsion, or in any case of emergency.

- Other risks

They are those of the surgical procedure.

3- In all instances

The use of MIFEGYNE® requires rhesus determination and hence the prevention of rhesus allo-immunisation as well as other general measures taken usually during any termination of pregnancy.

During clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses.

To avoid potential exposure of a subsequent pregnancy to mifepristone, it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after mifepristone administration.

Precautions for use

1- In all instances

In case of suspected acute adrenal failure, dexamethasone administration is recommended. 1mg of dexamethasone antagonises a dose of 400mg of mifepristone.

Due to the antiglucocorticoid activity of mifepristone, the efficacy of long-term corticosteroid therapy, including inhaled corticosteroids in asthmatic patients, may be decreased during the 3 to 4 days following MIFEGYNE's intake. Therapy should be adjusted.
A decrease of the efficacy of the method can theoretically occur due to the antiprostaglandin properties of non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin (acetyl salicylic acid). Use preferably non-NSAI analgesics.

2- Medical termination of developing intra-uterine pregnancy

Rare serious cardiovascular accidents have been reported following the intra muscular administration of the prostaglandin analogue sulprostone (withdrawn in 1992). No such cases have been reported since analogues of PGE_1 (gemeprost or misoprostol) have been used. For these reasons and as a special precautionary measure, the medical method is not recommended for use in women over 35 years of age and who smoke more than 10 cigarettes a day.

Method of prostaglandin administration

During intake and for three hours following the intake, the patients should be monitored in the treatment centre, which must be equipped with the appropriate equipment.

3- For the sequential use of MIFEGYNE® - Prostaglandin, whatever the indication

The precautions related to the prostaglandin used should be followed where relevant.

4.5 Interaction with other medicinal products and other forms of interactions

No studies to investigate possible interactions between mifepristone and other drugs have been carried out.

4.6 Pregnancy and lactation

In animals (see section 5.3 Pre-clinical safety data), the abortifacient effect of mifepristone precludes the proper assessment of any teratogenic effect of the molecule.

With subabortive doses, isolated cases of malformations observed in rabbits, but not in rats or mice were too few to be considered significant, or attributable to mifepristone.

In humans, the few reported cases of malformations do not allow a causality assessment for mifepristone alone or associated to prostaglandin. Therefore, data is too limited to determine whether the molecule is a human teratogen.

Consequently:

- Women should be informed, that due to the risk of failure of the medical method of pregnancy termination and to the unknown risk to the foetus, the control visit is mandatory (see Section 4.4 special warnings and special precautions for use).
- Should a failure of the method be diagnosed at the control visit *(viable ongoing pregnancy)*, and should the patient still agree, pregnancy termination should be completed by another method.
- Should the patient wish to continue with her pregnancy, the available data is too limited to justify a systematic termination of an exposed pregnancy. In that event, a careful ultra-sonographic monitoring of the pregnancy will be established.

Lactation

Mifepristone is a lipophilic compound and may theoretically be excreted in the mother's breast milk. However, no data is available. Consequently, mifepristone use should be avoided during breast-feeding.

4.7 Effects on ability to drive and to use machines

Not known.

4.8 Undesirable effects

Most frequently reported undesirable effects

- Urogenital
  - Bleeding
    Heavy bleeding occurs in about 5% of the cases and may require hemostatic curettage in up to 1.4% of the cases.
  - Very common uterine contractions or cramping (10 to 45%) in the hours following prostaglandin intake.
  - During induction of second trimester termination of pregnancy or labour induction for foetal death in utero during the third trimester, uterine rupture has been uncommonly reported after prostaglandin intake. The reports occurred particularly in multiparous women or in women with a caesarean section scar.

- Gastrointestinal
  - Cramping, light or moderate.
  - Nausea, vomiting.

- Undesirable effects related to prostaglandin use: nausea, vomiting or diarrhoea, and rarely hypotension (0.25%)

Other undesirable effects

- Hypersensitivity and skin
  - Hypersensitivity: skin rashes uncommon (0.2%), single cases of urticaria.
  - Single cases of erythroderma, erythema nodosum, epidermal necrolysis have also been reported.

- Other systems
  Rare cases of headaches, malaise, vagal symptoms (hot flushes, dizziness, chills have been reported) and fever.

4.9 Overdose

After extensive clinical use, no reports of acute intoxication have been reported.

In the event of accidental massive ingestion, signs of adrenal failure might occur. Signs of acute intoxication may require specialist treatment including the administration of dexamethasone.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

OTHER SEX HORMONE AND MODULATOR OF THE REPRODUCTIVE FUNCTION/
ANTIPROGESTOGEN (GO3 X B01: Urogenital System and Sex Hormones).

Mifepristone is a synthetic steroid with an antiprogestational action as a result of competition with progesterone at the progesterone receptors.

At doses ranging from 3 to 10mg/kg orally, it inhibits the action of endogenous or exogenous progesterone in different animal species (rat, mouse, rabbit and monkey). This action is manifested in the form of pregnancy termination in rodents.

In women at doses of greater than or equal to 1mg/kg, mifepristone antagonises the endometrial and myometrial effects of progesterone. During pregnancy it sensitises the myometrium to the contraction- inducing action of prostaglandin. During the first trimester, pre-treatment with mifepristone allows the dilatation and opening of the cervix uteri. While clinical data have demonstrated that mifepristone facilitates dilatation of the cervix, no data are available to indicate that this results in a lowering of the rate of early or late complications to the dilatation procedure.

In the event of an early termination of pregnancy, the combination of a prostaglandin analogue used in a sequential regimen after mifepristone leads to an increase in the success rate to about 95 per cent of the cases and accelerates the expulsion of the conceptus.

In clinical trials, according to the prostaglandin used and the time of application, the results vary slightly.

The success rate is up to 95.7% when misoprostol is used orally up to 49 days of amenorrhea, and with gemeprost applied vaginally, it reaches 98.7% up to 49 days of amenorrhea and 94.8% up to 63 days of amenorrhea.

According to the clinical trials and to the type of prostaglandin used, the failure rate varies. Failures occur in 1.3 to 7.5% of the cases receiving sequentially MIFEGYNE® followed by a prostaglandin analog, of which:

- 0 to 1.5% of ongoing pregnancies

- 1.3 to 4.6% of partial abortion, with incomplete expulsion
- 0 to 1.4% of hemostatic curettage

Combinations of mifepristone with other prostaglandin analogues have not been studied.

During the termination of pregnancy for medical reasons *beyond the first trimester*, mifepristone administered at a 600-mg dose, 36 to 48 hours prior to the first administration of prostaglandins, reduces the induction-abortion interval, and also decreases the prostaglandin doses required for the expulsion.

When used for labour induction of foetal death in utero, mifepristone alone induces expulsion in about 60% of cases within 72 hours following the first intake. In that event, the administration of prostaglandin or ocytocics would not be required.

Mifepristone binds to the glucocorticoid receptor. It doesn't bind to mineralocorticoid receptors; therefore, the risk of acute adrenal failure during mifepristone intake is negligible. In animals at doses of 10 to 25mg/kg it inhibits the action of dexamethasone. In man the antiglucocorticoid action is manifested at a dose equal to or greater than 4.5mg/kg by a compensatory elevation of ACTH and cortisol.

Mifepristone has a weak anti-androgenic action which only appears in animals during prolonged administration of very high doses.

5.2 Pharmacokinetic properties

After oral administration of a single dose of 600mg mifepristone is rapidly absorbed. The peak concentration of 1.98mg/l is reached after 1.30 hours (means of 10 subjects).

There is a non-linear dose response. After a distribution phase, elimination is at first slow, the concentration decreasing by a half between about 12 and 72 hours, and then more rapid, giving an elimination half-life of 18 hours. With radio receptor assay techniques, the terminal half-life is of up to 90 hours, including all metabolites of mifepristone able to bind to progesterone receptors.

After administration of low doses of mifepristone (20mg orally or intravenously), the absolute bioavailability is 69%.

In plasma mifepristone is 98% bound to plasma proteins: albumin and principally alpha-1-acid glycoprotein (AAG), to which binding is saturable. Due to this specific binding, volume of distribution and plasma clearance of mifepristone are inversely proportional to the plasma concentration of AAG.

N-Demethylation and terminal hydroxylation of the 17-propynyl chain are primary metabolic pathways of hepatic oxidative metabolism.

Mifepristone is mainly excreted in faeces. After administration of a 600mg labelled dose, 10% of the total radioactivity is eliminated in the urine and 90% in the faeces.

5.3 Preclinical safety data

In toxicological studies in rats and monkeys up to a duration of 6 months, mifepristone produced effects related to its antihormonal (antiprogesterone, antiglucocorticoid and antiandrogenic) activity.

In reproduction toxicology studies, mifepristone acts as a potent abortifacient. No teratogenic effect of mifepristone was observed in rats and mice surviving foetal exposure. In rabbits surviving foetal exposure, however, isolated cases of severe abnormalities occurred (cranial vault, brain and spinal cord). The number of foetal anomalies was not statistically significant and no dose-effect was observed. In monkeys, the number of foetuses surviving the abortifacient action of mifepristone was insufficient for a conclusive assessment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silica anhydrous, maize starch, povidone, magnesium stearate, microcrystalline cellulose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years.

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

3 tablets in blister (PVC / Aluminium).

6.6 Instructions for use and handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

EXELGYN
6, rue Christophe Colomb
75008 PARIS
France

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

November 2000.

APPENDIX 11.3.

STATUS OF CLINICAL TRIALS

APPENDIX 11.3.1

CLINICAL TRIALS IN PROGRESS

ONGOING CLINICAL TRIALS NOT SPONSORED BY THE COMPANY BUT FOR WHICH EXELGYN PROVIDED THE ACTIVE AND PLACEBO TABLETS

PRINCIPAL INVESTIGATOR and TRIAL CODE	COUNTRY	TITLE	N PATIENTS		SINGLE DOSE (mg)	Report
			ENROLLED	EXPECTED		
(b) (4)						

APPENDIX 11.3.2.

NAMED-PATIENTS STUDIES

NAMED PATIENTS

Named-patients studies
May 31st, 2002

41	with unresectable meningioma
1	with leiomyosarcoma
1	with adrenal tumors (Cushing syndromes)
1	with paraganglioma
1	with paraneoplastic syndrome
2	with psychotic depression
1	with neurofibromatosis type II
1	with ovarian cancer
49	**Patients**

APPENDIX 11.4

LINE LISTINGS OF INDIVIDUAL CASE HISTORIES

CIOMS LISTING

MIFEPRISTONE

Company number	Reaction term				
Date	Country	Type of report	labelled	Indication	Outcome
Reaction / event description					
Case comments					

SERIOUSNESS Yes

REPRODUCTIVE DISORDERS, FEMALE

S2002003F/MIF1 **PREGNANCY UNINTENTED**
F spontaneous N TERMINATION OF PREGNANCY Fetal malformation

UNINTENTED PREGNANCY, FETAL MALFORMATION:

This case from France involved a 25-year-old woman who received mifepristone 600 mg on (b) (6) followed by misoprotol 400 µg on (b) (6) for medical termination of pregnancy at 7 weeks gestation. She did not return for the control 2 weeks later.
On (b) (6) she came back to the hospital for an amenorrhea. An ultrasound examination showed a viable intra-uterine pregnancy corresponding to 15 weeks gestation and revealed embryo (LCC: 90 mm) with a cephalic abnormality (encephalocele).
On (b) (6) therapeutic termination of pregnancy was decided and performed. Post-abortum examination revealed a 92 g fetus which was malformed with meningo-encephalocele, finger defects on the left hand (oligodactylia) and feet (monodactylia) and dysmorphia.

Company comments:
There were no reported cases of malformation associated with use of misoprostol when used with mifepristone.

S2001020F/MIF1 **EXCESSIVE BLEEDING**
(b) (6) F spontaneous Y TERMINATION OF PREGNANCY Recovered

INCOMPLETE ABORTION, EXCESSIVE BLEEDING:

This case from France (Regional Centre of Pharmacovigilance) involved a 22-year-old woman. She received mifepristone 200 mg for medical termination of pregnancy at 12 weeks gestation, on (b) (6)
She changed her mind, decided to keep her pregnancy and did not take misoprostol. One day later on (b) (6) she experienced excessive bleeding and came to the emergency room. An incomplete abortion was diagnosed and curettage was performed. The patient recovered with sequelae.

Company comments:
Case of misuse. Non conformed uses with respect to the SmPC of Mifegyne®. Improper posology. Mifepristone incorrectly administered (medical TOP at 12 weeks of amenorrhea).

S2001025F/MIF1 **PREGNANCY UNINTENDED**
☐ F spontaneous Y TERMINATION OF PREGNANCY Recovered

UNINTENDED PREGNANCY:

This case from France involved a 32-year-old woman who received mifepristone 600 mg on (b) (6) and misoprostol 400 µg 2 days later for termination of pregnancy. The treatment failed and the patient requested surgical termination of pregnancy on (b) (6)

Company comments:

CIOMS LISTING

MIFEPRISTONE					
Company number	Reaction term				
Date	Country	Type of report	labelled	Indication	Outcome
Reaction / event description					
Case comments					

SERIOUSNESS ***Yes***

REPRODUCTIVE DISORDERS, FEMALE

S2001026F/MIF1 **PREGNANCY UNINTENDED**

☐	F	spontaneous	Y	TERMINATION OF PREGNANCY	Recovered

UNINTENDED PREGNANCY:

This case from France involved a 29-year-old woman who received mifepristone 600 mg on (b) (6) and misoprostol 400 µg 2 days later for termination of pregnancy. The treatment failed and the patient requested surgical termination of pregnancy on (b) (6)

Company comments:

S2001027F/MIF1 **PREGNANCY UNINTENDED**

☐	F	spontaneous	Y	TERMINATION OF PREGNANCY	Recovered

UNINTENDED PREGNANCY:

This case from France involved a 23-year-old woman who received mifepristone 600 mg on (b) (6) and misoprostol 400 µg 2 days later for termination of pregnancy. The treatment failed and the patient requested surgical termination of pregnancy on (b) (6)

Company comments:

S2001028F/MIF1 **PREGNANCY UNINTENDED**

☐	F	spontaneous	Y	TERMINATION OF PREGNANCY	Recovered

UNINTENDED PREGNANCY:

This case from France involved a 28-year-old woman who received mifepristone 600 mg on (b) (6) and misoprostol 400 µg 2 days later for termination of pregnancy. The treatment failed and the patient requested surgical termination of pregnancy on (b) (6)

Company comments:

S2001029F/MIF1 **PREGNANCY UNINTENDED**

☐	F	spontaneous	Y	TERMINATION OF PREGNANCY	Recovered

UNINTENDED PREGNANCY:

This case from France involved a 32-year-old woman who received mifepristone 600 mg on (b) (6) and misoprostol 400 µg 2 days later for termination of pregnancy. The treatment failed and the patient requested surgical termination of pregnancy on (b) (6)

Company comments:

CIOMS LISTING

MIFEPRISTONE					
Company number	Reaction term				
Date	Country	Type of report	labelled	Indication	Outcome
Reaction / event description					
Case comments					

SERIOUSNESS *Yes*

BODY AS WHOLE-GENERAL DISORDERS

S2002004UK/MIF1		DEATH			
(b) (6)	UK	spontaneous	N	TERMINATION OF PREGNANCY	

DEATH:

This case from UK involved a young woman who received mifepristone 200 mg on (b) (6) followed by misoprotol 800 µg two days later for medical termination of pregnancy at 7.5 weeks gestation. She was treated also by codeine and paracetamol for pain relief and azithromycin 1 mg antibiotic as prophylaxis of infection. The procedure went well and the patient was discharged home.
On (b) (6) evening, the patient started to feel unwell and reported pain in her leg, headache and racing heart. She reported to the hospital accident and emergency department but she collapsed and she died in the ambulance before her arrival at the hospital.
No information available at the moment of the time scale involved nor the details of her symptoms at the time of death.
Preliminary information from post-mortem indicates that one litre of blood was found in the stomach and gastric ulceration was identified.

Company comments:
The cause of the death is still unknown. Further details are requested. Results of the toxicology tests and the Coroners findings are still not available.

S2002001F/MIF1		CHEST PAIN			
(b) (6)	F	spontaneous	N	FETAL DEATH IN UTERO	Recovered

THORACIC PAIN, ISCHEMIC ACCIDENT:

This case from France involved a 29-year-old female patient without relevant medical history. She received mifepristone 600 mg on (b) (6) (b) (6) for fetal death in utero at 22 weeks gestation.
On (b) (6), another dose of mifepristone 600 mg was given, and the same day the patient experienced thoracic pain. She came to the emergency room, an ECG was performed and showed a subepicardial anteseptal ischemia. The patient was hospitalised in cardiology unit. Biological complementary exams were performed and showed very high level of antiphospholipid antibodies. This result together with the symptoms (Fetal Death in Utero + ischemia) allowed the physician to make the diagnosis of antiphospholipid Syndrome (systemic disease).
On (b) (6), cervical dilatation with laminarias was performed to induce dead foetus evacuation.
On (b) (6) expulsion occurred under peridural anaesthesia without any cardiovascular symptom. She was transferred to the intensive care unit and monitored during 24h. The patient recovered and had no additional complications.
Complementary exams were requested by the physician to confirm the diagnosis of systemic disease.

Company comments:
There is no known effect of mifepristone on the vessels. The relationship to Mifegyn® is unlikely in view of the fact that the patient was suffering from a latent systemic disease.

CIOMS LISTING

MIFEPRISTONE

Company number	Reaction term				
Date	Country	Type of report	labelled	Indication	Outcome
Reaction / event description					
Case comments					

SERIOUSNESS ***Yes***

BODY AS WHOLE-GENERAL DISORDERS

S2001022F/MIF1 **EDEMA**
(b) (6) F spontaneous Y TERMINATION OF EARLY PREGNANCY Recovered

ALLERGIC REACTION, PALPEBRAL EDEMA:

This case from France involved a 19-year-old woman who received mifepristone 600 mg on (b) (6) for medical termination of pregnancy.
On (b) (6), she received at 6:45 a.m. misoprostol, Temgesic® (buprenorphine), Monocline® (doxycycline) and Primperan® (metoclopramide). At 8a.m., she received Pro-Dafalgan® (propacétamol) and Profenid® (kétaprofène). She vomited immediately and experienced bilateral palpebral edema without any cardiovascular and pulmonary symptom. The hemodynamic situation was correct. She was treated immediately with Celesten® (betaméthasone) and she left the hospital the same day. Cutaneous tests were performed for Cytotec® (misoprostol), Temgesic®, Monocline®, Pro-Dafalgan®, Profenid® and Monocline®. All were negative.

Company comments: Expected and listed adverse event

S2001030F/MIF1 **ALERGIC REACTION**
(b) (6) F spontaneous Y TERMINATION OF EARLY PREGNANCY Recovered

CYTOTEC ALLERGIC REACTION:

This case from France involved a patient who received mifepristone and misoprostol for medical termination of pregnancy on (b) (6).
The patient developed allergic reaction 2 hours after taking misoprostol, she had pallor, tachycardia, hypotension. The patient was hospitalized and treatment was given. The medical termination of pregnancy failed and the patient requested surgical termination of pregnancy which was performed. Cutaneous allergic tests were performed for misoprostol, mifepristone and trinordiol. The tests were negative for mifepristone and trinordiol. Misoprostol test was strongly positive and the drug became contra-indicated for the patient.

Company comments: Expected and listed adverse event

CIOMS LISTING

MIFEPRISTONE					
Company number	Reaction term				
Date	Country	Type of report	labelled	Indication	Outcome
Reaction / event description					
Case comments					

SERIOUSNESS Yes

RESISTENCE MECHANISM DISORDERS

S2001019F/MIF1		SEPTICEMIA			
(b) (6)	F	spontaneous	Y	TERMINATION OF EARLY PREGNANCY	Recovered

STREPTOCOCCUS SEPTICEMIA, ENDOMETRITIS, ARTHRITIS, ICTERUS, ANEMIA:

This case from France involved a 29-year-old woman who was given mifepristone 400 mg on (b) (6) for medical termination of pregnancy while she was at 7.3 weeks of amenorrhea. She received misoprostol (400 µg x 2) two days later on the (b) (6) The patient did not bleed very much during the three hours observation period and the expulsion did not occur. She went home with a prescription for an ultrasound examination, analgesics and oral contraception.
On (b) (6), the patient experienced fever (40°C), vomiting and diarrhea. After examination, the doctor diagnosed febrile arthritis of the left knee. The patient came to emergency room with icterus, important metrorrhagia and pelvic pain at the gynaecological examination. An ultrasound was done and showed a normal uterus with a normal size. Hemoglobin level was 8.7 g/l, SGPT 69 and SGOT 96, bilirubin level was 66 µmol/l and βHCG were 47,000 mUI/ml.
She was hospitalised and the diagnosis of endometritis with secondary localisation at left knee was done. She was treated with amoxicillin-clavulanic acid, netilmicin and oxytocin.
On (b) (6), at 1 a.m., vacuum aspiration was performed because of heavy bleeding and low hemoglobin level (6.9 g/l). The same day, at 6 a.m. the hemoglobin level decreased to 4.9 g/l and blood transfusion was performed. Hemocultures and bacteriological test of vaginal fluid were done and revealed a *Streptococcus dysgalactiae penicillin sensible*. The treatment was changed to amoxicillin and metronidazole.
On (b) (6) puncture of the knee showed 1,000 white blood cells (95% sterile polynuclear).
On an arthroscopy was performed and βHCG were 4,800 mUI-ml. Apyrexia was obtained after 72h of antibiotherapy.
On , gynaecologic problems were resolved, the outcome was favorable with a good status of the patient and normal clinical examination.

Company comments:
The dose of mifepristone (400 mg) was less than the recommended one (600 mg).

CIOMS LISTING

MIFEPRISTONE					
Company number	Reaction term				
Date	Country	Type of report	labelled	Indication	Outcome
Reaction / event description					
Case comments					

SERIOUSNESS No

REPRODUCTIVE DISORDERS, FEMALE

S20000024S/MIF2 PREGNANCY UNINTENDED

☐	S	spontaneous	Y	TERMINATION OF PREGNANCY	Normal baby

UNINTENDED PREGNANCY, NORMAL BABY:

This case from Sweden involved 20-year-old woman who was treated with mifepristone 600 mg followed by gemeprost 1mg at 8-9 weeks gestation . She came back to the hospital, after 4 weeks for control by urinary pregnancy test. The result was negative. She came back again later to the hospital and a 23 weeks pregnancy was shown by ultrascan. Application for late abortion was made but the authority did not approve (this case was reported in PSUR n°10: S2000024S/MIF).
The pregnancy was normal and a totally healthy baby girl was born on (b) (6)

Company comments:
This case has been reported retrospectively.

S2001031UK/MIF1 PREGNANCY UNINTENDED

☐	UK	spontaneous	Y	TERMINATION OF PREGNANCY	Ongoing

UNINTENDED PREGNANCY:

This case from UK involved 21-year-old woman who received mifepristone 200 mg at 17 weeks gestation for termination of pregnancy. She changed her mind and wanted to keep her pregnancy. More information is requested.

Company comments:
No other information, a follow-up has been required. This case has been reported prospectively.

S2001032UK/MIF1 PREGNANCY UNINTENTED

☐	UK	spontaneous	Y	TERMINATION OF PREGNANCY	Ongoing

UNINTENTED PREGNANCY:

This case from UK involved female patient who received mifepristone 200 mg and misoprostol 800 µg vaginally for termination of early pregnancy. She changed her mind and decided to keep her pregnancy. More information is requested.

Company comments:
No other information, follow-up has been required. This case has been reported prospectively.

CIOMS LISTING

MIFEPRISTONE

Company number	Reaction term				
Date	Country	Type of report	labelled	Indication	Outcome
Reaction / event description					
Case comments					

SERIOUSNESS ***No***

REPRODUCTIVE DISORDERS, FEMALE

S2001033UK/MIF1 **PREGNANCY UNINTENDED**
☐ UK spontaneous Y TERMINATION OF PREGNANCY Ongoing

UNINTENDED PREGNANCY:

This case from UK involved a woman who received mifepristone 600 mg for termination of pregnancy at 18 weeks of gestation. She changed her mind and decided to keep her pregnancy. More information is requested.

Company comments:
No other information, a follow-up has been required. This case has been reported prospectively.

S2001034UK/MIF1 **PREGNANCY UNINTENTED**
☐ UK spontaneous Y TERMINATION OF PREGNANCY Ongoing

UNINTENTED PREGNANCY:

This case from UK involved female patient who received mifepristone 200 mg at 9 weeks gestation for termination of pregnancy. She changed her mind and wanted to keep her pregnancy. More information is requested.

Company comments:
No other information, follow-up has been required. This case has been reported prospectively.

S2001035UK/MIF1 **PREGNANCY UNINTENDED**
☐ UK spontaneous Y TERMINATION OF PREGNANCY Ongoing

UNINTENDED PREGNANCY:

This case from UK involved female patient who received mifepristone 200 mg and misoprostol 600 µg vaginally followed by misoprostol 400 µg per os for termination of pregnancy at 10 weeks gestation.. The treatment failed and the patient decided to keep her pregnancy.

Company comments:
No other information, a follow-up has been required. This case has been reported prospectively.

CIOMS LISTING

MIFEPRISTONE					
Company number	Reaction term				
Date	Country	Type of report	labelled	Indication	Outcome
Reaction / event description					
Case comments					

SERIOUSNESS No

REPRODUCTIVE DISORDERS, FEMALE

S2001024D/MIF1 PREGNANCY UNINTENDED
☐ D spontaneous Y TERMINATION OF PREGNANCY

UNINTENDED PREGNANCY:

This case from Germany involved female patient who received mifepristone 600 mg on (b) (6) followed by misoprostol 400 µg 36 hours later for termination of pregnancy at less than 6 weeks amenorrhea.
She came back for control on (b) (6) She was bleeding and the ultrasound showed continuing intra-uterine pregnancy. The patient requested a surgical termination of pregnancy which was performed.

Company comments:

S2001023D/MIF1 PREGNANCY UNINTENDED
☐ D spontaneous Y TERMINATION OF PREGNANCY

UNINTENDED PREGNANCY:

This case from Germany involved a 24-year-old woman who received mifepristone 600 mg on (b) (6) followed by misoprostol 400 µg 2 days later for medical termination of pregnancy.
She came back for control on (b) (6) An ultrasound was performed and showed continuing intra-uterine pregnancy. Surgical termination of pregnancy was performed.

Company comments:

S2001017UK/MIF2 PREGNANCY UNINTENDED
☐ UK spontaneous Y TERMINATION OF PREGNANCY fetal death

UNINTENDED PREGNANCY, FETAL DEATH IN UTERO:

This case from UK involved a 22-year-old woman who received mifepristone 200 mg on (b) (6) followed by misoprostol 400 µg two days later for medical termination of pregnancy in the first trimester. The treatment failed and the patient decided to keep her pregnancy (this case was reported in PSUR n° 12, case # S2001017UK/MIF)
She came back for control on (b) (6) An ultrasound was performed and showed fetal death in utero with no fetal abnormality and a large placenta abruption. The abortion occurred on (b) (6)

Company comments:
Fetal death in utero is probably related to the large placenta abruption and not related to the early administration of mifepristone.

CIOMS LISTING

MIFEPRISTONE					
Company number	Reaction term				
Date	Country	Type of report	labelled	Indication	Outcome
Reaction / event description					
Case comments					

SERIOUSNESS ***No***

BODY AS WHOLE-GENERAL DISORDERS

S2001021F/MIF1		RASH			
(b) (6)	F	spontaneous	Y	UNRESECTABLE MENINGIOMA	Recovered

GENERALISED RASH, TOXIDERMA:

A 71 year-old female patient with relevant medical and surgical histories of unresectable meningioma, ovarian and uterine surgery and arterial hypertension. She received since (b) (6) mifepristone 200 mg.
On (b) (6) she experienced generalised macular rash.
In the investigator judgement the event is related to the drug mifepristone. The treatment was stopped and the patient recovered totally with an anihistaminic treatment (Zyrtec®).

Company comments:
Expected and listed adverse event.

S2002002D/MIF		ALLERGIC REACTION			
(b) (6)	D	spontaneous	Y	TERMINATION OF EARLY PREGNANCY	Recovered

ALLERGIC REACTION:

This case from Denmark involved female patient who received mifepristone 600 mg on (b) (6) for a medical termination of pregnancy. Five hours later, she begun to have exhantem on her arm and later over on the whole body.
She also experienced pressure over the breast and tendency for fainting. She was treated with antihistaminic agent and solumedrol 80 mg. The event disappeared and the patient totally recovered.

Company comments:
Expected and listed adverse event

APPENDIX 11.5

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Journal of Obstetrics and Gynaecology (2001) Vol. 21, No. 4, 386–388

GYNAECOLOGY

Setting up a one-stop mifepristone—misoprostol medical termination of pregnancy service for all gestations from 5 to 23 weeks—a review of 482 cases

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Summary
Mifepristone—misoprostol combination is increasingly being utilised for medical termination of pregnancy on account of its reported efficacy, safety and lower cost. Experience with this modality of effecting termination of pregnancy from 9 to 13 weeks' gestation is scanty. At the Scunthorpe General Hospital in the United Kingdom, we established a nurse-led, one-stop medical termination of pregnancy service using mifepristone and misoprostol for all gestations from 5 to 23 weeks. A review of the case records of 482 women who had medical termination of pregnancy at all gestations from 5 to 23 weeks from December 1997 to May 1999 was undertaken in order to assess the effectiveness and complications associated with the mifepristone—misoprostol protocol. Complete abortion was achieved in 406 (84%) women. Surgical evacuation was required to complete the abortion in 74 (16%) women. The complete abortion rate was similar across the spectrum, i.e. 87% in the 5–8-weeks group; 79% in the 9–13 weeks group; and 87% in those of ≥14 weeks. Two failures occurred: one of them proceeded to surgical evacuation after three courses of misoprostol, while the other continued with her pregnancy after one course. Three women (0·6%) required blood transfusion for haemorrhage, while two others were treated for infection. Oral mifepristone with or without vaginal misoprostol in an effective and safe regimen for termination of all pregnancies from 5 to 23 weeks' gestation.

Introduction

The medical option for termination of pregnancy is increasingly being utilised. The efficacy of mifepristone and misoprostol in this regard has been established (UK Multicentre Study, 1997; Ashok and Templeton, 1999; Gouk *et al.*, 1999). The other option, surgical evacuation of the uterus, although safe and effective, requires skilled personnel (Grimes and Cates, 1997). In addition, the medical option offers patients choice and is cheaper (Cameron *et al.*, 1996). Various regimens utilising mifepristone and misoprostol for terminating pregnancies at all possible gestations have been used (El-Refaey *et al.*, 1995; Ashok *et al.*, 1998; Ashok and Templeton, 1999).

Although the manufacturers of mifepristone recommend the use of a 600-mg dose pretreatment and gemeprost as the prostaglandin of choice, for termination of pregnancy, 200 mg of mifepristone and misoprostol (although not licensed for this indication) can be as effective (WHO, 1993; Webster *et al.*, 1996; Dickenson *et al.*, 1998). These have cost-saving implications. Using low-dose mifepristone and misoprostol as described in this text could save £157 per case compared to the manufacturer's recommendation (Table I).

Table I. Cost per termination of pregnancy by method

Method	*Cost per case*
Surgical	£226
Gemeprost	£175
Mifepristone/misoprostol	£18

Mifepristone is recommended for use at gestations of ≤8 and ≥13 weeks, but not from 9 to 12 weeks. It is in the latter area that experience is scanty. In this unit, prior to June 1997, most early pregnancy terminations were performed surgically while late termination involved using gemeprost. In June 1997, a medical termination of pregnancy clinic using mifepristone/misoprostol for all gestations from 5 to 23 weeks was established. This review was undertaken to assess the effectiveness of and problems associated with this method as the sole means of termination of pregnancy.

Methods

This service is provided by a specially dedicated termination of pregnancy clinic based exclusively on a day-case ward. It is led by specially trained nurses (additional qualifications include certificate in counselling) and supported by nursing and medical personnel, and the ultrasound department. We aim to see and treat patients within 2 weeks of referral (this target has been achieved in 90% of cases).

When a patient is referred, she first has an ultrasound examination to establish viable intrauterine pregnancy and gestational age. An occasional asymptomatic ectopic gestation is picked up at this stage. She then moves into the counselling room, during

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which time her wish to terminate her pregnancy is confirmed. She is assured of support, medical and surgical options for termination of pregnancy are discussed with her as well as future contraception.

If she elects to proceed with medical termination, the medications are usually commenced on the same day or the next day according to patient preference. Medication consists of mifepristone 200 mg orally. She is observed for 2 hours to ensure that she does not vomit and that the medication is retained. She goes home and returns 36–48 hours later when 800 mcg of misoprostol is administered vaginally. Those who are ≤8 weeks' gestation are observed for 6 hours and discharged. Most in this group (73%) expel the products of conception at this stage. Those who are ≥9 weeks' gestation receive further doses of misoprostol at 400 mcg orally 3-hourly for three doses if they had not expelled products of conception. This group may be observed overnight in hospital if necessary. In the occasional case in which the product of conception is not expelled, a repeat course of misoprostol is administered 24 hours later. The clinic staff check all products of conception for completeness. Contraception is commenced soon after abortion is complete.

When the patients go home, they are in contact with clinic staff and their GP by telephone. They are advised to report if unwell, if there is excessive bleeding, or offensive vaginal discharge. They are seen 2 weeks later to ensure that all is well. An ultrasound scan is performed in those women in whom the clinic staff did not visually confirm expulsion of products of conception, so as to ensure that abortion had occurred and was complete.

Results

The case records of 482 women who had mifepristone/misoprostol termination of pregnancy from June 1997 to May 1999 was reviewed. This represented 76% of all terminations of pregnancy during this period. This is compared to 27% in the period before June 1997 (Figure 1) The women were aged from 12 to 42 years with a mean of 24·2 years. Multiparous women made up 57·5% while 42·5% were nulliparous.

A total of 406 (84%) women had complete expulsion of the products of conception without any need for surgical intervention (made up of 403 women who succeeded after one course and three women who required repeat medication to succeed) (Figure 2). Seventy-four women did expel products of conception but required surgical evacuation to complete the process. Two women did not expel any products of conception—one was an 8 weeks' pregnancy that continued after one course of medication while the other was a 16 weeks' pregnancy which remained intact and had to have a surgical termination. A breakdown of the outcome into gestational age groups showed that complete success was achieved in 86·9% of those of ≤8 weeks' 79% in the 9–13 weeks' group, and 86·8% in the ≥14 weeks' group (Table II). Outcome was similar in multiparous and nulliparous groups with success rates of 84·9% and 83·6%, respectively.

The time from the administration of vaginal misoprostol to expulsion of the products of conception (misoprostol—abortion interval) ranged from 30 minutes to 29·5 hours across the board. Subdivided into gestational age groups, the mean misoprostol—abortion interval was 4·9 hours in the ≤8 weeks' 7·5 hours in the 9–13 weeks' group and 9·5 hours in the ≥14 weeks' group (Figure 3).

Haemorrhage requiring blood transfusion occurred in three patients (0·6%) and two (0·4%) patients were treated for infection.

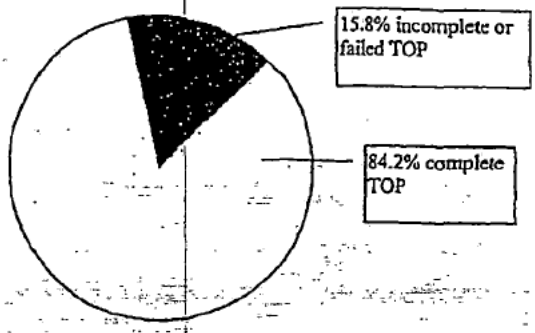

Figure 2. Overall outcome of mifepristone/misoprostol termination of pregnancy.

Table II. Outcome following mifepristone/misoprostol therapy

	Gestation		
	≤8 weeks (n=236)	9–13 weeks (n=169)	≥14 weeks (n=76)
Complete	205 (86·9%)	134 (79·2%)	67 (87%)
Incomplete	30 (12·7%)	35 (20·7%)	9 (11·6%)
Failed	1 (0·4%)	0	1 (1·3%)

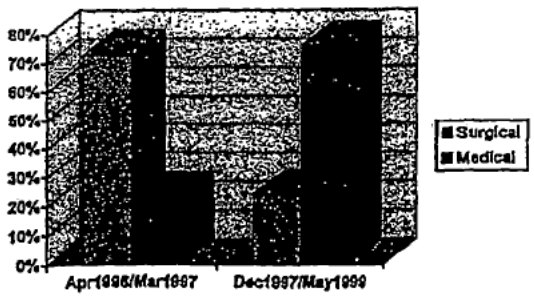

Figure 1. Proportion of termination of pregnancy performed surgically and medically before and after June 1997.

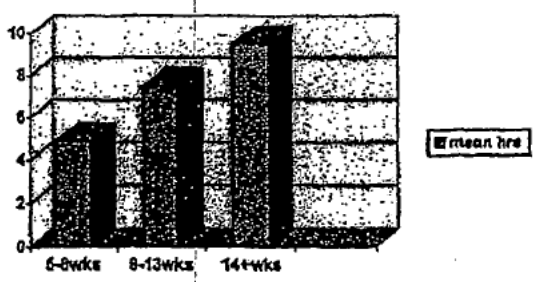

Figure 3. Mean misoprostol–abortion interval.

Discussion

Termination of pregnancy services are increasingly adopting methods that reduce cost and provide choice for women. Setting up a one-stop termination of pregnancy service is one way of achieving this aim. Providing all the service in one ward helped patient uptake of the service. A recent audit (unpublished) showed that 97% of all terminations of pregnancy in this hospital are now performed using the protocol described, the remaining 3% by the surgical method.

Our results add to the growing body of evidence that low dose mifepristone and misoprostol regimen offers an effective modality for terminating pregnancy at all possible gestations, and this has been shown to be cheaper (Hinshaw, 1999). Based on local costing (Table I), a saving of £208 and £157 accrues for each case of pregnancy terminated using this mifepristone/misoprostol protocol compared to the surgical or gemeprost options, respectively. Mifepristone is licensed for termination of pregnancy at ≤8 weeks and at ≥13 weeks' gestation. In most hospitals, surgical methods are used almost exclusively to effect termination of pregnancy from 9 to 13 weeks' gestation. Our success rate of 79% at 9–13 weeks further attest to the feasibility of a medical approach at this gestation (Ashok *et al.*, 1998a; Gouk *et al.*, 1999). Before June 1997, all the 168 women who presented for medical termination would have gone to theatre for suction termination. But following the introduction of this protocol, 133 of them had their wish accomplished without surgical intervention.

Our overall success rate of 84% is within the range of success rates reported in the literature, for those methods that used a similar regimen (Spitz *et al.*, 1998; Ashok *et al.*, 1998b). The success rate of 79% at 9–13 weeks could improve now that we are at the top end of the 'learning curve' since introducing the protocol in June 1997. This has nevertheless transformed the provision of termination of pregnancy service from a predominantly surgical procedure to an almost exclusively low-cost medical procedure.

Major complications are rare. Our blood transfusion rate of 0·6% is within the literature range of 0·4–0·7% (UK Multicentre Study, 1997; Gouk *et al.*, 1999). The prophylactic antibiotic regimen utilised in this protocol follows the recommendation of Sawaya *et al.* (1996), and the RCOG (1997). This seem effective since only two (0·4%) women were treated for infection. The low dose mifepristone/misoprostol protocol for termination of pregnancy at all gestations from 5 to 23 weeks is effective and safe. It reduces cost, releases theatre slots and staff, resources which are usually under pressure, for use by other competing needs. In addition, it offers women choice, especially those of 9–13 weeks' gestation who in most hospitals have no choice but surgical evacuation of uterus.

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First trimester abortion with mifepristone and vaginal misoprostol.

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First trimester abortion with mifepristone and vaginal misoprostol

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Abstract

This study assessed the efficacy and side effects of first trimester medical abortion using mifepristone and vaginally administered misoprostol. Medical abortion was first introduced in Denmark in December 1997, and the acceptability of this new approach in a Danish population was evaluated. The study included the first 100 women seeking medical abortion. The gestational age was from 33 to 56 days. All received 600 mg mifepristone (RU 486) orally followed 2 days later by vaginally administered misoprostol 400 μg. Success was defined as achieving complete abortion without the need for surgical evacuation. Ninety-three percent achieved a successful medical termination of pregnancy. Side effects were few, and the acceptability was high. Ninety percent of the women would prefer medical abortion in case of a new unwanted pregnancy. The combination of mifepristone and vaginally administrated misoprostol is effective, safe, has few side effects and is well accepted by Danish women.

Keywords: Early medical abortion; Vaginal misoprostol; Vaginal PGE_1; Danish population

1. Introduction

Medical abortion during the first 49–63 days of gestation is generally successful after using pretreatment with the progesterone antagonist mifepristone (Mifegyne®) followed by a prostaglandin E-1 analog [1–3]. Several medical regimens have been used, where the most common prostaglandin E-1 preparation in Europe is gemeprost (Cervagem®). Recently, the prostaglandin-E-1 misoprostol (Cytotec®) has been introduced. Most reports have been based on oral administration, but vaginal administration is associated with fewer side effects and improved efficacy [2,4–6].

Medical abortion is a new approach in Denmark, and the purpose of this study was to assess the efficacy, side effects and the acceptability of mifepristone followed by vaginal administration of 400 μg misoprostol 2 days later.

2. Materials and methods

The study was performed at the Department of Gynaecology, University Hospital of Aarhus, Denmark, from September 1998 to July 1999. During that period, 753 women underwent termination of pregnancy in the department. Women over the age of 18, requesting termination of pregnancy and with a gestation of less than 56 days, received written information about the methods offered before attending the clinic. They were all tested for chlamydia by their general practitioner and, if positive, treated with antibiotics prior to the day of attendance. All women underwent a transvaginal ultrasound scan to evaluate the gestational age. Two-hundred-eighty women (34.5%) were less than 56 days pregnant. If no medical contraindications to the mifepristone-misoprostol regimen were found, the woman was offered the choice between termination by vacuum aspiration or medical termination.

At the first visit, including ultrasound scan, a further 25 women did not fulfill inclusion criteria and were excluded. A total of 100 (39.2%) chose the medical abortion method and thus constitute the patients entered into the study.

Oral mifepristone 600 mg was administered either on the same day as the first visit to the clinic or within the following 4 days (day 1), and the women were allowed to go home 30 min later. They were informed that in some cases abortion might occur at home following the mifepristone administration, and an emergency telephone number was given. Thirty-six to 48 h later, they returned in the morning to the outpatient clinic (day 3). Here, vaginal misoprostol 400 μg was given (self administration) and 2 tablets containing 400 mg paracetamol and 28.7 mg codeinphosphat, administered

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Table 1
Data of the first 100 women undertaking medical abortion

Age (years; median; range)	29	[18–46]
Gestational age (days; median; range)	48	[33–56]
Nullipara	45	
Previous termination of pregnancy[a]	30	(32 %)

[a] n = 93.

orally. The patients were observed by the nurses for bleeding and pain over the next hours, permitting further administration of analgesic or antiemetic agents if necessary. If abortion had not taken place, evaluated by the amount of bleeding within the first 3 h, a further 400 μg misoprostol was administered vaginally. They were allowed to leave the hospital if bleeding and pain were acceptable 2–5 h after the last misoprostol administration. The nurses telephoned all patients on day 4. Two weeks later, the women had a vaginal ultrasound scan. If the thickness of the endometrium was less than 15 mm, with no sign of retained product, no further action was taken. If the thickness was more than 15 mm, β-hCG concentration was measured, and the woman was followed weekly by ultrasound scan until measurement of β-hCG was below detection level. Rhesus-negative women received anti-D (Rho) immunoglobulin at day 3.

All women were asked to fill in a daily chart concerning bleeding, pain, nausea, vomiting, diarrhea, and whether they had gone to work/done as usual over the next fortnight from day 1. The amount of bleeding was estimated by a visual analog score (VAS-scale) with a line (12 cm long) ranging from "no bleeding" to "heavy bleeding" at the ends, with the mark "like your period" in the middle. Likewise, the severity of pain was measured on a VAS-scale ranging from "no pain" to "severe pain," with the mark "moderate pain" in the middle. The satisfaction with the method was estimated on a VAS-scale ranging from "dissatisfied" to "very satisfied" (range 0 to 12) with "satisfied" in the middle. All medical records were reviewed 2 months after entry to the study to evaluate the success rate and complication.

3. Results

One hundred women (39.2%) chose the medical abortion method, and demographic data can be seen in Table 1. Five

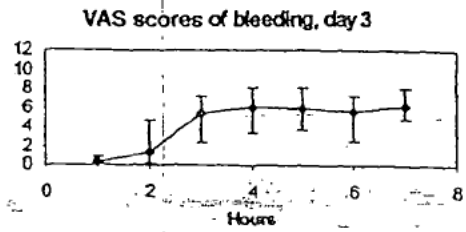

Fig. 1. Bleeding after misoprostol administration (day 3 after mifepristone administration). X-axis: hours after misoprostol administration; y-axis: score on VAS-scale. Median, 5 and 95-percentiles.

women did not attend the follow-up 14 days later, in spite of several letters/telephone calls. When contacted by telephone, all 5 reported cessation of bleeding and symptoms of pregnancy.

Side effects are presented in Table 2. After administration of mifepristone, 59% started to bleed with a median of 0.6 on a scale from 0–12 (range 0–11.6). Almost 4 of 5 women experienced pain with a median pain score of 1.1 (75 percentile: 2.6, total range 0–9) on a scale from 0 to 12, and 23 took paracetamol for the pain. The VAS scores of bleeding and pain after misoprostol administration (day 3 after mifepristone administration) are presented in Figs. 1 and 2.

Eighty-seven percent of the pregnancies were aborted at the hospital. Nine women believed they had aborted on day 2, and 4 that they had aborted on day 4. The nurses recorded when the women had been bleeding more heavily and probably aborted. A fixed time for abortion could be recorded for 84 women, and the time from administration of vaginal misoprostrol to abortion was a median of 3 h (75 percentile: 3 h and 30 min). An additional dose of misoprostol (400 μg) was administered to 9 women 3 h after the initial dose, as the bleeding was less than expected for an abortion to have taken place. Twenty women had extra analgesics, mainly paracetamol (1 g), and only one patient received an injection of pethidine. No other drugs were administered.

Figures 3 and 4 show the VAS scores of bleeding and pain from day 4 to 13.

At the follow-up 14 days after mifepristone administration, 66% were still bleeding, although it was mainly spotting (median 0.4 on the VAS-scale), and only 4% indicated that it was more than a period. Two patients marked pain of

Table 2
Side effects (percents and n in parentheses)

	Prior to abortion	After mifepristone administration (day 1) (n = 100)	After misoprostol administration (day 3) (n = 99)	Day 14 (n = 94)
Nausea	65% (65)	72% (72)	51% (50)	0
Vomiting	12% (12)	12% (12)	18% (18)	0
Diarrhea	–	–	3% (3)	0
Bleeding	–	59% (59)	100% (99)	66% (62)
Pain	–	79% (79)	98% (97)	5% (5)

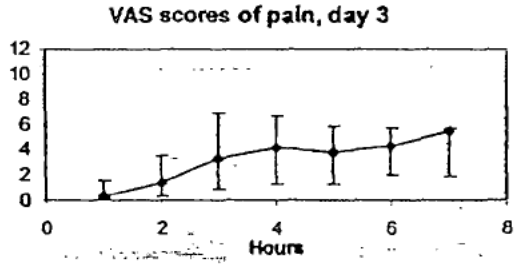

Fig. 2. Pain experienced after misoprostol administration (day 3 after mifepristone administration). X-axis: hours after misoprostol administration; y-axis: score on a VAS-scale. Median, 5 and 95 percentiles.

more than 5 on the VAS on day 14. None required analgesic at this time.

The endometrium was measured by ultrasound on day 14, and the median thickness was 9.2 mm (range: 3–18 mm, n = 87) (from edge to edge).

The overall success rate, defined as termination without use of evacuation, was 93% after 2 months of follow-up. No ongoing pregnancies were found at the 2-week follow-up. Four women were evacuated due to bleeding 7 to 9 weeks after administration of mifepristone, 2 had an evacuation due to infection (pyrexia, pain, discharge) at day 15 and 23, respectively, and one was evacuated due to severe headache occurring after administration of mifepristone; this patient did not receive misoprostol on day 3. Six of the 7 patients who had an evacuation had a gestation of more than 49 days.

Two patients were admitted to the ward due to bleeding and discharged the following day. Three women were given ergometrine tablets (Methergin®) orally for the next 3 days due to heavy bleeding, but none necessitating transfusion. No prophylactic antibiotics were given, and only the two women with clinical signs of infection received antibiotics.

All 100 women who had entered the study were asked to fill out a questionnaire on day 14. Approximately 14% felt that the bleeding had been more than expected. Likewise around 15% felt the pain and the nausea (16%) had been worse than expected. On the VAS-scale, satisfaction with

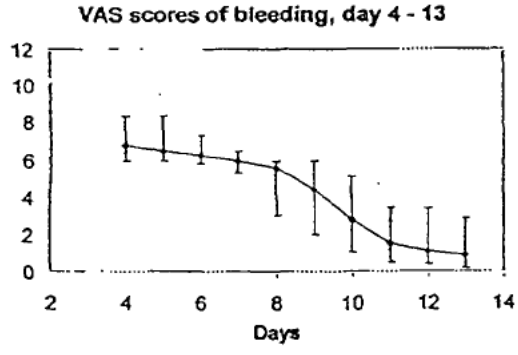

Fig. 3. Bleeding on day 4 to 13 after mifepristone administration. X-axis: days after mifepristone administration; y-axis: score on VAS-scale. Median, 5 and 95 percentiles.

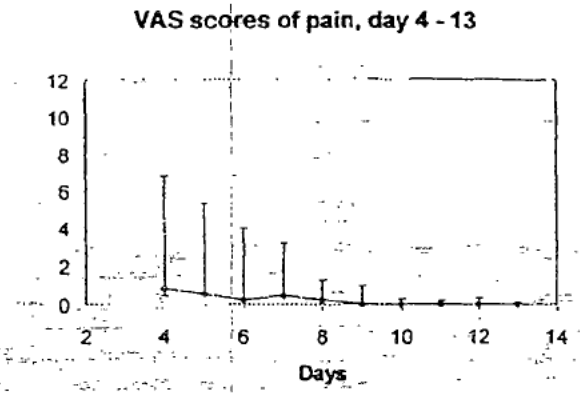

Fig. 4. Pain experienced on day 4 to 13 after mifepristone administration. X-axis: days after mifepristone administration; y-axis: score on VAS-scale. Median, 5 and 95 percentiles.

the method was a median of 12 (on a scale from 0 to 12; range 0–12). If they had to go through an abortion again, 90% would choose this method again. Of those who previously had experienced a surgical abortion (n = 26), 21 (81%) would choose the medical abortion.

Table 3 shows the influence of medical abortion on social life or working life. Sixty-two percent did go to work/did as usual on day 2, 68% on day 4, and only 1 or 2 women per day did not attend to their usual tasks from day 5 to 13 (n = 89).

4. Discussion

This study demonstrates that medical abortion using 600 mg mifepristone orally and 400 μg misoprostol vaginally is a well accepted, effective method of pregnancy termination for gestations less than 56 days. The success rate of 93% after 2 months of follow-up is similar to other studies for gestations less than 63 days [2,5,7–8]. In many studies the length of the follow-up period and the completeness of follow-up is difficult to evaluate. In this study, all medical records of the 100 women were evaluated 2 months after the medical abortion.

Thirty-nine per cent of the women who had the opportunity chose medical abortion. This is somewhat lower than reported in other countries [3,9–10,13], and could be due to the fact that medical abortion is a new method in Denmark; only 2 other hospitals had started the program at the time these data were collected. Moreover, as it has been shown

Table 3
Effect of medical abortion on attending work or social life

	Day 2 (n = 100)	Day 4 (n = 89)	Day 5–13 (n = 89)
Unaffected work/social life	62% (62)	68% (61)	98% (87)

that the attitude of the advising medical staff influences a woman's choice [3], we expect more women to choose medical abortion in the future, as the staff becomes more familiar with the method. The very fact that women have a choice in method is important, hence she is more likely to be satisfied with the treatment [11].

The few gastrointestinal side effects seen in our study are as expected after vaginal administration compared to oral administration [2]. Twenty per cent of our population required more analgesics (mainly paracetamol), than those given at the time of administration of misoprostol, but only one received intramuscular opiate analgesia. Reported analgesic requirements for early medical termination of pregnancy vary greatly between centres, ranging from 12.5% [1] to 68% [8]. In a Danish study using gemeprost 55% received pethidine [12]. In addition, the price of misoprostol is substantially less: DKK 5 (USD 0.6), less than 2% of the DKK 290 (USD 34.4) that gemeprost costs.

This study has shown that mifepristone and misoprostol vaginally for early medical abortion is well tolerated and effective with an overall success rate of 93%. No antiemetic agents were needed, analgesic requirements were minimal and few side effects were reported.

Acknowledgments

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O.S. Tang, K.J. Thong, D.T. Baird

Second trimester medical abortion with mifepristone and gemeprost: a review of 956 cases.

Contraception 2001; 64: 29-32

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Original research article

Second trimester medical abortion with mifepristone and gemeprost: a review of 956 cases

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Abstract

The treatment outcomes of 956 women undergoing second trimester termination of pregnancy with mifepristone and gemeprost were studied. The median gestational age was 16 weeks (range: 12–24 weeks). All women were treated with 200 mg mifepristone orally, followed 36 h later with 1 mg vaginal gemeprost administered every 6 h to a maximum of 4 doses in the first 24 h. A second course of 1 mg vaginal gemeprost was given 3-hourly in the next 12 h, if abortion had not occurred. Overall, 96.4% and 98.8% of the women aborted within 24 and 36 h, respectively. The median induction-to-abortion interval was 7.8 h (range: 0.5–109.9 h). The induction-abortion interval was longer in nulliparous women and women with a gestation age 17 weeks or above. Surgical evacuation of the uterus was performed in 11.5% of women for incomplete abortion or retained placenta. More multiparous women (16.7%) required surgical evacuation of uterus than did nulliparous women (7.3%; $p < 0.001$). Ten (0.1%) women failed to abort with gemeprost and required other methods for abortion. In conclusion, a combination of mifepristone and gemeprost is a safe, effective, and noninvasive method of medical abortion for second trimester pregnancy.

Keywords: Second trimester; Abortion; Mifepristone; Misoprostol

1. Introduction

Since the introduction of prostaglandin analogs for medical abortion more than two decades ago, medical methods have provided a safe alternative to surgical termination of pregnancy [1]. Although dilatation and evacuation is widely used in the United States, a combination of mifepristone and prostaglandin is the preferred method in the United Kingdom.

Different types of prostaglandin analogs have been used in the past 20 years for second trimester medical abortion. Currently, gemeprost (Cervagem, Farillon, Dagenham, UK) and misoprostol (Cytotec, Searle, Bucks, UK) are the two most common prostaglandin analogs used for this purpose. Both have been shown to be safe and effective when combined with mifepristone for second trimester abortion [2–4]. Although misoprostol is cheaper and stable at room temperature when compared with gemeprost, only the latter is licensed for the purpose of medical abortion.

Mifepristone (Exelgyn, UK) is a progesterone receptor blocker that increases the sensitivity of the uterus to prostaglandin analogs when administered to pregnant women [5]. The administration of 600 mg of mifepristone 36–48 h before gemeprost has been shown to shorten the induction-to-abortion interval [6]. Recently published data suggested that 200 mg is as effective as 600 mg for second trimester abortion [7].

The regimen used in present study was previously reported in a study of 100 women [2], and the purpose of this study was to report the effectiveness and safety of the same regimen in clinical practice over a period of 6 years.

2. Materials and methods

Nine hundred fifty-six consecutive women admitted to the Edinburgh Royal Infirmary for second trimester abortion from January 1994 to July 2000 were studied. Abortion was carried out under the conditions of the 1967 United Kingdom Abortion Act.

The gestational age was determined by menstrual history and clinical examination, and ultrasound was performed only if it was necessary as judged by the attending doctor. After the decision for termination of pregnancy was made, the women were referred to the Simpson Memorial Maternity Pavilion medical abortion unit where they were coun-

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Table 1
Characteristics of the 956 women who underwent midtrimester abortion

Characteristics	Gestation age		Parity		Total
	12–16 weeks n = 652	17–24 weeks n = 304	Nulliparous n = 531	Multiparous n = 425	n = 956
Median age in years (range)	21 (14–44)	22 (13–44)	19 (13–44)	26[a] (14–44)	22 (13–44)
Median gestation age in wks (range)	—	—	16 (12–24)	15.5 (12–21)	16 (12–24)
Parous (%)	44.9	43.4	—	—	44.5

[a] Significant difference by Mann–Whitney test, $p < 0.001$.

seled by a doctor and a nurse. The women were then given a date for administration of a single dose of 200 mg oral mifepristone in the medical abortion unit. The women were admitted to the unit 36 h later. One milligram of gemeprost was inserted to the posterior vaginal fornix every 6 h for a maximum of four doses over the first 24 h. If abortion had not occurred within the first 24 h, 1 mg of vaginal gemeprost was inserted every 3 h to a maximum of five doses over the next 12 h. Intravenous (iv) oxytocin in incremental dosage of up to 111 mU/min was started 36 h from the first pessary, if abortion had not occurred after the second course of gemeprost.

Analgesia [paracetamol 1 g, dihydrocodeine 30 mg, or intramuscular (im) diamorphine 7.5 mg] and antiemetic (im cyclizine 50 mg) were administered as required.

Intramuscular syntometrine (5 IU oxytocin and 0.5 mg ergometrine maleate; Alliance, UK) was administered following expulsion of the fetus and placenta. The product of conception was examined by the attending doctor for completeness. Surgical evacuation of the uterus was carried out if there was evidence of retained placenta or clinical suspicion of incomplete abortion.

SPSS for Windows Statistical Package was used for statistical analysis. Continuous variables were compared by Mann–Whitney test. Differences in proportions were analyzed with the chi-square test or Fisher's exact test as appropriate. A $p < 0.05$ was considered significant.

3. Results

Table 1 shows the characteristics of the 956 women who underwent second trimester abortion. The median gestation age was 16 weeks (range: 12–24 weeks), and 31.2% of them were above 16 weeks. Multiparous women were older than nulliparous women (median 26 years versus 19 years, $p < 0.001$). Table 2 shows the treatment outcomes of these 956 women. The median dose of gemeprost required was two, and the median induction-to-abortion interval was 7.8 h. Two (0.2%) women aborted after mifepristone without gemeprost. One of them was a nulliparous woman at 14 weeks of gestation, and the other woman, at 16 weeks of gestation, had three previous vaginal deliveries. Both of the women aborted at home and there was no excessive bleeding after abortion. Following insertion of gemeprost, 32.8% and 53.1% of women aborted within 6 and 8 h, and 80.5% and 96.4% aborted within 12 and 24 h, respectively. Overall, 98.8% of women aborted within 36 h (Fig. 1). The median induction-to-abortion interval was significantly longer in nulliparous (8.5 h) compared to multiparous women (6.7 h) ($p < 0.001$). Women with gestational age of 17 weeks or above had a significantly longer induction-abortion interval (8.8 h) than women less than 17 weeks (7.00 h; $p < 0.001$)

Overall, 110 (11.5%) women required surgical evacuation of the uterus for incomplete abortion. The rate of

Table 2
Treatment outcomes by parity and gestation age

	Gestation age		Parity		Total
	12–16 weeks n = 652	17–24 weeks n = 304	Nulliparous n = 531	Multiparous n = 425	n = 956
Median dose of gemeprost (range)	1 (0–14)	2[a] (1–14)	2[a] (0–9)	1 (0–14)	2 (0–14)
Median induction, in hours (range)	7.00 (1.3–48.2)	8.8[a] (0.5–109.9)	8.5[a] (0.5–57.3)	6.7 (1.25–109.9)	7.8 (0.5–1009.9)
Surgical evacuation of uterus for incomplete abortion (%)	77 (11.8)	33 (10.9)	39 (7.3)	71 (16.7)[b]	110 (11.5)
Need for other therapy (%)[c]	5 (0.8)	5 (1.6)	1 (0.2)	9 (2.1)[d]	10 (1.0)

[a] Significant difference by Mann–Whitney test, $p < 0.001$.
[b] significant difference by chi-square test, $p < 0.001$.
[c] Therapies include oxytocin, surgical evacuation of uterus, and hysterotomy.
[d] significant difference by Fisher's Exact test, $p = 0.007$.

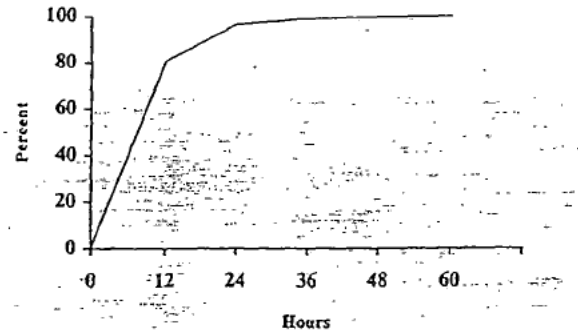

Fig. 1. Cumulative induction-to-abortion interval.

incomplete abortion was analyzed with respect to gestation, parity, and history of previous abortion. There was a trend ($p = 0.057$) toward a higher incidence of surgical evacuation in the 111 women with gestation of less than 14 weeks (17.1%) compared to women of greater than 14 weeks of gestation (10.8%). Women with a history of previous abortion had a significantly higher incidence of surgical evacuation (16.0%; $p = 0.001$) compared to women without a history of abortion (8.8%). Multiparous women had a significantly higher incidence of surgical evacuation (16.7%; $p < 0.001$) for incomplete abortion or retained placenta compared to nulliparous women (7.3%; Table 3).

Ten (0.1%) women failed to abort with gemeprost and required other methods for abortion. Seven (0.7%) women required an iv. infusion of oxytocin, two (0.2%) women at less than 14 weeks gestation needed surgical evacuation, and one (0.1%) woman underwent a hysterotomy. The woman who had a hysterotomy was 42 years old at 16 weeks of gestation. She failed to abort after nine doses of gemeprost and developed heavy vaginal bleeding requiring a blood transfusion during oxytocin infusion. An emergency hysterotomy was performed to terminate the pregnancy. Her hemoglobin concentration dropped from 11.9 g/dL to 7.5 g/dL prior to the hysterotomy. Three (0.3%) women were given more than nine doses of gemeprost. All of them were in the group of 10 women requiring other methods for abortion. The proportion requiring other methods for abortion was found to be higher in multiparous women.

Four patients (0.42%) stayed in hospital for more than 3 days. The woman who had a hysterotomy stayed for 5 days. The other three patients aborted after 48 h and also required surgical evacuation of the uterus for retained placenta. Blood transfusion was required only by the woman who had a hysterotomy. There was not a single case of cervical tear or cardiovascular complication.

4. Discussion

The results of the present series, which was larger than the previous study, of women who underwent second trimester termination of pregnancy confirms the efficacy of this combination regimen of mifepristone and gemeprost [2]. Out of the 956 women, 68.6% aborted within 10 h and could be managed as day-cases. The median induction-to-abortion interval (7.8 h) is comparable to previous studies using gemeprost or misoprostol in combination with mifepristone [2–4].

In this study, 11% of the women required evacuation of the uterus for retained placenta or incomplete abortion. Thirty percent of the women required evacuation of the uterus in our previous study using a similar regimen when pelvic ultrasound was used in addition to clinical judgment for the diagnosis of incomplete abortion or retained placenta [2]. In the past 6 years, our diagnosis of retained placenta or incomplete abortion has been based on clinical judgment alone, and this has reduced the proportion of women requiring surgical intervention. The surgical evacuation rate in the present study is comparable to the regimen using mifepristone and misoprostol (9.4%) [3].

The response of multiparous women was different from that of nulliparous women following treatment with the antiprogesterone, mifepristone and gemeprost. The induction-to-abortion interval of multiparous women (6.7 h) was significantly shorter than nulliparous women (8.5 h). This can be explained by the difference in the compliance of the cervix in the two groups of women. In contrast, multiparous women (16.7%) were found to have a significantly higher incidence of surgical evacuation of the uterus after medical abortion compared to nulliparous women (7.3%). Surgical

Table 3
Effect of obstetric history on the incidence of incomplete abortion

	Obstetric history				
	Nulliparous		Multiparous		
	No past history of previous abortion n = 390	History of previous abortion n = 141	No past previous history of abortion n = 209	History of previous abortion n = 216	Total n = 956
Surgical evacuation for incomplete abortion (%)	23 (5.9)	16 (11.3)[a]	30 (14.4)	41 (19.0)[b]	110 (11.5)

[a] History of previous abortion versus no history of previous abortion in nulliparous women ($p = 0.053$ by chi-square test).
[b] History of previous abortion versus no history of previous abortion in multiparous women ($p = 0.251$ by chi-square test).

evacuation is usually performed for incomplete abortion based on the clinical diagnosis of retained placenta, incomplete placenta, or excessive hemorrhage. In this study, the incidence of surgical evacuation was found to be higher in women with a previous history of abortion. Thus, women with a history of previous pregnancy that ended either in an abortion or full-term delivery were more likely to have retained placenta or residual trophoblast. It was reported that more parous women bled greater than 500 mL during termination of second trimester pregnancy by gemeprost alone [8]. The reason why a higher proportion of multiparous women failed to abort completely with this regimen of mifepristone and gemeprost is not known but is similar to recent reports on medical abortion in the first trimester [9,10]. A more efficient establishment of the pregnancy at a very early stage was suggested by one of the author as the reason for a higher failure rate in multiparous women [9].

The choice of surgical versus medical termination of pregnancy poses a dilemma to clinicians in the management of women at 12–14 weeks gestation [11]. Twenty percent of multiparous women in this study required surgical evacuation for incomplete abortion. In addition, the proportion of multiparous women who failed to abort with gemeprost was higher. Dilatation of the cervix is usually easier in multiparous women, and it may be more convenient and cost-effective to perform a dilatation and evacuation in this group of women. In skilled hands, dilatation and evacuation may require a shorter stay in the hospital, and women may possibly experience less pain compared to termination using this regimen of mifepristone and gemeprost.

The results of this study demonstrated that gemeprost is comparable to misoprostol in terms of efficacy and safety [3]. Misoprostol is cheap and stable at room temperature when compared to gemeprost. Oral misoprostol is available in many countries for treatment of peptic ulcer. Although vaginal misoprostol is commonly used with mifepristone for second trimester medical abortion, it is not licensed for this purpose. Moreover, gemeprost is the prostaglandin that clinicians usually resort to when the women fail to abort using misoprostol for termination of pregnancy in the second trimester [3,12,13].

In conclusion, a combination of mifepristone and gemeprost is a safe, noninvasive, and effective method for termination of pregnancy in the second trimester.

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A randomized comparison of medical abortion and surgical vacuum aspiration at 10-13 weeks gestation.

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A randomized comparison of medical abortion and surgical vacuum aspiration at 10–13 weeks gestation

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BACKGROUND: Since 1991, mifepristone in combination with a prostaglandin analogue has been licensed for termination of pregnancy in the UK at up to 9 weeks amenorrhoea, and since 1995, beyond 13 weeks. Surgical methods are used almost exclusively at 10–13 weeks amenorrhoea. METHODS: A patient-centred, partially randomized, controlled trial was carried out. Those who expressed a strong preference for either medical (n = 15) or surgical (n = 62) abortion were allocated to that method. The remainder agreed to be randomized. The medical method (n = 188) was mifepristone 200 mg followed by misoprostol up to 3 doses, and surgery (n = 180) was by vacuum aspiration under general anaesthesia. Outcome measures included efficacy rates, medical complications within 8 weeks of the procedure, patient preferences and acceptability. RESULTS: Among women who underwent medical abortion, 5.4% required a second procedure compared with 2.1% who had surgery, although this difference was not statistically significant. Side effects experienced were higher in women who underwent medical abortion compared with those who underwent surgery. There were no significant differences in the rates of major complications up to 8 weeks. Prior to termination, 80% of women had a preference for a method, with 72% preferring medical and 28% preferring surgical abortion. Following abortion, 70% of those who underwent medical termination and 79% who underwent surgery would opt for the same method in the future. CONCLUSION: Medical abortion is safe and effective at 10–13 weeks gestation and should be considered an option for those women who wish to avoid surgery and anaesthesia.

Key words: medical abortion/mifepristone/misoprostol/surgical vacuum aspiration

Introduction

In England and Wales the majority of abortions (72%) are carried out at 9–13 weeks gestation (Office for National Statistics, 1999), while in Scotland about one-third of all abortions are carried out at 10–13 weeks (Information and Statistics Division, 2000).

In the UK, mifepristone in combination with a prostaglandin analogue was licensed for the termination of pregnancy at up to 9 weeks amenorrhoea in 1991, and since 1995 has also been available for termination of pregnancy beyond 13 weeks. At present, surgical methods (vacuum aspiration) are used at 10–13 weeks amenorrhoea, and there is little published work on the use of medical methods (Ashok *et al.*, 1998a).

Vacuum aspiration is considered to be safe and effective but has been associated with major morbidity in up to 1% of women and minor morbidity in 10% (Joint Study of the Royal College of General Practitioners and the Royal College of Obstetricians and Gynaecologists, 1985), the major determinants of morbidity being gestational age and the procedure used to terminate the pregnancy. In the first trimester the complication rate is lowest at 7–8 weeks gestation (0.26 per 100 abortions) and increases progressively to 1.37 per 100 abortions at 13 weeks (Grimes and Cates, 1979). Vacuum aspiration, usually performed under general anaesthesia, is currently the method of choice at 10–13 weeks gestation.

The manufacturer's recommended regimen for early medical abortion comprises mifepristone 600 mg in combination with the prostaglandin analogue gemeprost. A randomized controlled trial comparing medical abortion with vacuum aspiration at gestations up to 9 weeks showed that although both methods were highly acceptable to women, medical abortion was more painful and less effective with advancing gestation (Henshaw *et al.*, 1993, 1994a,b).

Since then, a number of developments in the drug regimen have occurred based on randomized controlled studies (McKinley *et al.*, 1993; World Health Organization Task Force, 1993; El-Refaey *et al.*, 1995) and these led to the development in 1994 of a new medical regimen consisting of a reduced dose of mifepristone (200 mg) and the vaginal use of the

prostaglandin analogue misoprostol (El-Refaey and Templeton, 1994; Ashok *et al.*, 1998b, 1999). This prostaglandin has a number of advantages over gemeprost in that it is easily stored and transported and of very low cost.

This paper compares the efficacy, early medical sequelae (up to 8 weeks following termination) and acceptability of medical and surgical abortion at 10–13 weeks gestation.

Materials and methods

Study design

The preferred design for evaluating a new treatment or management policy is a randomized controlled trial, and this was adopted for the study. The partially-randomized patient preference (PRPP) design has been recommended for use in trials where motivational factors may produce bias in outcomes (Brewin and Bradley, 1989). In this study, a conventional randomized trial was conducted, alongside an assessment of preferences in those who did not wish to be randomized to one method or the other.

Study participants

The study was approved by the Grampian Research Ethics Committee and was conducted at Aberdeen Royal Infirmary. Women presenting for termination of pregnancy at 10–13 weeks amenorrhoea, gestation confirmed by transvaginal ultrasound, and fulfilling the requirements of the 1967 Abortion Act, were eligible for recruitment. They were also required to meet the following criteria: (i) eligible to undergo either surgical vacuum aspiration or medical abortion; (ii) singleton, viable intrauterine pregnancy; and (iii) ultrasonically estimated gestational age of 10–13 weeks at the time of termination. The exclusion criteria were: (i) suspected ectopic pregnancy; (ii) chronic adrenal failure; (iii) long term corticosteroid treatment; (iv) haemorrhagic disorder and treatment with anticoagulants; (v) known allergy to mifepristone; (vi) smokers >35-years-of-age with electrocardiogram abnormalities; and (vii) breast feeding.

Eligible women were given a standardized information sheet describing medical and surgical methods of abortion and were asked if they were willing to be allocated to a method of abortion. Women were also informed of side effects and complications of each method. Women who agreed to be randomized were assigned to a method by opening consecutive sealed opaque envelopes containing a random number generated by computer. The randomization was prepared by the trial statistician using a randomized block design with blocks of 2, 4, 6 and 8, to ensure equal numbers in each group during the study.

The women who declined to be randomized were asked by the study nurse the reasons for their decision. Those not wishing to be randomized because they had a strong preference for a particular treatment were identified. The women willing to participate if they received their preferred treatment option constituted a non-randomized prospective cohort.

A total of 486 women were recruited (400 in the randomized arm) in order to achieve a 90% power of detecting at the 5% significance level a difference of 10% in the level of acceptability between the two termination methods. Eighty-six women were recruited to the preference arm of the trial. A further 93 women eligible to participate declined to take part in either the randomized or preference arm of the study. Analysis was by intention to treat, and women allocated to a method of treatment were attributed to that method for the purpose of analysis, whether or not they underwent their allocated procedure. Five women randomized to the medical group had surgical treatment by choice and three women who were randomized to surgery had medical treatment.

Intervention

The two alternatives were medical or surgical abortion.

Medical termination

Women undergoing medical abortion were asked to attend the gynaecology ward and given 200 mg of mifepristone orally in hospital under nursing supervision. They were then admitted to the ward 36–48 h later, when misoprostol 800 µg was administered vaginally. If products of conception were not passed, a further two doses (400 µg) of misoprostol were given either orally or vaginally at 3 h intervals depending on vaginal bleeding. Women who had vaginal bleeding heavier than a normal period were given misoprostol orally. After products of conception were passed, women were observed in the ward for a further 4 h. Following administration of prostaglandin, pulse, blood pressure, temperature and systemic symptoms were monitored hourly. Women were given oral (paracetamol 500 mg plus dihydrocodeine 10 mg) or parenteral (morphine 10 mg) analgesia every 4–6 h as required.

If products of conception were not passed 3–4 h after the third dose of prostaglandin, a speculum examination was undertaken and any products of conception in the vagina or cervix were removed. If products of conception were not identified, an ultrasound scan was performed and surgical evacuation undertaken if necessary prior to discharge.

Surgical termination

Standard techniques were used to perform vacuum aspiration, under general anaesthesia. Women were admitted to the day surgery unit and were given 800 µg of misoprostol for cervical priming 3 h pre-operatively.

In all other respects (e.g. counselling, infection screening) there were no differences between the two groups. All women were screened for genital tract infection including *Chlamydia trachomatis* and treated if necessary.

Women who underwent medical termination were invited to return to the hospital 14–21 days after the termination of pregnancy for follow-up. At this visit, if vaginal bleeding had not ceased then an ultrasound scan was done and high vaginal and endocervical swabs taken if indicated. Patients were commenced on antibiotics or curettage performed if necessary. Those undergoing surgical termination of pregnancy were followed up by their referring doctor, usually at ~14 days post-procedure.

Outcome measures

These included efficacy, major medical complications and relatively minor short-term physical symptoms. Patient preferences prior to termination and acceptability following the procedure were also assessed. These were measured by self administered questionnaires prior to the procedure following randomization, prior to discharge and at 2–3 weeks following termination.

Efficacy and immediate medical complications prior to discharge

The efficacy of the procedure was defined as complete uterine evacuation without the need for a second procedure [subsequent surgical (re)curettage or medical regimen] within 8 weeks of abortion.

Women were asked to complete a modified 'menstrual distress questionnaire' as well as a visual analogue scale for pain, after termination and prior to discharge. The former was used to assess symptoms such as nausea, vomiting, headache, hot flushes, dizziness, tiredness and diarrhoea on a five point scale (none to very severe) (Henshaw *et al.*, 1994c). Analgesia use in hospital was also documented.

Medical sequelae at 2 weeks following the procedure

Complications recorded at the follow-up visit and unscheduled visits to hospital were documented.

Table I. Characteristics of study subjects

Group	n	Estimated gestation (days)	Age (years)	Body mass index	Primigravid n (%)	Previous induced abortion n (%)	Chlamydia-positive n (%)
Randomized medical	188	71.8 (7.2)	25.5 (6.9)	23.4 (3.7)	80 (42.6%)	55 (29.3%)	11 (5.9%)
Randomized surgical	180	73.0 (7.0)	24.8 (6.7)	23.5 (3.8)	82 (45.6%)	54 (30.0%)	15 (8.3%)
Preference medical	15	71.9 (7.6)	29.3 (7.0)	23.1 (2.4)	3 (20.0%)	5 (33.3%)	0
Preference surgical	62	74.0 (5.9)	26.0 (6.4)	23.3 (4.0)	17 (27.4%)	24 (38.7%)	4 (6.5%)
Total	445	72.0 (7.0)	25.4 (6.8)	23.4 (3.8)	182 (40.9%)	138 (31.0%)	30 (6.7%)

Values are mean (SD), except where n (%).

A further questionnaire was completed and returned by post 2–3 weeks following the procedure to assess the following: (i) duration and severity of vaginal bleeding recorded on a menstrual calendar (each day on the menstrual calendar was subdivided into five to indicate the severity of bleeding, none to flooding). The values were added to give the total vaginal bleeding score (TVBS); (ii) a visual analogue scale to assess pain and analgesia use following discharge; (iii) a record of the time taken off work and to return to normal activity.

Medical sequelae at 8 weeks following the procedure

A third questionnaire was completed by the family doctor at 8 weeks following termination and all medical problems attributable to the abortion were documented. Women experiencing more than one problem were classified for analysis according to the primary complaint.

Major and minor complications attributable to the termination up to 8 weeks following the procedure were assessed. Major complications were classified according to categories previously defined (Joint Study of the Royal College of General Practitioners and the Royal College of Obstetricians and Gynaecologists, 1985). The minor complications are listed in Table V.

Unscheduled visits to hospital related to abortion were recorded and the termination database reviewed for complications related to abortion.

Preference and acceptability of procedure

Preference for a particular method was included in the questionnaire completed following randomization and prior to the procedure. Acceptability was assessed with regards to preferred future method by means of questions included in the 2–3 weeks questionnaire, returned by post.

Statistical analysis

The data were entered into a personal computer-held database and analysed using the Statistics Package for Social Sciences program. The principal analysis compared the outcomes in the two arms of the randomized controlled trial. Independent and paired *t*-tests were used for continuous variables with a normal distribution, and Mann–Whitney's *U*-test for ordinal or non-parametric continuous variables. The χ^2 test or Fisher's Exact test, as appropriate, was used for independent nominal data and McNemar's test for paired data describing dichotomous variables. Confidence intervals (95% CI) were applied where appropriate. Comparisons were made between the randomized women and those entering the preference cohort with regard to their characteristics and outcomes.

Results

A total of 486 women were recruited, 400 to the randomized and 86 to the preference arm of the trial. Thirty-four (7.0%) women who had agreed to participate in the study subsequently decided to continue with their pregnancy, seven withdrew (1.4%) and one (0.2%) woman failed to attend for termination and subsequently had a midtrimester medical termination of pregnancy. Thus, a total of 445 women were enrolled in the study, 368 in the randomized and 77 in the preference group. Figure 1 shows the numbers recruited and the study design.

The 445 women were allocated to four groups: those randomized to medical abortion [n = 188 (51.1%)], those randomized to surgery [n = 180 (48.9%)], those who had a strong preference for medical abortion [n = 15 (3.4%)], and those with a strong preference for vacuum aspiration [n = 62 (13.9%)]. Thus, a total of 203 (45.6%) underwent the medical method and 242 (54.4%) vacuum aspiration. There were no differences between the groups in any baseline physical or sociodemographic characteristics (Table I).

Women treated as day cases included 179 (88.2%) of those undergoing medical abortion and 222 (91.7%) undergoing surgical abortion.

For descriptive purposes, the data in certain sections have been combined for women who underwent a particular method either by choice or chance.

Medical abortion

Of the 203 women allocated to the medical group, 45 (22.2%) experienced some vaginal bleeding following mifepristone administration and prior to the administration of prostaglandin; nine (4.5%) women rated this to be heavier than a normal period. One (0.5%) woman aborted on mifepristone alone, prior to the administration of prostaglandin. The median time interval from administration of mifepristone to prostaglandin administration was 44.00 h (range 33.83–48.58).

The median number of doses of prostaglandin required was 2 (range 0–3). Products of conception were identified by inspection in 192 (94.6%) women. Twenty women (9.9%) also had abortion confirmed on ultrasound scan prior to discharge. Of the 203 women who underwent medical abortion 139 (68.5%) aborted within 6 h of prostaglandin administration. The median induction abortion interval was 5.00 h (range 2.00–27.58). Following the third dose of prostaglandin, 57 women (28.1%) did not pass products of conception within 3–4 h and required a speculum examination.

Surgical abortion

All 242 surgical terminations were carried out under general anaesthesia on a dedicated theatre list. The consultant responsible for patients carried out 159 (65.7%) of the vacuum aspirations. The median time interval between cervical priming and surgical evacuation was 2.42 h (range 0.17–7.00).

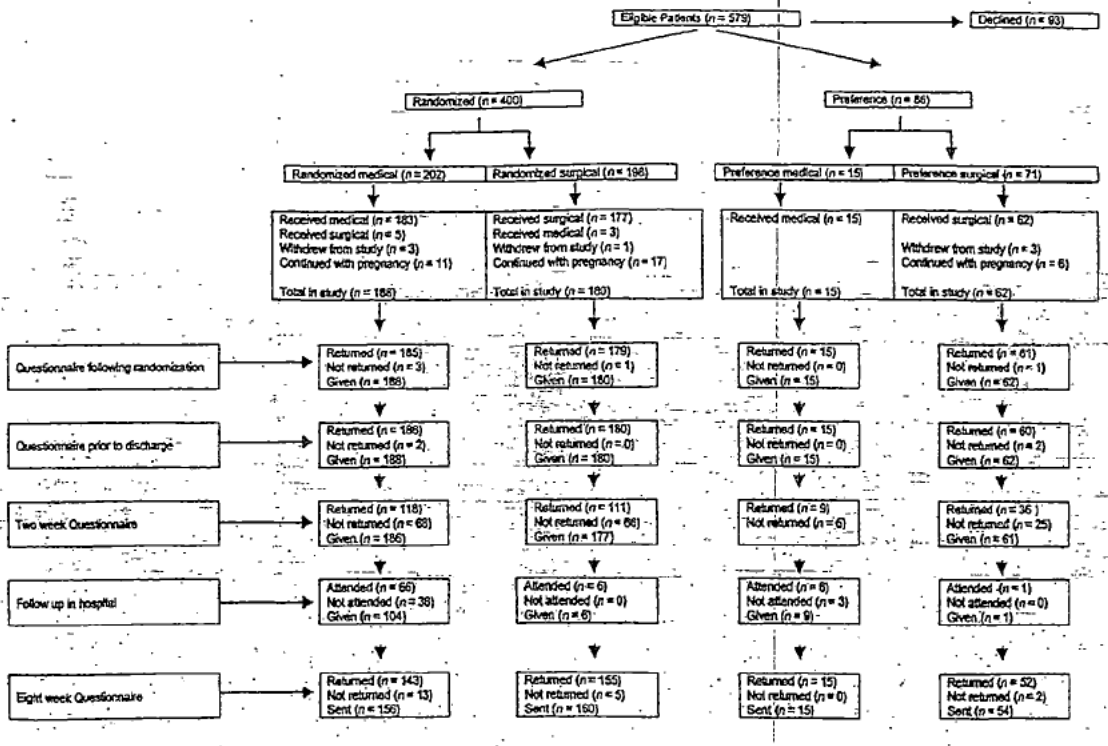

Figure 1. Study design and numbers recruited.

Efficacy and immediate medical complications prior to discharge

There were no significant differences in overall efficacy between medical abortion and vacuum aspiration. Gestation did not influence efficacy in either group (Table II). Of the 11 (5.4%) failures in the medical group who subsequently had surgery, three (1.5%) had a continuing pregnancy, one (0.5%) a missed abortion and seven (3.4%) had incomplete abortions. Surgical evacuation following failed medical abortion was undertaken prior to discharge in 10 (90.9%) women, and within 2 weeks of the procedure in one woman. Products of conception from five women were sent for histological examination and chorionic villi were identified in four of these. Of the five women (2.1%) who required a second procedure in the surgical group, medical treatment was undertaken following a failed attempt to dilate the cervix at vacuum aspiration in one woman (0.4%). Surgical (re)curettage was undertaken in the other four women (1.7%) for incomplete abortion within 4 weeks of the first procedure. Products of conception were identified in all three women where histological examination was requested.

Among women who were randomized, the overall pain score [median (range)] experienced by women who underwent medical abortion was 6.2 (0–10) and with vacuum aspiration 2.5 (0–10), indicating a significant difference between the two groups ($P < 0.0001$). Similarly, women who underwent the medical method [7.6 (0.6–9.9)] in the preference group experienced significantly more pain than those who underwent vacuum aspiration [2.1 (0–9); $P < 0.0001$). However, women who were randomized to the medical method had significantly lower pain scores [5.7 (0–10)] following analgesic administration compared with those randomized to surgery [7.7 (0–10); $P < 0.0001$). Such a significant difference was not seen in the pain scores following analgesia administration in the preference group ($P = 0.53$). The median (range) scores in the medical and surgical groups were 6.7 (0.3–9.3) and 6.8 (0.1–10.0) respectively.

Table II. Efficacy of abortion method according to gestation

Gestation	Medical abortion *n* (%) *n* = 203	Surgical Abortion *n* (%) *n* = 242	*P*-value
64–70 days			
Total number	105 (51.7)	108 (44.6)	NS
Failed	3 (2.9)	0 (0)	
Complete abortion	102 (97.1)	108 (100)	
71–77 days			
Total number	52 (25.6)	57 (23.6)	NS
Failed	4 (7.7)	3[a] (5.3)	
Complete abortion	48 (92.3)	54 (94.7)	
78–84 days			
Total number	32 (15.8)	63 (26.0)	NS
Failed	4 (12.5)	2 (3.2)	
Complete abortion	28 (87.5)	61 (96.8)	
85–91 days			
Total number	14 (6.9)	14 (5.8)	–
Failed	0 (0)	0 (0)	
Complete abortion	14 (100)	14 (100)	
Overall			
Total number	203	242	NS
Failed	11 (5.4)	5 (2.1)	
Complete abortion	192 (94.6)	237 (97.9)	

[a]In one woman medical treatment was undertaken following an attempt at surgery due to inability to dilate the cervix.
NS = not significant.

Table III. Side effects experienced by women in the ward

	Randomized			Preference		
	Medical abortion *n* (%) *n* = 186	Surgical abortion *n* (%) *n* = 180	*P*-value	Medical abortion *n* (%) *n* = 15	Surgical abortion *n* (%) *n* = 60	*P*-value
Nausea	128 (69.2)	50 (27.8)	< 0.0001	9 (60.0)	11 (18.3)	0.001
Vomiting	91 (49.2)	15 (8.3)	< 0.0001	7 (46.7)	3 (5.0)	< 0.0001
Diarrhoea	79 (42.5)	8 (4.5)	< 0.0001	7 (46.7)	0 (0)	< 0.0001
Abdominal pain	182 (97.8)	163 (90.6)	0.003	15 (100)	53 (88.3)	NS
Vaginal bleeding	178 (97.8)	166 (94.3)	NS	12 (80.0)	53 (91.4)	NS
Tiredness	159 (85.5)	127 (70.9)	0.001	10 (66.7)	45 (75.0)	NS
Headache	51 (27.6)	28 (15.6)	0.005	6 (40.0)	4 (6.7%)	0.001
Hot flushes	74 (40.0)	21 (11.7)	< 0.0001	5 (33.3)	5 (8.5)	0.012
Dizziness	82 (44.3)	39 (21.0)	< 0.0001	7 (46.7)	10 (16.7)	0.013

NS = not significant.

Table IV. Short-term medical sequelae (2–3 weeks following the termination)

	Randomized				Preference			
	Medical *n* = 118	Surgical *n* = 111	*P*-value	CI *n* = 9	Medical *n* = 36	Surgical	*P*-value	CI
Total number of days bleeding Mean (SD)	14.21 (4.8)	11.21 (5.9)	< 0.0001	1.59, 4.41	13.0 (4.1)	10.8 (4.7)	NS	–1.47, 5.85
Total vaginal bleeding score Mean (SD)	37.63 (13.7)	23.33 (14.8)	< 0.0001	10.58, 18.01	31.50 (8.96)	22.42 (13.35)	NS	–0.84, 18.43
Overall pain since termination Median (range)	2.1 (0–9.5)	1.6 (0–9.8)	NS	–	0.4 (0.1–6.2)	1.4 (0–6.0)	NS	–
Most severe pain since termination	3.9 (0–10)	2.5 (0–9.9)	NS	–	1.5 (0.2–9.9)	3.1 (0–9.2)	NS	–

Median (range).
CI = confidence interval; NS = not significant.

Of the 203 women who underwent medical abortion, 61 (30.0%) required no analgesia, 120 (59.1%) requested oral analgesia only, and 22 (10.9%) requested parenteral opiate analgesia. All women who underwent surgical termination were given diclofenac per rectally 100 mg or paracetamol per rectally 1000 mg in theatre following the procedure. However, a further 96 (39.7%) women required additional analgesia with 91 (37.6%) women requesting oral analgesia and 5 (2.1%) requesting parenteral opiates.

Side effects experienced by women on the ward are shown in Table III. Four (2.0%) women who had medical abortion required syntometrine to control bleeding. Two (0.8%) women in the surgical group had a blood loss >500 ml, one (0.4%) woman requiring a blood transfusion.

Medical sequelae at 2–3 weeks following the procedure

Of the 386 women randomly allocated, 229 (60%) returned the questionnaire, 118 (64%) of whom underwent the medical method and 111 (62%) who had vacuum aspiration. Of the 76 in the preference group, 45 (60%) returned the questionnaire, 9 (60%) in the medical group and 36 (58%) in the surgical group.

Short-term sequelae 2–3 weeks following the two methods of termination are shown in Table IV. The duration and total vaginal bleeding score was greater in women randomized to medical abortion. The median (range) time taken to return to normal activity was 2.5 days (0–14) in women who underwent medical abortion and 2.5 days (0–20) in those who underwent vacuum aspiration with no significant difference between the two groups. There were no differences in median (range) time taken to return to work, 2.0 days (0–21) in the medical group and 2.0 days (0–21) in the surgical group.

At 2–3 weeks following the procedure there was no difference in the level of pain experienced by women between the medical and surgical groups, randomized or in the preference arm (Table IV). Following discharge from hospital, of the women who returned questionnaires, overall (both randomized and preference) 12 (9.4%) women who underwent medical abortion and 11 (7.5%) who underwent vacuum aspiration required analgesia with no significant difference between the two groups.

All (both randomized and preference) women who underwent medical abortion were invited to attend follow-up 2 weeks later in hospital. Of these, 113 (55.7%) agreed to attend for follow-up, of whom 72 (63.7%) attended. The remaining 41 (36.3%) women failed to keep their hospital appointment. The remaining 90 (44.3%) women who declined the initial invitation to attend hospital were followed up by their family doctor. Women undergoing surgical abortion were followed up by the family doctor, and only seven (2.9%) women followed up in hospital for medical reasons.

Table V. Medical sequelae assessed (at 8 weeks following the abortion)

	Medical Abortion n (%) n = 158	Surgical Abortion n (%) n = 207	95% Confidence interval for difference between proportion[a]	*P*-value
Contacted family doctor	30 (19.0)	43 (20.8)	−0.100, 0.065	NS
Presumed pelvic infection requiring antibiotic treatment	7 (4.4)	17 (8.2)	−0.087, 0.011	NS
Psychiatric and psychological morbidity	10 (6.3)	10 (4.8)	−0.033, 0.063	NS
Abnormal abdomino-pelvic pain and or vaginal bleeding	5 (3.2)	8 (3.9)	−0.045, 0.031	NS
Other morbidity	8 (5.1)	8 (3.9)	−0.036, 0.047	NS

[a]The confidence intervals include zero and hence the differences between the two groups are not significant at the 5% level.
NS = not significant.

Of the 72 women who underwent medical abortion and were followed up in hospital, six required oral antibiotics for suspected pelvic infection. All seven women who were followed up in hospital following vacuum aspiration required oral antibiotics for suspected infection.

Medical sequelae at 8 weeks following the procedure

Of the 445 women in the study, 385 (86.5%) agreed to the researchers contacting the family doctor at 8 weeks following the procedure to complete a questionnaire. Information was obtained from family doctors in 365 (94.8%) of these. Overall, 73 (20.0%) women consulted the family doctor with problems related to termination. There was no significant difference in the consultation rates between the medical and surgical group. Seven (4.4%) women who had medical and 17 (8.2%) who had surgical treatment were given oral antibiotic treatment by the family doctor for presumed pelvic infection (Table V).

There were no significant differences in the rates of major complications within 8 weeks of abortion. Two (0.8%) women in the surgical group and one (0.5%) woman in the medical group required i.v. antibiotics for presumed pelvic infection.

In total, 15 of the 445 women in the study had an unscheduled visit to hospital, six (3.0%) in the medical and nine (3.7%) in the surgical group. Of these, one (0.5%) women in the medical group and seven (2.9%) who had vacuum aspiration were re-admitted ($P = 0.04$).

Of the 41 women who underwent medical abortion but failed to keep their hospital appointment, information was obtained from the family doctor in 33. Thus, in only eight women was no follow-up information obtained.

Preferences and acceptability

Prior to termination and following randomization, 351 (80%) of 441 women who returned the questionnaire had a definite preference for a particular method. Of these, 253 women (72%) preferred the medical method and 98 (28%) preferred vacuum aspiration ($P < 0.0001$).

Following termination, 118 women who underwent the medical method and 111 women who had vacuum aspiration returned questionnaires, but only 67 (35.6%) women who had the medical method and 96 (53.3%) who underwent surgery answered the question regarding future preferred method. Forty-seven women (70%) who underwent medical termination would opt for the same method in future, and 76 women (79%) who underwent vacuum aspiration would opt for the same method in future—a statistically significant difference between the two groups ($P < 0.0001$).

Discussion

This study is a robust comparison of medical and surgical abortion. A pilot study had previously shown the feasibility of medical abortion at 10–13 weeks gestation (Ashok *et al.*, 1998a). A large number of women were randomized in this study in a single centre in which all data were collected prior to discharge. Furthermore, the termination database and all hospital notes could be scrutinized for re-admission and complications related to termination. There was a very good response from family doctors with nearly 95% of those contacted responding to the questionnaire at 8 weeks following the procedure. None of the women in either group (medical or surgical) was discharged home prior to confirming interruption of the pregnancy. All women with a continuing pregnancy following the medical regimen were identified and had evacuation of products of conception prior to discharge.

Although the drop-out rate was higher than expected (short-term follow-up rate with regards to acceptability), which would directly affect the power calculation, the results achieved are believed to be a true reflection of differences between the groups. However, data regarding problems related to termination were obtained from family doctors and in only eight women who underwent medical abortion was no information obtained. All these women had passed products of conception prior to discharge.

Overall, 11.8% of women who underwent medical abortion and 8.3% who underwent surgery were managed as in-patients. The majority of women who required overnight admission had geographical reasons.

Following randomization but prior to termination, nearly 80% of women had a definite preference for a particular method. Of these, the majority preferred the medical method. Of those who underwent medical abortion, 70% would opt for the same method in future while 79% who underwent vacuum

aspiration would opt for the same in future—a statistically significant difference. Based on these results, it appears that medical abortion is less acceptable than surgery, although the response was from a small number of women who underwent either procedure (one-third of all women who underwent medical abortion and half of who underwent surgery returned the questionnaire), which highlights difficulties in post-termination surveys.

Medical abortion has proven to be a safe and effective alternative to vacuum aspiration in the early first trimester and for midtrimester termination of pregnancy (Ashok and Templeton, 1999). The efficacy is up to 97.5% overall and at gestations of 7–9 weeks ~97% (Ashok *et al.*, 1998b). Even when the efficacy falls to 94% at 9 weeks gestation, acceptability among women remains high, as demonstrated in a previous randomized study (Henshaw *et al.*, 1993). To demonstrate a significant difference of 2–3% in efficacy, as found in this study, would have required 1750 women, but the clinical relevance would have been doubtful given the level of acceptability.

There is now increasing experience of medical abortion in the late first and early second trimester of pregnancy in China (Cheng, 1999). Mifepristone in an oral 200 mg dose in combination with vaginal misoprostol of up to three doses has an efficacy of 94.0%. The vaginal administration of misoprostol was more effective than the oral route. In our study we used a combination of vaginal and oral misoprostol with success rates similar to the above study. It has been shown that in the second trimester, provided the first dose of misoprostol is administered vaginally, there is no advantage in the vaginal administration of subsequent doses (El-Refaey and Templeton, 1995).

Re-admission rates to hospital were lower than in previous studies with only 1.8% of women requiring re-admission (Henshaw *et al.*, 1994c). This may be associated with our current policy of pre-operative screening for pathogenic organisms. However, significantly more women in the surgical group were re-admitted following termination, although there were no significant differences between the two groups in family doctor consultation rates or in the requirement for antibiotics for presumed pelvic infection.

The current care provided to women undergoing medical abortion in the UK includes in-patient hospitalization on a day case basis. Medical abortion using mifepristone and home administration of misoprostol has been shown to be feasible in the USA at gestations up to 63 days (Schaff *et al.*, 2000). Schaff and colleagues showed no difference in efficacy in relation to gestation, with medical abortion being highly acceptable (91%). The feasibility of carrying out the procedure at home needs to be evaluated in different settings and in the context of further studies.

In summary, medical abortion is as safe and effective as vacuum aspiration at 10–13 weeks gestation. The introduction of a medical method of abortion at 10–13 weeks could have a considerable impact on the provision of medical services, as well as increasing women's choice of methods, particularly for those women who wish to avoid surgery and anaesthesia.

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Mifepristone and misoprostol for early abortion when no gestational sac is present

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Abstract

The study was conducted to determine whether the administration of mifepristone followed by vaginal misoprostol can induce an abortion in early pregnancy when no gestational sac is present on sonogram. This report presents a prospective, pilot study of 30 healthy adult women, pregnant and seeking an abortion, and with no gestational sac on sonogram. All women had a baseline serum chorionic gonadotropin (hCG) level measured prior to using mifepristone 200 mg orally followed by misoprostol 800 mcg vaginally 48 h later, and then returned up to 4 days later for a repeat sonogram and serum hCG level. Women with initial hCG levels > 2000 IU/L were evaluated for ectopic pregnancy. At the first follow-up visit, if the hCG decreased by >50%, the women were followed with home pregnancy (25 IU/L) tests weekly until negative. If the levels did not decrease by 50%, a second dose of misoprostol was given. Surgical intervention was indicated for persistent hCG levels or excessive bleeding. Of the 30 women enrolled, the mean number of days of amenorrhea was 40 (SD 9) days. Two women had surgical intervention for continuing pregnancy, 2 had ectopic pregnancies, and 1 was lost to follow-up. Complete medical abortions occurred in 25/30 (88%) women, but when recalculated, in 25/27 (93%) women who completed the protocol and who did not have an ectopic pregnancy. There was 1 adverse event in a woman with an ongoing pregnancy who then received methotrexate. She was hospitalized a day later with a complicated pelvic infection and likely methotrexate-induced pneumonitis. Twenty-three women had a decrease in hCG at first follow-up visit of >50%. All 27 women who completed the protocol found the overall regimen acceptable. Mifepristone followed at 48 h by vaginal misoprostol were effective and acceptable in inducing an abortion in very early pregnancy. There may be a higher incidence of failure in very early pregnancies. Documentation of a complete abortion by hCG level is necessary to ensure the pregnancy is neither ongoing nor ectopic.

Keywords: Abortion; Mifepristone; Misoprostol

1. Introduction

Mifepristone for medical abortion was approved by the US Food and Drug Administration in September 2000. It is highly effective when combined with the prostaglandin misoprostol 2 days later for up to 7-week pregnancy, with efficacy rates ranging from 92–98% [1–6].

An intrauterine gestational sac on sonogram usually is first seen in a 5-week intrauterine pregnancy [7]. In recent US medical abortion trials, inclusion criteria have required a gestational sac to be present on sonogram [8,9]. In contrast, women in France do not routinely have a sonogram examination, but the mandatory 7-day waiting period prior to using mifepristone, would likely ensure that the pregnancy is beyond ≥5 weeks gestation. Consequently, there is little information about the effectiveness of mifepristone and very early pregnancy prior to a gestational sac present on sonogram.

The advantages of offering very early medical abortion are the following: 1) identifying an ectopic pregnancy in an asymptomatic phase by ultrasound and hCG levels; and 2) reducing the anxiety of waiting when a woman knows she wants an abortion. The disadvantages of offering an early mifepristone abortion when no gestational sac is present are: 1) treating an ectopic pregnancy with an inadequate regimen with mifepristone; and 2) over-treating a spontaneous miscarriage when mifepristone is not needed. Alternatively, women can wait until an intrauterine pregnancy is confirmed by sonogram thereby excluding an ectopic pregnancy or use methotrexate that is effective in inducing an early abortion or treating an early ectopic pregnancy [10–12].

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The objective of this pilot study was to determine whether women with no gestational sac on sonogram should be offered mifepristone for medical abortion.

2. Material and methods

This was a prospective study of 30 women at a single site. The study had institutional review board approval. Inclusion criteriad included: 1) age ≥ 18; 2) good health; 3) positive sensitive pregnancy test and wanting an abortion; 4) a normal bimanual examination; and 5) no gestational sac on vaginal probe sonogram. Additional inclusion and exclusion criteria have been previously reported [8,9]. On day 1, women had a medical history, a gynecologic examination and a vaginal probe sonogram. All women had Rh blood typing, a hemoglobin, and baseline serum human chorionic gonadotropin (hCG) level. Rh-negative women received Rh immune globulin. Women were administered mifepristone 200 mg orally in the office. If the initial or subsequent hCG levels were >2000 IU/L with no gestational sac visible on sonogram, the woman was evaluated for ectopic pregnancy. On day 3, women inserted 4, dry 200 μg tablets of misoprostol (total 800 μg) vaginally at home and returned to the office up to 4 days later for a repeat vaginal probe sonogram and hCG level. At this visit, if the hCG had deceased by >50% from baseline, the woman was followed by phone with home pregnancy tests weekly until negative. Otherwise, a second dose of misoprostol was administered vaginally and the woman returned at her option from 1 day later to day 15. If a third visit was needed and if the hCG had decreased by >50%, the woman was followed by phone with home pregnancy tests weekly until negative. Surgical intervention was indicated for persistent hCG level or excessive bleeding. Women reported by phone or postcard when their bleeding stopped. Women were considered lost to follow-up if there was no known outcome after repeated attempts by phone and certified letter.

The primary outcome measures were as follows: 1) efficacy of the regimen without surgical intervention; 2) side effects; 3) adverse outcome; and 4) woman's perception of the procedure.

Women were interviewed about symptoms and use of medications at all visits. After either a >50% decrease in hCG levels or a surgical intervention occurred, a final questionnaire was administered that rated the woman's agreement about her acceptability of: 1) overall procedure; 2) cramping pain; 3) bleeding; 4) side effects from the medications; 5) time waiting until the abortion was over; 6) willingness to use misoprostol at home; 7) willingness to recommend the procedure; and, 8) willingness to choose the procedure again. The Likert scale ranged from *strongly disagree*, *disagree*, *neutral*, *agree*, to *strongly agree*. *Agree* and *strongly agree* were combined in this analysis.

3. Results

Thirty women were enrolled from February through December 1999. Twenty-two (73%) were white, 4 (13%) African American, and 4 (13%) Hispanic. The mean age was 28.2 (SD 7.7) years. The initial mean gestational age by last menstrual period was 40.3 days (SD 9.0). The mean initial hCG level was 547 IU/L (SD 477), excluding the woman with an initial hCG of 16,922 IU/L who had an ectopic pregnancy.

Two women had surgical intervention for continuing pregnancy. One woman had an increase in her hCG level from 1000 IU/L to 5350 IU/L on day 4, a visible gestational sac on follow-up, and an uncomplicated aspiration curettage on day 12. The other woman's course was complicated. Her initial hCG was 385 IU/L which rose over the next 2 weeks to 1312 IU/L, and then to 1814 IU/L. She had no findings on sonogram. Although feeling well, she was considered a study failure and was given methotrexate to treat an early intrauterine pregnancy or an occult ectopic pregnancy. She presented 24 h later with acute abdominal pain and pelvic tenderness. Her white blood cell count was 18,500 with 93% neutrophils and 4% bands. She had a diagnostic aspiration curettage and an abdominal laparoscopic examination on day 29. Both procedures confirmed a pelvic infection despite negative cervical cultures for chlamydia and gonorrhea. Pathology from the curettings revealed an inflammatory exudate and trophoblastic tissue confirming an intrauterine pregnancy. On the first post-operative day, the woman was noted to have mild tachypnea, an oxygen saturation of 80%, and a chest film showing bilateral, nonspecific, patchy alveolar densities with small effusions consistent with fluid overload, mild acute respiratory distress syndrome possibly due to her pelvic infectious process, or mild pneumonitis from methotrexate [13]. After 24 h of antibiotics, oxygen therapy and diuretics, the oxygen saturation improved and the woman had an uncomplicated recovery. Her hCG levels decreased precipitously post curettage, also consistent with having had an intrauterine pregnancy.

Two women had ectopic pregnancies; one presented with 39 days of amenorrhea and an initial hCG level of 16,922 IU/L. A formal sonogram revealed a right adnexal mass and she underwent a salpingectomy without further complications. The other woman was gravid 10, para 3 with a history of a heterotopic ectopic pregnancy 2 years earlier. Her hCG levels rose from 1,326 IU/L on day 1 to 5,598 IU/L 1 week later. A formal sonogram showed 2 right adnexal masses diagnosed as twin ectopic pregnancies measuring 2.9 cm and 3.0 cm each. She was treated successfully with methotrexate. One woman refused to return for follow-up care. Her outcome was not documented and she was considered "lost-to-follow up."

Complete medical abortions occurred in 25/30 (88%) women and in 25/27 (93%) women excluding the woman who was lost to follow-up and the two women who had ectopic pregnancies. No woman experienced excessive bleeding. Twenty-three women had a decrease in hCG at

first follow-up of >50%. Of the six women who had increases in hCG levels, three had minimal elevations (mean of 33% at first follow-up) that decreased precipitously (<50% of baseline value) by the next visit. Of the other three women with hCG increases at first follow-up (mean of 268% from baseline), two had ongoing pregnancies and 1 had an ectopic pregnancy.

Of the 26 women with a documented bleeding cessation date, the mean length of bleeding was 12.4 days (SD 12). Twenty-one (70%) women reported using an oral narcotic for pain. Twenty-seven women (90%) but 100% of responders to the post treatment questionnaire found the regimen acceptable.

4. Discussion

This pilot study used a protocol that differs from the FDA approved regimen in that a lower dose of mifepristone (200 mg) was used, a higher dose of misoprostol (800 mcg) was administered, and misoprostol was used vaginally rather than orally and at home. This regimen has proven to be highly effective in our previous trials.

Women who present for a medical abortion with a very early pregnancy and no gestational sac visible on sonogram are a dilemma for clinicians. Some of these women may undergo an unnecessary medical abortion because they have a failed pregnancy (missed abortion) and would eventually bleed spontaneously, though some of these women will require a non-elective aspiration curettage for excessive bleeding. Other women will have an ectopic pregnancy that requires additional evaluation and treatment. Amenorrhea of more than 35 days, with no sac present, is less consistent with an early intrauterine pregnancy. An hCG greater than the discriminatory level (>2000 IU/L for vaginal probe ultrasound or >3600 IU/L for abdominal probe ultrasound) will help to identify a woman at risk for an ectopic pregnancy [14]. Most of these women, realizing that they have an unintended pregnancy, albeit, early, failed or ectopic, will want some intervention.

Women with no gestational sac on sonogram are at risk for ectopic pregnancy as noted in the two women in this trial. Ectopic pregnancy must also be considered when a sonogram is not used initially and either serial hCG levels are rising or there is no vaginal bleeding after misoprostol. Treatment for early ectopic pregnancy should be commenced as soon as possible to reduce morbidity. Methotrexate is most effective in early ectopic pregnancy [10].

Unexpected were the two women who had ongoing pregnancies. This is considerably higher than the expected 1% of ongoing pregnancies found in other mifepristone studies [5,6] and requires further study. Since the availability of the commercial Mifeprex, we have had another woman who presented with an initial hCG of 150 IU/L and had an ongoing pregnancy after this regimen. In all cases, women with very early pregnancies will require documentation of completion. Methotrexate is an alternative treatment for very early medical abortion and may result in fewer ongoing pregnancies.

Excessive bleeding, the most common cause for surgical intervention in most medical abortion trials, did not occur in this pilot study. The possibility of excessive bleeding requires the availability of 24 h surgical aspiration skills. There is evidence that blood loss is related to gestational age so less excessive bleeding is expected with early intervention [15] i.e., early intervention may be the safest time to offer medical abortion service.

There was one unexpected and serious adverse event in one of the two women who had an ongoing pregnancy. She received methotrexate for an occult pregnancy and then presented with a pelvic infection and a likely methotrexate-induced pneumonitis. She also had a diagnostic laparoscopy and iv fluids that may confuse the clinical course. Infection after medical abortion is very rare because there is no instrumentation of the uterus. Pneumonitis is also rare after methotrexate and has not been previously reported following medical abortion. The woman recovered completely.

5. Conclusion

In this pilot study, low-dose mifepristone 200 mg and home administration of vaginal misoprostol 800 μg at 48 h were effective and acceptable to women seeking a very early medical abortion. Ectopic pregnancy must be considered when no gestational sac is present on initial sonogram. There may be a higher rate of ongoing pregnancies when offering mifepristone in very early pregnancy and therefore documentation of a complete abortion is necessary to ensure the pregnancy is neither ongoing nor ectopic.

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Successful long-term treatment of refractory Cushing's disease with high-dose mifepristone (RU 486).

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Successful Long-Term Treatment of Refractory Cushing's Disease with High-Dose Mifepristone (RU 486)

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An extremely ill patient, with Cushing's syndrome caused by an ACTH-secreting pituitary macroadenoma, experienced complications of end-stage cardiomyopathy, profound psychosis, and multiple metabolic disturbances. Initially treated unsuccessfully by a combination of conventional surgical, medical, and radiotherapeutic approaches, he responded dramatically to high-dose long-term mifepristone therapy (up to 25 mg/kg·d). Treatment efficacy was confirmed by the normalization of all biochemical glucocorticoid-sensitive measurements, as well as by the significant reversal of the patient's heart failure, the resolution of his psychotic depression, and the eventual unusual return of his adrenal axis to normal. His 18-month-long mifepristone treatment course was notable for development of severe hypokalemia that was attributed to excessive cortisol activation of the mineralocorticoid receptor, which responded to spironolactone administration. This case illustrates the efficacy of high-dose long-term treatment with mifepristone in refractory Cushing's syndrome. The case also demonstrates the potential need for concomitant mineralocorticoid receptor blockade in mifepristone-treated Cushing's disease, because cortisol levels may rise markedly, reflecting corticotroph disinhibition, to cause manifestations of mineralocorticoid excess. (*J Clin Endocrinol Metab* 86: 3568–3573, 2001)

CHRONIC EXPOSURE TO excessive corticosteroids in Cushing's syndrome (CS) leads to the development of multiple metabolic abnormalities, including glucose intolerance, dyslipidemia, hypertension, osteoporosis, and weight gain (1). Cushing's disease (CD) accounts for approximately 70% of cases of endogenous CS. The standard initial treatment of CD is transsphenoidal adenomectomy, which achieves cure rates of 70–80% (1). Pituitary macroadenomas (size > 1 cm) are more difficult to cure than microadenomas (size < 1 cm). Patients suffering residual or recurrent disease undergo repeat transsphenoidal hypophysectomy, external beam pituitary irradiation, medical adrenolytic therapy, or surgical adrenalectomy to control the hyperadrenocorticism (1, 2). However, no particular therapy is completely satisfactory. Repeat transsphenoidal surgery results in high relapse rates, therapeutic effects from pituitary radiotherapy are delayed, the steroidogenic enzyme inhibitors for chemical adrenalectomy (metyrapone, mitotane, aminoglutethimide, ketoconazole) are often limited by severe toxicity and inadequate cortisol suppression, and surgical approaches to accomplish total adrenalectomy may not fully extirpate adrenocortical tissue (1, 2). Adrenalectomy also carries the risk of rapid residual pituitary corticotroph growth, *i.e.* Nelson's syndrome.

We describe a patient with refractory CD and multiple medical comorbidities who exhausted conventional therapies but was successfully treated with high-dose mifepristone (RU 486), a glucocorticoid receptor (GR) antagonist (3), as a bridge until the therapeutic effects of delayed radiation therapy became manifest. Not only did the patient's hypothalamic-pituitary-adrenal axis return to normal, but his multiple medical problems all dramatically reversed. During mifepristone therapy, the patient, in addition, required spironolactone, a mineralocorticoid receptor (MR) antagonist, to ameliorate cortisol-induced MR activation, a result of elevated serum cortisol produced by mifepristone-induced corticotroph disinhibition.

Case Report

The patient was a 51-yr-old African-American retired mechanic who was diagnosed with diabetes mellitus type 2 and hypertension, 6 yr before his evaluation at our institution. One year before admission, he developed recurrent syncope. Transthoracic echocardiography showed severe left ventricular hypertrophy (LVH) and left ventricular ejection fraction (LVEF) of 20%. Coronary angiography revealed an isolated 60% occlusion of the left anterior descending artery that underwent percutaneous transluminal angioplasty and stenting. In the 6 months before admission, the patient was treated, at three other hospitals, for recurrent upper and lower extremity abscesses. Several incision and drainage procedures did not yield any microbial etiology. An increased frequency of syncopal episodes, concomitantly with New York Heart Association functional class IV symptoms, led to the patient's referral for evaluation of cardiac transplantation at our facility.

At the time of arrival at our institution, the patient's medications included digoxin, captopril, carvedilol, hydralazine, isosorbide, and insulin. Physical examination showed a wheelchair-bound man, with rounded facies, appearing chronically ill and acutely in distress. His blood pressure was

Abbreviations: 11βHSD, 11β-hydroxysteroid dehydrogenase; BPRS, brief psychiatric rating scale; CD, Cushing's disease; CS, Cushing's syndrome; GR, glucocorticoid receptor; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MR, mineralocorticoid receptor; MRI, magnetic resonance imaging.

130/82, pulse was 92 and regular, height was 1.78 m, and weight was 80 kg. The patient was somnolent and unable to provide any medical history. He was extremely weak and had striking muscular atrophy of the extremities. There were no abdominal striae, but there was palpable hepatomegaly and prominent pedal edema. He had fluctuant, warm, red, tender lesions involving the right upper and left lower extremities. When the patient tried to stand, he developed syncope.

During the subsequent hospitalization, chest radiography showed diffuse cardiomegaly, an electrocardiogram revealed LVH with secondary repolarization abnormality, and a repeat echocardiogram demonstrated LVEF of 22%, concentric LVH, and left ventricular enlargement. The patient's cardiomyopathy was deemed out of proportion to the isolated coronary atherosclerosis. *Cryptococcus neoformans* was cultured from the extremity abscesses, serum *Cryptococcus* antigen titers were positive (1:512), urine and sputum cultures revealed *Candida albicans*, and a left toe skin culture grew *Trichophytum rubrum*. The patient was started on flucytosine and fluconazole to treat the cryptococcosis. His glycemic control was poor, despite using more than 100 U insulin per day. Retinal examination showed diabetic retinopathy, and urine studies revealed proteinuria.

To screen for possible CS, a low-dose (1 mg) dexamethasone overnight suppression test was performed, demonstrating a nonsuppressed serum cortisol (1493 nM). ACTH-dependent CS was diagnosed by finding concomitant elevated ACTH (81 pM) and serum cortisol levels (>828 nM). High-dose (8 mg) dexamethasone did not suppress the cortisol (1294 nM). CRF levels were undetectable. Magnetic resonance imaging (MRI) revealed a cystic 2 × 1-cm pituitary mass (Fig. 1). Formal visual field testing was negative. Computed tomography of the adrenal glands showed bilateral hyperplasia. Despite failure of the high-dose dexamethasone suppression (including a repeat test using 32 mg dexamethasone), the patient was diagnosed with CD (4) but was deemed too ill to undergo confirmatory inferior petrosal sinus sampling. The patient's antifungal regimen was changed to include ketoconazole, because this imidazole derivative can inhibit steroidogenesis (5). However, ketoconazole was incompletely effective, and metyrapone was started, but the latter was abruptly discontinued after coincident development of atrial arrhythmias, requiring cardioversion.

During the patient's transsphenoidal adenomectomy, all visible traces of a soft cystic tumor were removed, but invasion of adjacent structures precluded complete surgical extirpation. A postoperative MRI scan confirmed residual tissue in the sella turcica. Histopathological analysis revealed a necrotic adenoma. A predominant pituitary cell type was unidentifiable by immunohistochemistry, because all immunostaining was inadequate because of the necrotic state of the specimen. Postoperatively, ACTH and cortisol levels declined but remained abnormally elevated (Fig. 2). Ketoconazole was reinstituted at 1200 mg/d to inhibit steroidogenesis. One month later, the patient underwent 3-dimensional conformal external beam radiotherapy, receiving 5040 cGy to the pituitary bed in 28 fractions over 6 wk. On ketoconazole, the patient developed extreme nausea and elevated transaminases (ALT 228 IU/L), necessitating a change to mitotane therapy (2 g/d) for 2 months. His ACTH remained more than 18 pM; and serum cortisol, more than 773 nM. His gonadal axis declined: total testosterone, 1.9 nM (normal, 12.1–24.9); free testosterone, 0.01 nM (normal, 0.04–0.11); and FSH, less than 1 IU/L (normal, 1.55–9.74). He was started on im testosterone therapy.

On psychiatric evaluation, the patient was severely depressed, with a 21-item Hamilton depression rating scale score of 27 (normal, <5). Although he denied symptoms of overt psychosis, his brief psychiatric rating scale (BPRS) was 38 (normal, <18). He showed significant cognitive impairment, as indicated by grossly diminished scores on multiple aspects of the paragraph recall test and the Stroop color-word test.

Materials and Methods

Serum cortisol was measured using the IMMULITE competitive immunoassay (Diagnostic Products Corp., Los Angeles, CA), whereas ACTH was determined by ARUP Laboratories (Salt Lake City, UT) using a chemiluminescent immunoassay. Other measurements were per-

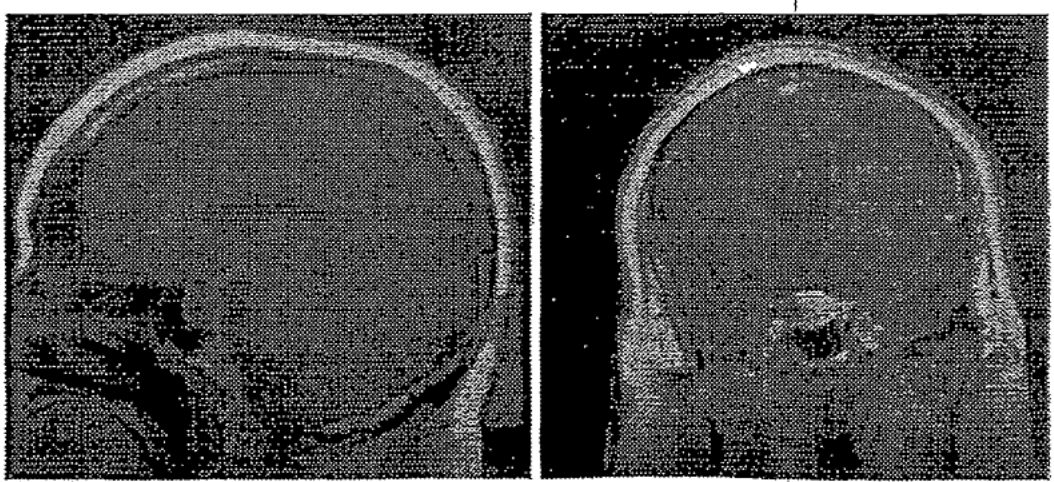

FIG. 1. Brain MRI images of a 51-yr-old man with CD. Sagittal T1-weighted (*left panel*) and coronal T1-weighted postgadolinium (*right panel*) MRIs of the brain demonstrate a cystic pituitary mass measuring approximately 2 × 1 cm.

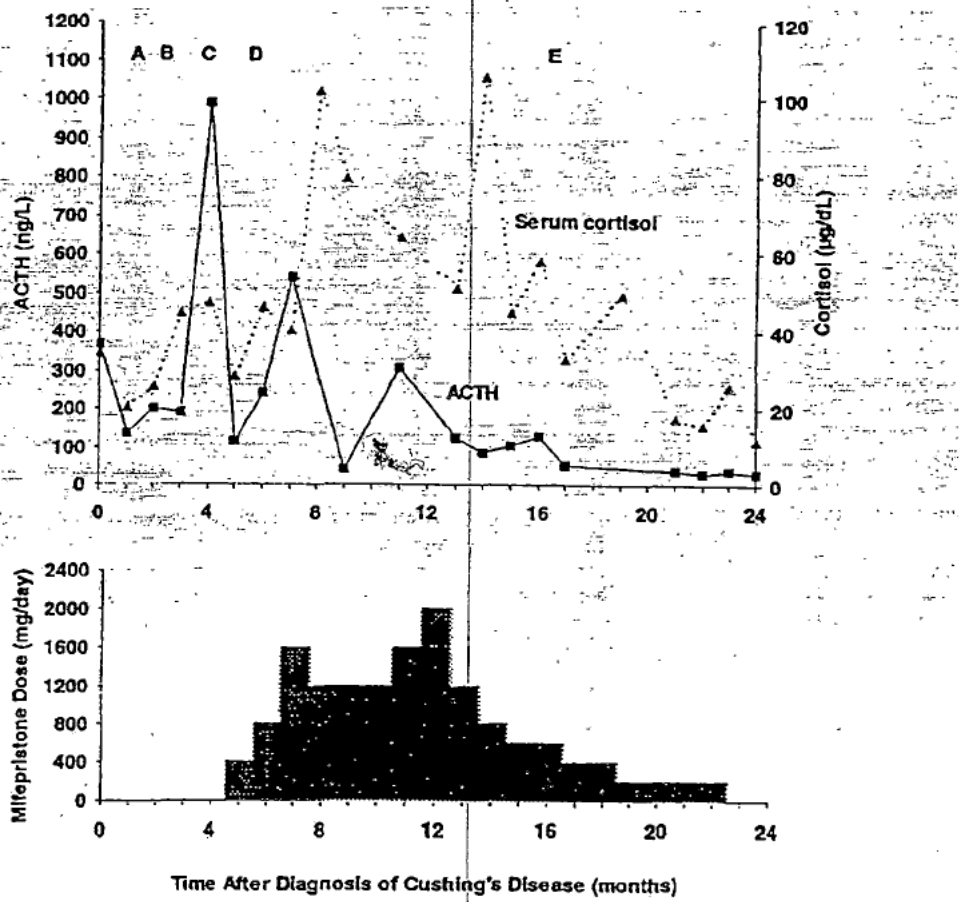

FIG. 2. Adrenal axis function in a man with CD treated with mifepristone. Note that measurements of serum cortisol are expressed in μg/dl (1 μg/dl = 27.59 nM), and those of ACTH are expressed in ng/L (1 ng/liter = 0.22 pM). A, Transsphenoidal resection of pituitary adenoma; B, start of external beam radiotherapy; C, end of external beam radiotherapy; D, medical adrenolytic therapy; E, acute adrenocortical insufficiency.

formed in the Stanford Clinical Laboratory using standard procedures. Bone mineral densitometry was assessed by dual-x-ray absorptiometry employing a Hologic, Inc. (Bedford, MA) QDR 4500 apparatus. Neuropsychiatric testing used the Hamilton depression rating Scale (HAMD-21), brief psychiatric rating scale, Stroop color-word test, and paragraph recall test, as reported previously (6).

Results

The patient remained extremely ill, and it was anticipated that the radiotherapy would not show benefit for at least 1 yr. Chemical adrenalectomy had been unsuccessful, and the patient's cardiac status was considered too tenuous to undergo adrenalectomy, even via a laparoscopic approach. Given the lack of feasible effective therapies, the patient was initiated on mifepristone at 400 mg/d (~6 mg/kg·d). This was done with his informed consent, permission from the human subjects committee, and an Investigational New Drug approval from the Food and Drug Administration. It was hoped that mifepristone, begun 5 months after diagnosis of CD, would control the hypercortisolism until the radiotherapy took effect.

During the initial 8 months of mifepristone treatment, the dose was gradually increased to a maximum of 2000 mg/d (~25 mg/kg·d) in response to continued signs of hypercortisolism (Fig. 2). It was recognized that the fluctuating, but persistently elevated, serum ACTH and cortisol could not accurately reflect therapeutic efficacy, because mifepristone antagonizes the hypercortisolemic effects at the receptor level, not by altering corticosteroid production (7). Severe hypokalemia (potassium < 3 mM) developed, requiring high-dose potassium replacement and initiation of spironolactone therapy. However, clinical findings attributable to CS slowly improved, and the mifepristone dosage was titrated downwards over the following 10 months. The accompanying fall in ACTH and cortisol concentrations likely represented delayed effects of radiotherapy, although spontaneous improvement could not be ruled out (8). In month 10 of mifepristone therapy, at 800 mg/d (~10 mg/kg·d), the patient experienced an episode of suspected adrenocortical insufficiency, manifested by weakness, orthostatic hypotension, and hypoglycemia (serum glucose ~1.1 mM, not on antidiabetic drugs), which necessitated dexamethasone bolus therapy and mifepristone dose reduction, to which he responded.

By month 18 of mifepristone therapy, the patient's overall appearance was markedly improved, and he now walked unassisted. The ACTH had fallen (<8.8 pM), and the serum cortisol was not only suppressible, by low-dose dexamethasone to 30 nM, but was also normally responsive to exog-

enous corticotropin (from 433 to 1112 nM). Presuming an intact hypothalamic-pituitary-adrenal axis, the mifepristone dose was tapered and discontinued.

Of the severe metabolic, cardiovascular, and neuropsychiatric dysfunction (Table 1) associated with CD, the most remarkable improvement in this patient was his transformation from a wheelchair-bound heart-transplant candidate to an active individual walking 1–2 miles a day. The echocardiographic finding of a marked increase in LVEF, to 35–40%, corroborated this observation. The multiple fungal infections did not recur after cessation of antifungal agents. The severe insulin resistance abated, and glycemic control remained in a desirable range without the use of antidiabetic medications. The marked hypertriglyceridemia regressed without therapy. Markers of bone turnover and bone mineral density improved. The hypokalemia resolved, and the blood pressure has been well controlled, with the remaining antihypertensives consisting of carvedilol and furosemide to treat the congestive heart failure. Other medications included levothyroxine [to treat mild hypothyroidism; FT_4, 10.2 pM (normal, 9.0–25.7); TSH, 7.22 U/L (normal, 0.4–4.0)], im testosterone, and digoxin.

The patient's neuropsychiatric status improved dramatically. His elevated BPRS score, indicating psychosis, entirely resolved; and his mood normalized. His cognition improved substantially, with dramatic correction in all aspects of the Stroop color-word and paragraph recall tests. After recovery, the patient revealed that he had been far more psychotic than he had admitted at the onset of mifepristone treatment, describing previous visual hallucinations and feelings of being observed by unseen people. He had not initially acknowledged these symptoms because he thought that he would "sound crazy" (which indicates preserved insight).

Discussion

17β-hydroxy-11β-(4-dimethylaminophenyl)-17α-(1-propynyl)-estra-4,9-dien-3-one, also known as RU 38486, RU 486, or mifepristone is a potent antagonist of both glucocorticoid and progestin receptors (3). Its clinical properties yield an effective contraceptive, as well as abortifacient; and it may have potential benefit in treating CS, unresectable meningioma and leiomyoma, refractory endometriosis, metastatic breast cancer, and even psychotic depression (6, 9). We describe a patient with a pituitary macroadenoma, causing refractory CD, associated with multiple severe physiologic derangements that regressed after amelioration of hypercortisolism. Mifepristone was used successfully to antagonize the effects of hypercortisolism while awaiting the delayed remission induced by pituitary irradiation. Our report, describing the highest dose of mifepristone achieved for the longest duration reported in a patient with CS, coincides with the recent approval of mifepristone for usage in the United States, and it supports the utility of this therapy in managing hypercortisolism.

Previous reports have described clinically therapeutic mifepristone usage in more than 14 patients with CS (10, 11). A potential adverse effect experienced by these and other patients treated with high-dose mifepristone for long periods involves episodes of possible adrenal insufficiency that cannot be confirmed biochemically but that resolve after exogenous glucocorticoid administration and mifepristone

TABLE 1. Hormonal, metabolic, cardiovascular, and neuropsychiatric indices at diagnosis of Cushing's disease and before, during, and after mifepristone therapy

Index	At initial diagnosis	At start of mifepristone therapy	During mifepristone therapy	After mifepristone therapy	Normal values
Hormonal					
ACTH (pM)	81	20	28	6	2.9–11.4
Serum cortisol (nM)					
Fasting	949	1076	1402	320	166–580
After dexamethasone, 1 mg	1493	—	—	30	<138
Exogenous insulin use (U/d)	115	70	40	0	0
Metabolic					
Serum osteocalcin (nM)	—	0.80	6.43	7.66	0.99–2.39
Bone mineral density (g/cm^2)					
Left total hip	—	—	0.795	0.822	age-dependent
Lumbar spine (1–4)	—	—	0.977	0.989	age-dependent
Hemoglobin A1c (%)	11.5	10.4	7.7	6.9	4–6%
Serum cholesterol (mM)					
Total	—	8.11	7.17	5.28	<5.18
HDL	—	0.91	0.54	0.85	>0.91
LDL	—	—	—	3.52	<3.37
Fasting triglycerides (mg/dl)	—	4.83	5.48	2.00	<2.26
Potassium (mM)	4.0	4.2	3.0	4.4	3.5–5.0
Cardiovascular function					
New York Heart Association functional class	IV	IV	II–III	I	0
Estimated left ventricular ejection fraction	19%	—	30%	35–40%	>50%
Neuropsychiatric function					
21-Item Hamilton-D score	—	27	18	8	<5
BPRS score	—	38	20	18	18

HDL, High-density lipoprotein; LDL, low-density lipoprotein; —, not available.

dose reduction (cited within Refs. 3 and 11). The difficult monitoring of therapeutic efficacy stems from the lack of a biomarker of GR activity. Because mifepristone antagonizes the GR of the pituitary corticotrophs, as well as that of peripheral tissues, its administration causes disinhibition of ACTH release, with consequently increased levels of ACTH and serum cortisol (7). Thus, patients undergoing mifepristone treatment may manifest seemingly paradoxical findings of elevated circulating ACTH and cortisol concentrations accompanying symptoms of adrenocortical insufficiency. In our patient's case, the additional inhibition of MR by spironolactone may have further contributed to the symptoms that suggested adrenal insufficiency.

Notable aspects of this patient's case include the pronounced, yet reversible, cardiac failure, as well as the severe hypokalemia. These clinical effects may be attributable to abnormal overactivation of MR. In physiological settings, the enzyme 11β-hydroxysteroid dehydrogenase (11βHSD) converts cortisol, an avid GR- and MR-binding glucocorticoid, to its 11-keto analog (cortisone), a non-GR, non-MR-binding glucocorticoid (12). This conversion protects the MR from cortisol, thereby maintaining the *in vivo* specificity of MR activation by aldosterone, which circulates in concentrations 100-1000 times less than that of cortisol. However, in CS, where the capacity of 11βHSD to guard the MR is overwhelmed or impaired, illicit cortisol overstimulation of MR leads to hypokalemic alkalosis and hypertension (13). Because mifepristone inhibits cortisol binding to GR, but not to MR, and causes ACTH disinhibition to further exacerbate endogenous hypercortisolism (which is likely to have provoked hypokalemia in this case), we treated this patient, in addition, with the MR antagonist spironolactone. The combination therapy was intended to prevent deleterious effects of cortisol- mediated receptor activation by achieving dual blockade of GR and MR.

The end-stage heart failure that dramatically improved, after the amelioration of glucocorticoid excess, raises the question of whether the cardiomyopathy was directly caused by hypercortisolism (14, 15). Patients with endogenous CS are commonly affected by severe LVH out of proportion to the degree of concomitant hypertension (14, 15), and this LVH frequently leads to heart failure. Are such adverse cardiovascular findings in CS mediated by cortisol activation at the GR and/or at the MR level? MRs have been reported to occur not only in kidney epithelium but also in myocardium, and increased cardiac fibrosis is seen in endomyocardial biopsies from CS patients (14), reminiscent of the fibrosis and other abnormalities attributed to aldosterone-associated MR activation in congestive heart failure (16). The same processes contributing to the progression of heart failure are effectively attenuated or reversed by antialdosterone therapy (17, 18). Thus, it is possible that the cardiomyopathy of CS may result from cortisol-mediated overstimulation of myocardial MR, just as the features of apparent mineralocorticoid excess in CS may result from cortisol-mediated overactivation of renal epithelial MR, with both abnormal findings being manifested in the setting of overwhelmed or defective 11βHSD activity.

The patient's marked elevation in serum cortisol and ACTH was nonsuppressible after high-dose dexamethasone; this is consistent with other reports of pituitary macroadenomas causing CD and does not necessarily denote an ectopic ACTH syndrome (4). Furthermore, it can be postulated that the hormonally aggressive behavior of the patient's macroadenoma potentiated not only the cardiomyopathy but also the hypokalemia and hypertension, the latter two findings of which are much more commonly observed in CS patients with ectopic ACTH-secreting tumors (13). A striking clinical result of this case is the reappearance of an ostensibly normal hypothalamic-pituitary-adrenal axis, at the patient's most recent evaluation; this result is uncommonly reported, given that the treatment of refractory CD tends to render patients adrenocortical-deficient.

The association between hypercortisolism and neuropsychiatric symptoms has been known for decades, with an estimated prevalence of psychiatric dysfunction of more than 40% in patients with CS (19). Psychosis and cognitive impairment are noted less commonly than depression, but this may stem from the use of inappropriate detection techniques. If suitable tests to reveal psychosis and impaired cognition are used, it is possible that the symptoms of patients with CS would best be classified as psychotic major depression or major depression with cognitive impairment. Our patient's features of depression improved markedly after treatment of CS, although he exhibited residual insomnia and anxiety. However, the psychosis totally abated, and cognition normalized. Interestingly, the recognition of the link between adrenal axis dysfunction and affective disorders has led to successful use of mifepristone in treating psychotic depression, as detailed in a separate report (6).

In conclusion, an improved understanding of the interactions between glucocorticoids, mineralocorticoids, receptors, and end-organ effects, in conjunction with the rational application of receptor antagonists, can lead to directed therapy of the numerous morbidities associated with severe CS. In this report, combination use of mifepristone and spironolactone allowed the dramatic reversal of cardiovascular, metabolic, and neuropsychiatric abnormalities in a patient with refractory CD.

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Medical management of early fetal demise using a combination of mifepristone and misoprostol.

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Medical management of early fetal demise using a combination of mifepristone and misoprostol

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BACKGROUND: This study aims to assess the efficacy of a combination of mifepristone and misoprostol in the management of missed miscarriage and anembryonic pregnancy. METHODS: Data of 220 consecutive women with miscarriage, undergoing medical evacuation of the uterus were collected prospectively at an early pregnancy assessment unit in a tertiary referral hospital. Each woman received a single oral dose of mifepristone 200 mg and 36–48 h later vaginal misoprostol 800 μg. Three hours following the first dose, two further doses of misoprostol, 400 μg each, were administered vaginally or orally at 3 h intervals. Women who failed to pass products of conception were offered repeat medical regime with misoprostol. Success was defined as complete uterine evacuation within 3 days, without the need for surgical evacuation. RESULTS: The overall success rate of medical management was 84.1%. Mifepristone alone induced natural expulsion of products of conception in 18.1% of women. The median dose of misoprostol required was 1600 μg and the median induction miscarriage interval after first prostaglandin administration was 8.04 h (range: 0.58–50.54 h). Of the 142 women who were symptomatic at presentation the medical regime failed in 30 (21.1%), compared with five (6.4%) failures of the 78 who were asymptomatic ($P = 0.007$). Of the 35 women who had surgical evacuation, eight required an emergency curettage for bleeding. CONCLUSIONS: The combination of oral mifepristone 200 mg with vaginal or oral misoprostol is an alternative to surgical management of early fetal demise, although it is not as effective as surgery.

Key words: anembryonic pregnancy/fetal demise/mifepristone/misoprostol/missed miscarriage

Introduction

The terms 'delayed miscarriage or early fetal demise' denote missed miscarriage (presence of a non-viable embryo/fetus) and blighted ovum (anembryonic pregnancy with absent embryonic echo) (RCOG Study Group, 1997). The two conditions are felt to represent different aspects of the same clinical process. A blighted ovum results from an early disturbance of normal embryonic development. In missed miscarriage, an intrauterine sac is seen with an embryo without cardiac activity. Apart from the distinction made at the time of vaginal scan, no clinically significant differences are observed between the two conditions. The diagnosis of early fetal demise has become more common since the introduction of transvaginal ultrasound, and accounts for ~21% of all miscarriages seen in our early pregnancy assessment unit (EPAU) in Aberdeen.

The clinical management of miscarriage has changed little over the years and up to 88% of women undergo surgical uterine evacuation (Hemminki, 1998). There are well-documented risks associated with surgical uterine evacuation (Farell *et al.*, 1982; Heisterberg *et al.*, 1986) and potential cost savings (Hughes *et al.*, 1996) can be generated by promoting alternative strategies of management. The success of expectant management of missed miscarriage appears too low to justify its routine use in clinical practice (Jurkovic *et al.*, 1998), although it may be an acceptable approach in individual patients. Various medical regimens with or without the anti-progesterone, mifepristone, and a prostaglandin analogue have been described to treat early fetal demise. Their efficacy vary widely from 25–92%, depending on the type of miscarriage, outcome measures used, the dose, duration and route of prostaglandin administration (El-Refaey *et al.*, 1992; Creinin *et al.*, 1997).

Based on our experience of first trimester abortion (El-Refaey and Templeton, 1994; El-Refaey *et al.*, 1995; Ashok *et al.*, 1998), we developed a regimen comprising mifepristone 200 mg followed by a combination of the vaginal or oral administration of misoprostol (800–1600 μg) for the management of early fetal demise. We now report our experience of this regimen in 220 consecutive cases.

Materials and methods

A consecutive series of 220 women with 'delayed miscarriage' (missed miscarriage and anembryonic pregnancy) between 6 and 13 weeks, during the period 1998–1999, were studied. All women had chosen to undergo medical rather than surgical treatment. The study was performed in the EPAU at Aberdeen Maternity Hospital. The

Table I. Comparison of details of women with missed miscarriage and blighted ovum

	Missed miscarriage (n = 139)	Anembryonic pregnancy (n = 81)	P value
Age (mean ± SD)	31.67 ± 6.39	31.61 ± 5.61	NS
Multiparity	97 (69.7%)	53 (65.4%)	NS
Previous miscarriages	47 (33.8%)	20 (24.6%)	NS
Symptomatic at presentation	89 (64.0%)	53 (65.4%)	NS
Medical evacuation on mifepristone alone	30 (21.5%)	10 (12.3%)	NS
Medical evacuation on full regimen	87/109 (79.8%)	58/71 (81.6%)	NS
Surgical evacuation	23 (16.5%)	12 (14.8%)	NS
No analgesia	55 (39.5%)	23 (28.4%)	NS
Parenteral analgesia	22 (15.8%)	16 (19.7%)	NS
Readmission	8 (5.7%)	6 (7.4%)	NS

NS = not significant.

assessment of gestational age was based on menstrual history and all ultrasound measurements (crown–rump length, gestational sac diameter) were within the first trimester. The diagnosis of missed miscarriage was confirmed on ultrasound by the absence of a fetal heart pulsation when the crown–rump length was >6 mm and of an anembryonic pregnancy by absent fetal pole in a gestational sac >25 mm in diameter. Successful treatment was defined as complete uterine evacuation using medical regimen without the need for surgical intervention.

All women with a miscarriage were counselled appropriately, and were offered a choice of medical or surgical treatment. Women who consented to medical management received a single oral dose of 200 mg of mifepristone in hospital. Unless miscarriage occurred following administration of mifepristone alone, which was confirmed by ultrasound scan on patients who gave a history of heavy bleeding prior to misoprostol administration, women were admitted to the EPAU 36–48 h later. On admission, four tablets (a total of 800 μg) of misoprostol were inserted into the posterior vaginal fornix by a nurse. Following administration of the first dose, a further two doses of misoprostol (two tablets each) 400 μg were given vaginally every 3 h. If bleeding was heavy misoprostol was administered orally. If products of conception were passed on the ward, the women were observed for 4 h before being allowed home. Following misoprostol administration pulse, blood pressure, temperature and systemic symptoms were monitored hourly. Oral (paracetamol 500 mg plus dihydrocodeine 10 mg) or parenteral analgesia (morphine 10 mg) was administered every 4–6 h as required. Patients who failed to pass products of conception overnight were offered a choice of either repeat medical regimen (misoprostol 800, 400, 400 μg at 3 h intervals, orally or vaginally) or surgical evacuation. Complete uterine evacuation was confirmed clinically by observing expelled products of conception and speculum examination. In the event of uncertainty ultrasound scan was performed.

All women were offered a follow-up appointment within 2 weeks of treatment, at the hospital or in the community (referring doctor or midwife). Those women who were allowed home without passing products of conception on the ward were given an emergency telephone number for contacting staff if they were concerned at any time. The women were followed up in the hospital with ultrasound assessment undertaken if indicated.

Data were analysed using the SPSS for Windows Statistical Package (Kinnear and Gray, 1994). In presenting the results, continuous variables are presented as means with standard deviations and ranges. Categorical variables are given as numbers (percentage) and associations were tested using the Fisher's exact or χ^2 tests as appropriate. Kaplan–Meier survival analysis was used to compare (by means of the Log Rank test) the cumulative miscarriage rates in relation to parity. Differences were regarded as statistically significant if $P < 0.05$.

Results

Of the 220 women with early fetal demise, 139 (63.1%) had a missed miscarriage and 81 (36.8%) had an anaembryonic pregnancy. A comparison of patient characteristics, presentation, treatment outcome, induction–miscarriage interval and complications between the two groups is shown in Table I. There were no significant differences.

The mean ± SD age of the 220 women was 31.6 ± 6.1 years (range 16–44). Of the 220 women, 67 (30.4%) were primiparous and 153 (69.5%) had one or more previous pregnancies. The mean gestation, by best estimate at the time of mifepristone administration, was 10.1 ± 1.84 weeks of amenorrhoea (range 6–13). At presentation to the EPAU, 84 (38.2%) had vaginal bleeding, five (2.3%) had pain and 53 (24.1%) had both pain and bleeding. Seventy-seven (35%) women were asymptomatic and the diagnosis was made at the routine first visit scans.

Of the 220 women, 44 complained of heavy bleeding within 48 h of mifepristone administration alone and in 40 complete miscarriage was confirmed on ultrasound scan. Four had emergency curettage for heavy bleeding. The treatment outcome is summarized in Figure 1. Among the 176 women who went on to receive misoprostol, complete miscarriage occurred in 145 (without the need for surgical intervention). Thus, the overall success rate was 185/220 (84.1%). The indications for surgical intervention are shown in Table II. Eight women had emergency curettage for bleeding, four before and four after misoprostol administration. A total of seven women had a blood loss >500 ml but none required a blood transfusion.

Of the 142 women who were symptomatic at presentation (pain/bleeding) the medical regime failed in 30 (21.1%) who required surgical evacuation of the uterus, while five (6.4%) women of the 78 who were asymptomatic (diagnosis of non-viable pregnancy on routine ultrasound) required surgical intervention—a statistically significant difference ($P = 0.007$). Of the 185 patients who had a successful outcome, complete

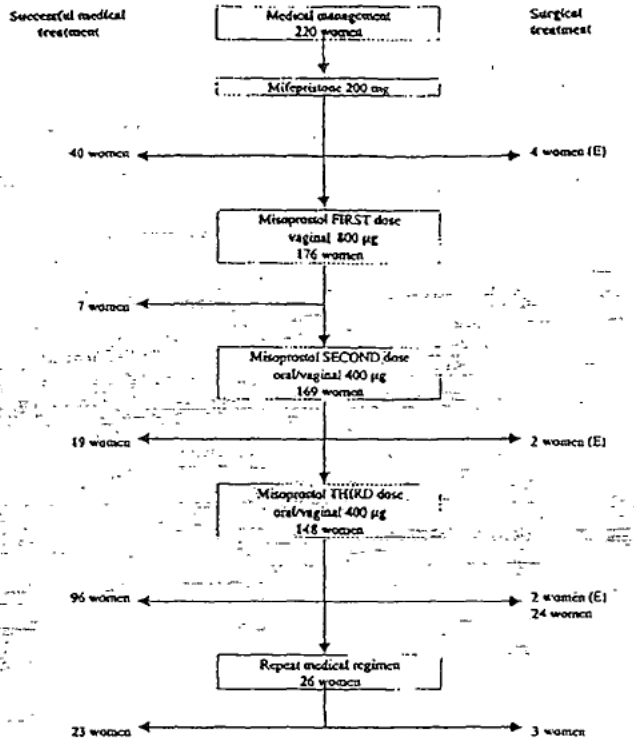

Figure 1. Outcome of medical treatment in 220 consecutive women with early fetal demise. E indicates women who had emergency curettage.

Table II. Indications and time interval for surgical intervention

Indications	Total number (%)
Emergency curettage for bleeding	8 (22.8)
Incomplete miscarriage	14 (40.0)
No products passed	6 (17.1)
Patient choice	6 (17.1)
Molar pregnancy	1 (2.8)
Total	35 (15.9)
Misoprostol to surgical intervention interval	
Before misoprostol	4
Up to 3 days	22
4–14 days	5
≥15 days	0

uterine evacuation was confirmed clinically in 130 (70.3%) and ultrasonically in 51 (27.6%).

The median number of misoprostol doses required was three (800 + 400 + 400 µg). Of the 54 women who did not miscarry following overnight stay (three doses of misoprostol), 28 (51.9%) opted for surgical evacuation. The medical regimen was repeated in the remaining 26 patients, of whom 23 (88.5%) had a complete miscarriage. Of the 176 women who received the full mifepristone/misoprostol regimen, the induction-miscarriage interval could be accurately determined in 148 (84%) and of these, 74 (50.0%) miscarried within 6 h of receiving first dose of misoprostol. The median induction–miscarriage interval was 8.04 h (range among those observed:

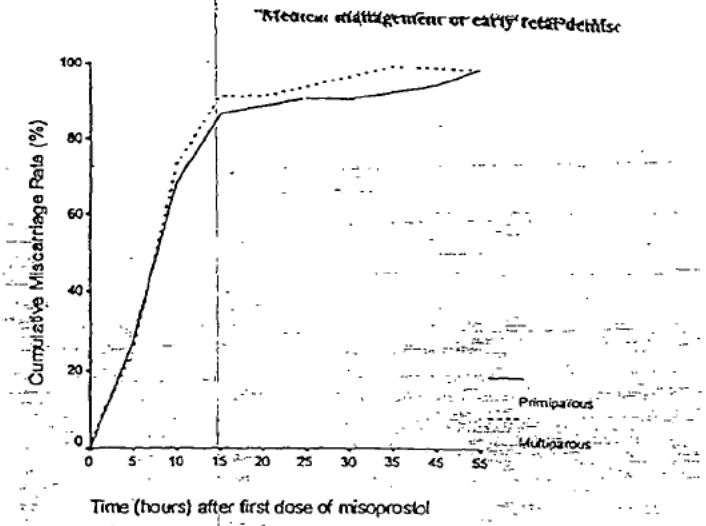

Figure 2. Cumulative percentage of women who miscarried in relation to parity, by 5 h intervals from the time of administration of first dose of misprostol.

0.58–50.54). The median (range) induction–miscarriage interval was 8.16 h (2.0–50.54) and 8.0 h (0.58–30.92) in primigravid and multigravid patients respectively. The two groups were compared by Kaplan–Meier survival analysis and no significant difference was found between the two groups (Log Rank test). The cumulative frequency of induction–miscarriage interval is shown in Figure 2.

Data on analgesic use were recorded in 219 women in the study. Of these, 78 (35.6%) required no analgesia (including 40 women who miscarried following mifepristone alone). 101(46.1%) required oral analgesia only, two received diclofenac suppositories and 38 (17.4%) required parenteral opiate analgesia.

Fourteen (6.3%) women who had had medical treatment for miscarriage required readmission. Of these, four (1.8%) had presumed pelvic infection, five (2.2%) required surgical curettage for prolonged bleeding, four (1.8%) had problems unrelated to the miscarriage and one (0.5%) had a molar pregnancy. One hundred (45.5%) women were given follow-up appointments in hospital, of which 82 (82%) attended. Sixty-three (28.6%) women declined an appointment and the remaining 57 (25.9%) were followed up in the community (referring doctor or midwife).

Discussion

To our knowledge, this study of 220 women represents the largest reported series of the medical regimen for early pregnancy demise. Although incomplete miscarriage may be managed with misoprostol alone (Henshaw *et al.*, 1993; Chung *et al.*, 1997), in the presence of an intact sac and closed cervix (early fetal demise), priming with the antiprogesterone mifepristone makes the regimen more effective (El-Refaey *et al.*, 1992; Hinshaw, 1997). The overall success rate of our regimen was 84.1%, but the true efficacy—by excluding women who had surgical evacuation by choice—was 86.4%.

Nielsen *et al.* reported a success rate of 52% using a combination of 400 mg of mifepristone and 400 µg of

Table III. Published data on regimens of medical management of miscarriage and their efficacy

Study	Regimen	Efficacy (%)
Pandian *et al.*, 2001[a]	Misoprostol 600 µg, 400 µg, 400 µg–2 hourly (PO)	84.8
Demetroulis *et al.*, 2001[b]	Misoprostol 400 µg (PV)	82.5
Nielsen *et al.*, 1999[b]	Mifepristone 400 mg Misoprostol 400 µg (PO)	82.0
Nielsen *et al.*, 1997[c]	Mifepristone 400 mg Misoprostol 400 µg (PO)	52
Creinin *et al.*, 1997[c]	Misoprostol 400 µg (PO)	25
	Misoprostol 800 µg (PV)	88
Herabutya and O-Prasertsawat, 1997[c]	Misoprostol 200 µg (PV)	83.3
Hughes *et al.*, 1996[c]	Mifepristone 200 mg Misoprostol 400 µg, 600 µg, 400 µg (PO)	89.1
Chung *et al.*, 1997[b]	Misoprostol 400 µg, 400 µg, 400 µg–over 48 h (PO)	70.6
Egarter *et al.*, 1995[c]	Gemeprost 1 mg	76.7
de Jonge *et al.*, 1995[a]	Misoprostol 400 µg (PO)	13
Chung *et al.*, 1994[b]	Gemeprost 1 mg	45.4
Henshaw *et al.*, 1993[a]	Sulprostone 0.5 mg (i.m.) or Misoprostol 400 µg (PO)	96
Lelaidier *et al.*, 1993[c]	Mifepristone 600 mg	82
El–Rafeay *et al.*, 1992[c]	Mifepristone 600 mg Misoprostol 400 µg, 200 µg 2 h apart (PO)	96

[a]Incomplete miscarriage.
[b]Incomplete miscarriage, missed miscarriage and anembryonic pregnancy.
[c]Missed miscarriage and anembryonic pregnancy.
PO = per oral; PV = per vaginal; i.m. = intramuscular.

misoprostol, both taken orally with 13% of women requiring emergency curettage (Nielsen *et al.*, 1997). In our series, emergency surgical intervention was necessary in only 3.6%. Medical treatment may have been less successful in the Nielsen study because of the smaller dose (400 µg) of misoprostol administered by the oral route rather than the vaginal route. Vaginal administration of misoprostol has been shown to be more effective in comparison with the oral route in the context of medical management of miscarriage and first trimester termination of pregnancy (El-Refaey *et al.*, 1995; Creinin *et al.*, 1997). Plasma concentrations and bio-availability of misoprostol tend to be greater and prolonged when administered vaginally compared with the oral route (Zieman *et al.*, 1997). In our study, split analysis showed that the medical regimen was more effective in women who were asymptomatic at presentation (93.5%) with a non-viable pregnancy being diagnosed on routine scanning as opposed to women who presented with pain and/or bleeding (78.8%). In comparison Nielsen *et al.* only included women who were asymptomatic at presentation and had an efficacy rate of only 52% (Nielsen *et al.*, 1997).

In our study we used clinical parameters for defining success of the method. Once products of conception were passed and bleeding ceased, we did not perform an ultrasound scan to confirm an empty uterus unless indicated. However studies suggesting a lower efficacy with the medical regimen made ultrasound scan assessment of all women following treatment to confirm an empty uterus (Nielsen *et al.*, 1997). Only five of the women in this series required subsequent surgical evacuation following discharge from hospital for prolonged bleeding. Our work confirms no real advantage in scanning all women following treatment. In addition to increasing surgical evacuation rates this would also increase the use of resources.

The natural expulsion of products of conception with 200 mg of mifepristone alone occurred in 18.1% of women, while Lelaidier *et al.* reported 82% expulsion rates using a dose of 600 mg of mifepristone alone (Lelaidier *et al.*, 1993). It has been shown that for termination of early pregnancy a single dose of 200 mg mifepristone is as effective as 600 mg, when used in combination with a prostaglandin analogue (WHO Task Force, 1993). However a higher dose of mifepristone may be required for medical treatment of miscarriage, probably due to a change in progesterone receptor sensitivity, and this is reflected in the higher success rate (96%) from our early study using 600 mg (El-Rafaey *et al.*, 1992). This needs to be confirmed in the context of future studies. Mifepristone is relatively expensive and a reasonable success rate (>80%) can be achieved by using a combination of 200 mg mifepristone with misoprostol. Misoprostol is cheap, effective and does not require special storage facilities, hence is a promising alternative in the developing world. Most published studies using misoprostol alone for medical management of delayed miscarriage have a success rate of 13–83% (de Jonge *et al.*, 1995; Herabutya and O-Prasertsawat, 1997). Should mifepristone be unavailable, regimens using misoprostol alone may have a place in clinical practice. Table III summarizes published data with respect to medical regimens and success rates.

Demetroulis *et al.* showed that a single dose of misoprostol 800 µg administered vaginally was successful in 82.5% of women with early pregnancy failure, which included women with incomplete miscarriage, missed miscarriage and anembryonic pregnancy (Demetroulis *et al.*, 2001). If women with an incomplete miscarriage were excluded the failure rate of misoprostol alone for medical management of missed miscarriage and anembryonic pregnancy would have been 23.1% in the above study. This confirms the results from our

series and previous studies that priming with the anti-progesterone mifepristone makes the regimen more effective (El-Refaey *et al.*, 1992; Hinshaw, 1997). Demetroulis *et al.* (2001) also showed that 82.5% of women who underwent the medical regimen for early pregnancy failure were satisfied with treatment compared with 58% of those who underwent surgical treatment.

Medical termination of pregnancy up to 9 weeks, using a combination of mifepristone and misoprostol, had an efficacy of 97.5% (El-Refaey *et al.*, 1994). More recently the feasibility of medical abortion has been shown at gestations between 9 and 13 weeks to have an efficacy of 95% (Ashok *et al.*, 1998). However medical management of early non-viable pregnancy has a much lower efficacy, probably attributable to low progesterone concentrations following fetal demise. The lower failure rate of the medical regime in asymptomatic women compared with symptomatic may also be explained by the same hypothesis. The side effects of misoprostol have not been assessed in this study. However it is well known in the context of medical abortion that the commonest side effects experienced by women are gastro-intestinal (El-Refaey *et al.*, 1995).

Patient acceptability has been shown to be similar between surgical and medical evacuation for incomplete miscarriage and early fetal demise (RCOG, 2000). Acceptability tends to decrease with increasing symptoms and gestation. The uptake of the medical regimen for early fetal demise at our EPAU was 45%. It may be possible to introduce medical management without admission to the EPAU, particularly at early gestations. Out of 54 who did not miscarry following overnight stay, 26 women (48.1%) opted for repeat regimen; 23 (88.5%) were successful. This emphasises the value of offering repeat medical treatment if the standard regimen fails.

Eighteen women did not attend hospital follow-up and 28.6% of women declined an appointment. The Grampian Region is unusual in terms of its catchment population, and there is only one main hospital within a radius of 50 miles. While acknowledging that an unknown number of women may have consulted their General Practitioner with symptoms and minor complications, it can be assumed that any women with a significant complication would have been referred to hospital for further treatment.

In conclusion, medical treatment with 200 mg of oral mifepristone in combination with 800, 400 and 400 μg of vaginal misoprostol given sequentially at 3 h intervals is an effective and safe alternative to surgical and expectant management of early fetal demise. Therefore extending the availability of medical management of early fetal demise at EPAU would reduce the need for surgery and associated complications. Finally, medical management increases women's choice of methods.

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Feasibility of administering mifepristone as a once a month contraceptive pill.

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Feasibility of administering mifepristone as a once a month contraceptive pill

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Many women find the idea of a once-a-month contraceptive pill an attractive concept. Mifepristone has been shown to be effective as a contraceptive if administered in the early luteal phase. We tested the contraceptive efficacy of 200 mg of mifepristone on day luteinizing hormone (LH) + 2 in a group of 32 women who used a fertility monitor to identify the LH surge. We also recruited a control group, comprising 20 women who were trying to conceive. In this group, 12 women conceived during a total of 50 control cycles (probability of pregnancy 0.25–0.32). Women in the treatment group contributed to a total of 178 cycles and there were two pregnancies (probability of pregnancy 0.01). An LH surge was not detected in 34 cycles (19.1%). In 20 cycles (11.2%) this was due to imperfect use while 14 were monitor method failures (7.9%). Treatment with mifepristone in the early luteal phase did not disrupt the cycle length but women reported slight vaginal bleeding in 15% of the cycles. The combination of a home-use fertility monitor with once-a-month administration of mifepristone (especially if mifepristone is administered at the early luteal phase) is an acceptable contraceptive option with minimal side effects. Unfortunately, it is difficult to envisage how an easier way of defining the correct timing, which required less compliance, could be devised.

Key words: contraceptive/home use fertility monitor/LH surge/Mifepristone/once-a-month pill

Introduction

Hormonal contraception is used by almost 100 million women world-wide. However, many women are deterred from using it because of perceived risks to health such as breast cancer or side effects such as weight gain. Most of the risks and the side effects are the results of prolonged exposure to steroids and many women, in a variety of cultural settings, find the idea of a pill which they need take only once each month, an attractive concept (Rimmer *et al.*, 1992; Glasier *et al.*, 1999).

Progesterone is essential for the establishment and maintenance of human pregnancy. The anti-progesterone mifepristone is a synthetic 19-norsteroid, which acts by blocking the action of progesterone at the receptor level (Spitz and Bardin, 1993), and thus, has multiple potential anti-fertility actions. When administered in the early luteal phase mifepristone retards endometrial development, without disturbing the timing of menses (Swahn *et al.*, 1988; Berthois *et al.*, 1991; Maentausta *et al.*, 1993). It also alters uterine contractility to a pattern more usually seen in the late luteal phase (Gemzell-Danielsson *et al.*, 1990). In 1993 Gemzell-Danielsson and colleagues conducted a pilot study in which a single dose of 200 mg of mifepristone was given in the early luteal phase [2 days following the surge of the lutenizing hormone (LH) in urine]. Out of 124 cycles in which coitus took place during the fertile period, only one pregnancy was observed (Gemzell-Danielsson *et al.*, 1993). There was no disruption of the timing of the subsequent menstrual bleed, although in 35% of the cycles slight vaginal bleeding was reported 2–3 days after treatment.

The main problem in developing a once-a-month contraceptive is finding a means that, both reliably and easily, identifies the start of the LH surge. Gemzell-Danielsson tried to solve this problem by using the LH sticks for home urine testing (Ovu-quick; Organon). In their study 12 out of 169 cycles were deemed to be anovulatory. However, it is not possible to determine if the LH surge truly was absent, or if the method failed to detect a surge. The woman may have read the test result wrongly or even failed to perform a test on the appropriate day.

Unipath (Bedford, UK) have developed a technology that can be used in the home to monitor changes in urinary hormones. This system comprises disposable test sticks and a hand held monitor, which together are used to detect changes in the levels of oestrone-3-glucuronide (E3G), a urinary metabolite of oestradiol, and LH, to indicate the potentially fertile days leading up to ovulation. The time from the first significant rise of LH in the urine to ovulation is reported to be around 24–48 h (Collins, 1996). The monitor thus should provide a convenient method of identifying the early luteal phase. Summary data for up to six consecutive cycles can be stored in the monitor memory and these data can be retrieved.

We investigated the contraceptive efficacy of 200 mg of mifepristone on day LH + 2 in a group of women who used this monitor to identify the LH surge.

Materials and methods

This was a single centre study in healthy female volunteers, approved by the Lothian Research Ethics Committee. All subjects gave written informed consent to participation. Fifty-two sexually active women, with regular (25–32 day) menstrual cycles were recruited from a large Family Planning Clinic in Edinburgh. If the women had a significant medical condition or if they or their partners had a history of fertility problems, they were excluded from the study.

Treatment group

Thirty-two women were recruited to the treatment group. None had been taking hormonal preparations within the 2 months prior to the start of the study and all had had at least two spontaneous menstrual periods since stopping hormonal contraception. All women underwent screening at the time of recruitment including a routine physical and gynaecological examination. A venous blood sample was taken for full blood count, serum biochemistry and liver function. The study started on day 1 of the menstrual period following screening, and lasted for up to seven consecutive menstrual cycles in which subjects took 200 mg mifepristone once per month.

Control group

The control group consisted of 20 healthy women with regular menstrual cycles who were trying to become pregnant (for less than 6 months prior to the enrolment in to the study) and hence, were not using contraception. They were provided with a monitor, which they used according to the manufacturer's instructions. Women were advised that their chance of conception would be higher if they were to have sexual intercourse during the fertile period, identified by the monitor. The controls took part in the study until pregnancy occurred or for a maximum of six cycles if they did not conceive.

Procedure

All subjects and controls were provided with a home use hormone monitoring system (Unipath, Bedford, UK). The system comprises a hand-held monitor and disposable dual-assay urine test sticks, and is used to simultaneously detect LH and E3G levels in early morning urine. The monitor optically measures the intensity of the lines that form on the test sticks after sampling, and the system will delineate three levels of fertility (Low, High and Peak Fertility) according to the optical signal changes detected. Low fertility will be displayed from day 1 of the cycle, until the hormone levels rise above the baseline levels. A change from low to high fertility is triggered by detection of elevated E3G levels, to concentrations typically between 20 and 30 ng/ml. The change from high to peak fertility is triggered by the detection of an LH surge, typically with a concentration >30 IU/l.

Peak fertility is displayed on the day of the LH surge and on the following day. Subsequently high fertility is displayed for 1 day prior to a return to low fertility. At the start of each menses, the subjects pressed the 'm' button on their monitor to initiate that cycle of use, at a time suitable for testing the first urine of the day. For the rest of the month, the subjects were required to consult the monitor display each morning (3 h either side of the time when 'm' button was set) to determine whether they needed to perform a test that day. Beyond this 6 h time window the monitor would not accept a test. The system requests one test every day for up to a total of 10 or 20 tests, depending on the length of the woman's cycle, and the timing of her LH surge. Embedded software within the monitor collects and analyses data from each cycle to identify and display fertility status to the user, and stores data for several months.

Mifepristone (Laboratories Exelgyn, Paris, France) was taken 2 days after the day of the first day of peak fertility (LH surge). With each cycle, subjects followed the same protocol, and were reviewed by the investigator monthly, on day LH + 2. Just before taking the 200 mg tablet of mifepristone, a venous blood sample was taken, and later assayed for progesterone. At the beginning of the study, if the LH surge was not identified by day 21 of the cycle, the subject was instructed to continue testing, but mifepristone was not given in that cycle. The subject was also advised to use barrier contraception from day 21 until the onset of the next menses. After the second pregnancy (which occurred due to a failure in detecting an LH surge), we changed this practice. We calculated the estimated day of LH surge for each month based on information from the previous cycles. If the women did not detect an LH surge either within 3 days after the anticipated day of LH surge or by day 19, a blood sample was taken for rapid serum progesterone assay. If the progesterone level was >5nmol/l and if the woman was at risk of pregnancy, mifepristone was administered.

All subjects and controls kept a menstrual record card, recording all vaginal bleeding experienced during the study and the days on which they had sexual intercourse. Subjects also marked the first day of the peak fertility as identified by the monitor and the day of taking the study medication.

If menstruation was overdue by more than one week the investigator performed a pregnancy test. Provided this was negative, the subject continued in the study and the next cycle was deemed to start with the onset of menses. Since the effect of mifepristone taken in very early pregnancy is unknown, and teratogenic effects could not be ruled out, women who would not consider terminating any pregnancy were not recruited to the treatment group.

At the end of the study, the subjects attended for a final visit, when a routine physical and gynaecological examination was performed. Full blood count, serum biochemistry and liver function were reassessed.

The following definitions were created for the purpose of the study.

Imperfect use: was defined as failure to detect an LH surge through performing the test incorrectly (e.g. dipping a test stick in urine 30 or more min before it being read by the monitor), or failing to perform tests as requested by the monitor.

Monitor method failures: were defined as failure to detect an LH surge despite performing all tests as requested.

High fertile days: days preceding the urinary LH surge as indicated by the monitor to be potentially fertile.

Peak fertile days: The first day of a significant rise in urinary LH detected by the monitor, and the following day.

The fertile period: of the cycle was defined as 3 days before until 2 days after the urinary LH surge (LH–3 to LH+2).

Exposure cycles: were cycles in which women reported having sexual intercourse at least once during the fertile period.

Statistical analysis

Cycle lengths and serum progesterone concentrations were compared by two-sample *t*-tests. Confidence limits for efficacy were derived from confidence limits for relative risk calculated by the Greenland and Robins method (Greenland and Robins, 1985).

Results

Table I shows the demographic characteristics of the women who took part in the study.

Table I. Demographic data.

	Treatment group (n = 32)	Control group (n = 20)
Age		
Range	18–39	26–40
Mean (± SD)	30 (± 5.4)	32.9 (± 4.5)
BMI		
Range	19–38	21–29
Mean (± SD)	23.6 (± 4.3)	23.8 (± 2.7)
Smokers (%)	7 (21.9)	1 (5)
Non-smokers (%)	21 (65.6)	16 (80)
Ex-smokers (%)	4 (12.5)	3 (15)
Previous pregnancies		
1+ (%)	19 (59.4)	14 (70)
Never been pregnant (%)	13 (40.6)	6 (30)
Ever abortion (%)	15 (46.9)	5 (25)
Married/Co-habiting (%)	28 (87.5)	20 (100)
Single (with a regular boy friend) (%)	4 (12.5)	0 (0)

The women in treatment group were slightly younger (mean age 30 years) than those in the control group (mean age 32.9 years). Otherwise there were no differences between subjects and controls.

The probability of pregnancy in the control group

Twenty women were recruited to the control group and three withdrew before completing the study. Two withdrew from the study as they found using the system 'too stressful' and one withdrew because she no longer wished to plan a pregnancy. Data were collected from 50 control cycles during which 12 pregnancies occurred. Average frequency of intercourse was 1.7 episodes per week in the 39 control cycles in which the women kept a record of their sexual activity. In 37 cycles women had intercourse at least once during the fertile period (FP). In two cycles intercourse did not occur during the FP, while in 11 cycles the exposure status was unknown, as women failed to keep a record of sexual activity. Eight pregnancies occurred in the first exposure cycle.

If we assume that all 11 cycles from which information on sexual activity was lacking were exposure cycles, the probability of pregnancy was 0.25. However if those cycles were all non-exposure cycles, the probability of conception would be 0.32. Therefore among the control group the overall probability of pregnancy if sexual intercourse took place at least once during the fertile period lies between 0.25–0.32.

Contraceptive efficacy of the method

Thirty-two volunteers were treated with a single dose of 200 mg of mifepristone administered in the luteal phase of the cycle as their sole method of contraception between one and seven cycles. They contributed a total of 178 cycles, and in 167 cycles mifepristone was administered. Eight women withdrew from the study before completion; two women moved out of the area, three ended their relationship, two conceived during the study and one lost confidence in the method.

Two clinical pregnancies occurred in the 178 cycles studied. The first pregnancy was a true treatment failure, which occurred in a woman (para 1) who took mifepristone on day 14 (LH + 2) of her first treatment cycle. She opted for a surgical termination of pregnancy, which was performed at 8 weeks of gestation (confirmed by ultrasound scanning). In the second woman (para 3), an LH surge was not identified in her third study cycle hence she did not receive treatment with mifepristone, menses did not occur and on day 37 after her last menstrual period an ectopic pregnancy was diagnosed and treated surgically. In a third woman a biochemical pregnancy was diagnosed (serum βHCG only rising to 34 IU/l), which was spontaneously and completely aborted by day 34 of the third study cycle after taking mifepristone on day 14 (LH + 2). This woman continued in the study and completed six treatment cycles.

The mean frequency of sexual intercourse was 1.8 episodes per week in 167 treatment cycles in which sexual activity was recorded. If we assume the probability of pregnancy in the treatment group is similar to the control group (0.25–0.32), the expected number of clinical pregnancies during the 178 cycles (in which 140 were exposure cycles) studied should be between 35–48.3. The observed number was two. Therefore, the efficacy of the method is 94.3% (95% confidence interval 75.4–98.7) – 95.9% (95% CI 82.5–99.0).

When calculating the efficacy of the method, we excluded the 29 cycles during which women were not exposed to a risk of pregnancy, and the three cycles in which mifepristone was taken in the follicular phase.

Contraceptive efficacy of luteal phase administration of mifepristone

In 145 cycles in which mifepristone was taken in the early luteal phase (within 2 days of the urinary LH surge) 117 were exposure cycles (Table II). Exposure status was unknown in eight cycles and in 20 cycles women were not at risk of pregnancy. In the 117 exposure cycles, there was only one clinical pregnancy.

In 19 (10.7%) cycles, no LH surge was declared by the monitor but mifepristone was given as coitus had taken place during the fertile period of the cycle (calculated according to the usual cycle length and usual day of LH surge). Occurrence of ovulation was confirmed by serum progesterone of >5 nmol/l in all 19 cycles and treatment was administered prior to day 21 of the cycle in each case [between day 13–21 of the cycle, mean 16.9 (SD ± 2.1) days]. There were no pregnancies in these cycles.

If the probability of pregnancy in all exposure cycles in the study is 0.25–0.32 (the same as that of the control group), between 34–46 clinical pregnancies would be expected in the 136 ovulatory cycles in which mifepristone was taken in the luteal phase. The observed number was one. Hence, the contraceptive efficacy of luteal phase mifepristone is between 97.1% (95% CI 78.00–99.6) – 97.8% (95% CI 83.9–99.7).

Performance of the home use hormone monitor

In 140 treatment cycles an LH surge was identified by the monitor, which equates to 90.9% LH surge detection when calculated for perfect use cycles; and 80.5% when imperfect use cycles are also included in the total. In 127 cycles this

Table II. Treatment cycle details.

	Total no. cycles	Exposure cycles	Unknown exposure	No Exposure
Mifepristone administered	167	136	8	23
In follicular phase	3	0	0	3
In luteal phase	164	136	8	20
Early luteal phase	145	117	8	20
LH + 2	127	100	7	20
LH + 1	17	16	1	0
LH + 0	1	1	0	0
In luteal phase (unknown LH status)	19	19	0	0
Mifepristone not given	11	5[a]	0	6[b]
Total	178	140	8	29

[a]LH surge missed, at risk of pregnancy but after day 21.
[b]Anovulatory cycle $n = 1$, LH surge missed and no risk of pregnancy $n = 5$).

was confirmed by a subsequent rise in serum progesterone of >5 nmol/l in the early luteal phase. This information was not available from nine cycles (blood samples lost or not collected). In the remaining four cycles serum progesterone was between 2–5 nmol/l, 1 or 2 days following the urinary LH surge as detected by the monitor. This may have been due to an early detection of the first significant rise in urinary LH. None of these five cycles were prolonged after taking mifepristone, hence it is unlikely that they were anovulatory.

There was a total of 38 (21.3%) cycles in which an LH surge was not detected. Among them, one (0.6%) was an anovulatory cycle, defined by serum progesterone not rising above 5 nmol/l in the mid-luteal phase. In three (1.7%) other cycles we administered mifepristone on day 19, before the monitor had identified an LH surge. Serum levels of progesterone (taken on the day of administering mifepristone) confirmed that in these cycles mifepristone was administered in the follicular phase. All three cycles were prolonged (43–52 days).

In the remaining 34 cycles an LH surge probably occurred (as suggested by a rise in serum progesterone of >5 nmol/l) but was not identified by the monitor. Fourteen were missed due to monitor method failure (7.9%) and 20 were a consequence of imperfect use of the system (11.2%).

Cycle length

Mifepristone when given in early luteal phase did not significantly affect the cycle length ($P = 0.35$). The mean of the usual cycle length was 28.3 days (SD ± 1.3) and during the treatment cycles it was 28.0 days (SD ± 1.9).

Side effects

Women kept a record of vaginal bleeding in 139 out of the total 144 cycles where mifepristone was taken on LH + 2. Mifepristone induced vaginal bleeding within 72 h in 21 cycles (15%). In a further 19 cycles, our volunteers took mifepristone in the luteal phase but the LH status was not known. In 17 of those cycles (>89%), mifepristone induced a vaginal bleed.

Serum progesterone values in blood samples taken just prior to mifepristone administration were available for 136 cycles. The mean serum progesterone value was significantly ($P < 0.0001$) higher in those cycles where mifepristone induced bleeding when compared to the mean value for the cycles without bleeding [21.72 (SD ± 9.04) nmol/l versus 13.33 (SD ± 6.23) nmol/l].

Two women spontaneously reported improvement of their pre-menstrual symptoms during cycles in which mifepristone was administered, while one reported worsening. In one woman hepatic alanine aminotransferase (ALT) was elevated at 103 IU/l (normal range 10–40 IU/l) at the end of the study but returned to normal within 2 months. One woman complained of diarrhoea 12 h post mifepristone in one cycle, three reported menstrual cramping within 72 h of taking mifepristone; two women reported a reduction in menstrual blood loss.

Discussion

A single dose of 200 mg of mifepristone administered once a month is an effective contraceptive method with an overall efficacy of 95% increasing to 97% if administered at the correct time (i.e. the early luteal phase). Thus our results are in agreement with the findings of a previous study (Gemzell-Danielsson *et al.*, 1993).

One criticism of previous work in this field has been the lack of a suitable control group for the subjects studied. Unlike the Gemzell-Danielsson study, we were able to compare the results with a contemporaneous control group using the same methodology in the same cultural setting. In this control group, if sexual intercourse took place on a fertile day the probability of a pregnancy was 0.25–0.32. The calculated probability of pregnancy in a cohort of couples monitored during a study of natural family planning (WHO, 1983) was 0.486 if intercourse took place 3 days prior to and a day after the peak day of mucus discharge. The difference in the probability of pregnancy between our study and a variety of other published series (Table III) may be explained by the fact that we have extended our definition of the fertile period to 6 days (3 days prior to the urinary LH surge until 2 days after). Other authors (Wilcox *et al.*, 1995) have calculated that the likelihood of conceiving during an ovulatory cycle to be 0.37 (95% confidence interval 0.31–0.48) if daily sexual intercourse took place during a 6 day fertile period (four days before and a day after ovulation). The lower frequency of intercourse in

Table III. Probability of clinical pregnancy.

	No. of exposure cycles	No. of pregnancies	Probability of pregnancy
Wilcox *et al.*, 1995[b]	129	34	0.26
Our control group[b]	37–48	12	0.25–0.32
Our treatment group[b] (monitor + mifepristone)	140–151	2	0.01
Our treatment group[b] (mifepristone in luteal phase)	136–143	1	0.007
Gemzell-Danielsson *et al.*, 1990[a]	124	1	0.008
WHO study[a]	72	35	0.48

[a]The length of the fertile period defined as 4 days.
[b]The length of the fertile period defined as 6 days.

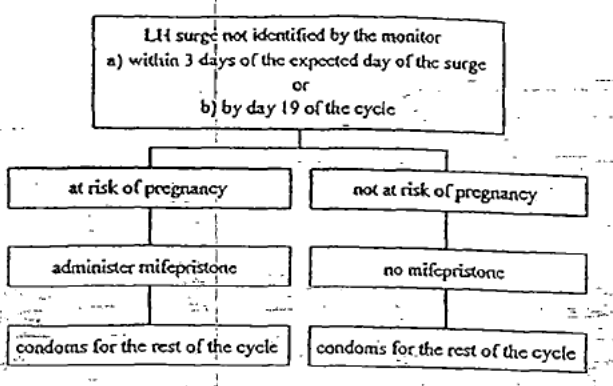

Figure 1. Algorithm for administering mifepristone when the LH surge is not identified

our group (untimed intercourse averaging 1.7 per week) may also explain the lower probability of pregnancy.

The limiting factor in this once-a-month approach to administering anti-progesterone is the accurate detection of the LH surge. Clearly, the failure to detect accurately the LH surge has a big impact on the overall effectiveness of the method. Using laboratory assay of LH in blood or urine to identify ovulation is neither practical nor convenient for long term use in the general population. The monitor provided us with an opportunity to overcome these problems. Gemzell-Danielsson *et al.* (1993) reported 49% accuracy using home LH detection sticks (Gemzell-Danielsson *et al.*, 1993). Although the monitor performed better (over 80.5% accuracy), both of these methods remain below the required standard. We studied 32 women over a total of 178 cycles. Imperfect use of the system accounted for failure to identify an LH surge in 11.8% cycles while 7.9% were due to monitor method failure. Compliance difficulties are associated with all contraceptives and non-compliance in ~12% of cycles is probably no worse than with any other method which demands action from the user, for example, compliance rates reported from oral contraceptive pill users range from 3.4–100% (Wheble *et al.*, 1981; Molloy *et al.*, 1985; Hamilton and Hoogland, 1989). Although our study population consisted of women who were motivated and committed and some of them already had experience in using natural family planning methods, they found the short, inflexible testing window set on day 1 of the cycle to be particularly demanding. This is inconsistent with couples using the monitor in order to get pregnant (Bonnar *et al.*, 1999). The prevalence of imperfect use is likely to rise in the general population compared with that typical of a research study.

During the course of the study we developed an algorithm (Figure 1) for the administration of mifepristone if an LH surge was not identified. In 19 exposure cycles (out of 28 cycles in which an LH surge was not identified) mifepristone was administered using this algorithm and there were no pregnancies. Given that the methods available to be used in real life to time the administration of mifepristone cannot be 100% accurate, such an algorithm will be essential to deal with a missed LH surge.

In our study, mis-timed administration of mifepristone led to predictable effects. When administered during the proliferative phase of the menstrual cycle, mifepristone inhibited follicular development, and delayed the mid cycle LH surge, leading to a delay in ovulation and subsequent prolongation of the menstrual cycle (Liu *et al.*, 1987; Luukkainen *et al.*, 1988; Swahn *et al.*, 1988). Ovulation may occur later in that cycle, leaving women at risk of conception. In our study, when administered in the late follicular phase (in error) in three cycles, mifepristone prolonged the cycle length (43–52 days). The women were advised to use condoms for the remainder of that cycle and none of the three cycles resulted in pregnancy.

Administration of mifepristone in the mid or late luteal phase induces a bleed within a few days of treatment, which may or may not be followed by a second bleed at the time of expected menstruation (Shoupe *et al.*, 1987; Swahn *et al.*, 1988). In our study, in 17 out of the 19 cycles where mifepristone was taken after ovulation (the LH status unavailable and probably later than on LH + 2), inter-menstrual vaginal bleeding occurred (89.5%). Moreover, there was an increased risk of bleeding seen in those women who may have taken mifepristone slightly later in the LH + 2 window. The mean serum progesterone concentration was significantly higher in those women who had bleeding after taking mifepristone within LH + 2, when compared with those who did not. The higher serum progesterone value in some on LH + 2, could be due to a delayed identification of the first significant rise in urinary LH, or because of a more rapid increase in serum progesterone due to early ovulation. Nevertheless, in our group of women, in all cycles where mifepristone induced a vaginal bleed, a second bleed occurred at the time of the expected menses. Therefore, while the bleeding may have been inconvenient, it did not jeopardise efficacy or continued use of the method. There was less inter-menstrual bleeding (15% of the cycles) reported in our study when mifepristone was taken within LH + 2, less than half of that reported by Gemzell-Danielsson *et al.* (32%) (Gemzell-Danielsson *et al.*, 1993). This is possibly due to the fact that the majority of women in our study received mifepristone at the correct time. In their study, in 51% of the cycles, mifepristone was taken between 3 and 5 days after the LH surge.

In conclusion, the use of the combination of home use

fertility monitor with once-a-month administration of mifepristone (especially if mifepristone is administered at the early luteal phase) is an attractive contraceptive option with minimal side effects. However, to be an effective contraceptive method, the women have to be committed to using a device, which identifies the LH surge, in order that the pill can be taken at the correct time in the cycle. Whilst this regimen may be acceptable to motivated women, it may be regarded as too complicated for others to adopt on a routine basis. There was evidence of such non-compliance in this study, with 11.2% of LH surges being missed as a consequence of imperfect use of the monitor. Unfortunately, it is difficult to envisage how an easier way of defining the correct timing, which obligated less compliance, could be devised.

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Efficacy of mifepristone followed on the same day by misoprostol for early termination of pregnancy: report of a randomised trial

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Objective To examine the clinical efficacy of mifepristone 600 mg followed on the same day or two days later by misoprostol 400μg orally in women undergoing medical termination of pregnancy whose pregnancies have a gestational age up to 49 days.

Design Prospective, randomised trial.

Setting Clinical research office.

Participants Eighty-six women, requesting elective termination of a pregnancy which has a gestational age of ≤ 49 days.

Methods After administration of mifepristone 600 mg, participants were randomised to take misoprostol six to eight hours later (Group 1) or 48 hours later (Group 2). Women returned for a follow up evaluation 24 ± 1 hours after taking the misoprostol. Participants in Group 1 who had not aborted received a second dose of misoprostol to take 48 hours after the mifepristone. All women returned approximately two weeks after receiving mifepristone. If termination of pregnancy had still not occurred and the pregnancy was non-viable, the woman returned again in three weeks.

Main outcome measures Rate of complete abortion 24 hours after administration of misoprostol.

Results At 24 hours after receiving misoprostol, 21/42 (50%, 95% CI 35%, 65%) women in Group 1 and 40/44 (91%, 95% CI 82%, 99%) women in Group 2 had complete abortions. By follow up two weeks later after the administration of mifepristone, 40/42 (95%, 95% CI 89%, 100%) women in Group 1 and 43/44 (98%, 95% CI 93%, 99%) women in Group 2 were known to have complete abortions. Nausea, vomiting or diarrhoea in women using the standard regimen (Group 2) occurred in 68%, 36%, and 20%, respectively.

Conclusions After treatment with mifepristone 600 mg, administration of misoprostol 400 μg orally on the same day is not as effective at causing abortion within the first 24 hours compared with the standard time interval of 48 hours between medications.

INTRODUCTION

In Europe and China more than three million women have received mifepristone, an antiprogestin, in a treatment regimen for medical termination of pregnancy. Complete abortion at gestations up to 49 days occurs in 64% to 85% of women when mifepristone is used alone in doses of 140mg to 1600mg administered over one to 10 days[1]. However, when mifepristone is followed two days later by a prostaglandin analogue, the efficacy rate for complete abortion increases to 87% to 97%[2].

Misoprostol is an inexpensive, orally active prostaglandin analogue that is used for the prevention of gastric ulcers induced by non-steroidal anti-inflammatory drugs; the dose is 200μg four times daily. Its effects on uterine tone are similar to those of other prostaglandin analogues[3]. When misoprostol 400μg orally is administered 48 hours after mifepristone 600mg, abortion occurs in 92% to 97% of women whose pregnancies have a gestational age of ≤ 49 days[4,5]. Side effects are similar to those reported with other prostaglandin analogues. Currently, misoprostol is the prostaglandin analogue most commonly used with mifepristone for early abortion.

The largest clinical evaluation of the mifepristone–misoprostol combination was an American multicentre trial involving 17 sites, including free-standing clinics, Planned Parenthood clinics and university hospitals[5]. The protocol was similar to that used in common practice in France. Woman received mifepristone 600mg orally, and returned two days later to receive misoprostol 400μg orally. Approximately 25% of participants had bleeding that was equivalent to or heavier than their menses during the interval between the medications; only 11% of those women (3% of the total study population) had aborted. A total of 2015 women with a gestation of up to 63 days were included in the final analysis. The complete abortion rate up to 49 days' gestation was 92%; however, the rate declined to 83% from 50 to 56 days amenorrhoea and

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77% from 57 to 63 days amenorrhoea. The time of expulsion was known for 1468 women, of whom 84% aborted within 24 hours after the administration of misoprostol[5].

Based on these, and many other published trials, the standard time to administer the prostaglandin analogue after mifepristone is 36 to 48 hours. The endometrium of a non-pregnant uterus begins to thin between 18 and 32 hour after the administration of antiprogestin[6]. Studies have demonstrated that the myometrium has more reactive contractility to low dose prostaglandin after treatment with mifepristone[7]. However, there are no studies that identify the time interval at which the increased reactivity to prostaglandin analogues occurs in a pregnant uterus.

It is therefore worthwhile to investigate the efficacy of administration of a low-dose prostaglandin analogue sooner than 48 hours after the administration of mifepristone. Regimens with a shorter interval between mifepristone and misoprostol, if effective, would lessen the time necessary for a medical abortion to occur and, potentially, increase acceptability. In addition, since approximately 55% of women bleed during the 48 hours between mifepristone and misoprostol with the standard regimen[5], administration of the drugs on the same day would decrease such an undesirable side effect.

This study was performed as a preliminary evaluation of the efficacy of mifepristone and misoprostol given on the same day for medical termination of a pregnancy with a gestational age of up to 49 days. Due to funding restrictions, we tested the hypothesis that the standard regimen would have resulted in expulsion within 24 hours of misoprostol in 90% of women treated with the standard regimen (i.e. the 48 hour interval between mifepristone and misoprostol) and 65% in women treated on the same day. If the regimens did appear similarly effective, then a larger study would be performed to test equivalence.

METHODS

Healthy women at least 18 years of age were enrolled in a prospective, randomised trial approved by the Institutional Review Board of Magee-Womens Hospital of the University of Pittsburgh Health System. Entry criteria included: 1. a singleton intrauterine pregnancy not exceeding a gestation age of 49 days as documented by vaginal ultrasound; 2. requesting an elective abortion; 3. willing to comply with the schedule of visits; 4. willing to have a surgical abortion if indicated; 5. adequate venous access for multiple phlebotomies; and 6. access to a telephone.

Exclusion criteria included: 1. contraindications to mifepristone including chronic systemic corticosteroid administration or adrenal disease; 2. contraindication to misoprostol including glaucoma, mitral stenosis, sickle cell anaemia, poorly controlled seizures, or known allergy to prostaglandins; 3. haemoglobin less than 10 gm/dL; 4. cardiovascular disease including angina, valvular disease, arrhythmia, or cardiac failure; 5. known coagulopathy or treatment with anticoagulants; 6. pregnancy with an intrauterine device *in utero*; and 7. breastfeeding.

Women who enrolled signed an informed consent form and agreed to suction evacuation of the uterus, should the pregnancy be viable (defined as the presence of cardiac activity on vaginal ultrasound) 14 days after initiating the study. Vaginal ultrasound was performed and gestational age estimated using the following criteria: gestational age (days) = mean sac diameter (mm) + 30[8], or embryonic pole (mm) + 42[9]. Mean sac diameter ([length + width + depth]/3) was used to estimate gestational age only when no embryonic pole is present. Estimated Gestational Age was based on the last menstrual period; however, if the ultrasound estimate differed by four days or more from the gestational age by the last menstrual period, the ultrasound estimate was used.

On the day of consent, a history and physical examination, baseline haemoglobin, and blood graph were performed. At least 24 hours after obtaining consent (as required by the Pennsylvania Abortion Control Act), the women ingested mifepristone 600mg in front of a member of the research staff, if all of the entry criteria were met. The day of this visit was considered study day one. If the woman's blood graph was Rh-negative, she also received Rh-immune globulin 50 μg intramuscularly.

The women were given two tablets of misoprostol 200 μg to take home. They were randomised to take the misoprostol six to eight hours (Group 1) or 48 hours (Group 2) after taking the mifepristone. Randomisation was performed using a random number table to create 100 women in each of the two groups; the group was assigned by opening the next sequentially numbered sealed opaque envelope. The randomisation sequence and preparation of the envelopes were performed by a person unrelated to the study. The researchers and medical staff were not blinded to group assignment.

All participants were given written instructions with a 24-hour phone number for emergencies. The directions stated to call the Research Office if vaginal bleeding exceeded two soaked sanitary towels in one hour for two consecutive hours. All women received a prescription for 20 tablets of codeine phosphate 30 mg. The women were instructed to use ibuprofen or acetaminophen initially and to use the prescribed narcotic only if necessary.

All women returned 24 ± 1 hours after taking the misoprostol, at which time they were questioned about side effects that occurred during the interval between mifepristone and misoprostol and after the misoprostol, as well as the time of administration of the misoprostol. When questioned about severity of bleeding, the women

were instructed that "bleeding" was defined as flow equal to or heavier than menses, and "spotting" was flow lighter than menses. A vaginal ultrasound scan was performed. If the woman was in Group 1 and the gestational sac was still present, she was given an additional 400 μg (two tablets) of misoprostol to take orally 48 hours after she received the mifepristone.

All women returned for a follow up visit between days 14 and 20. A history of events since the prior visit was obtained. A vaginal ultrasound scan was performed if the examination at the last visit had not demonstrated absence of the gestational sac. If the gestational sac and embryonic cardiac activity were present, a surgical termination of pregnancy was performed. If the gestational sac was still present without cardiac activity, the women returned in three weeks (day 36) at which time her history was taken and another ultrasound scan performed. If the vaginal ultrasound scan on day 36 showed the gestational sac to be still present, the woman was offered a surgical termination of pregnancy. If she declined intervention at this time then she was followed at one or two weekly intervals until she either aborted or requested a surgical abortion. All women were permitted at any time to request a surgical procedure rather than continuing to wait for expulsion.

Statistical analysis

The sample size was estimated based on complete abortion rates 24 hours after the misoprostol, of 90% with the standard regimen (48-hour interval) and 65% with administration of the misoprostol six to eight hours after the mifepristone. A sample of 86 women was calculated to have an 80% power to detect this difference using the z-statistic at a two-tailed significance level of 0.05[10]. Statistical analyses were performed using Fisher's exact test, Wilcoxon non-parametric rank tests, and χ^2 analysis with Yates' correction where appropriate. The procedure was considered successful if complete abortion occurred without requiring a suction evacuation of the uterus. Body surface area was calculated using a body surface area table[11].

RESULTS

The characteristics of the women are presented in Table 1. One (2.3%) of the women in Group 2 aborted during the interval between mifepristone and misoprostol. She called the office with heavy bleeding beginning 27 hours after the mifepristone; ultrasound evaluation in the office confirmed expulsion of the pregnancy, so she was instructed not to use the misoprostol. Of the remaining 43 women in Group 2, forty-two (97.6%) used the misoprostol 48 hours ± 0.5 hours after the mifepristone. The other woman used the misoprostol two hours after the 48-hour mark. All of the women in Group 1 used the misoprostol at the correct time.

At 24 hours after receiving misoprostol, 21/42 women in Group 1 (50%, 95% CI 35%, 65%) and 40/44 women in Group 2 (91%, 95% CI 82%, 99%) had complete abortions (RR = 0.55 [95% CI 0.42, 0.73]). By follow up two weeks after the mifepristone, 40/42 women in Group 1 (95%, 95% CI 89, 100%) and 43/44 women in Group 2 (98%, 95% CI 93%, 100%) were known to have complete abortions (RR = 0.97 [95% CI 0.90, 1.06]). One woman in Group 1 was lost to follow up after she received the mifepristone; as her final outcome could not be verified, her treatment was considered to have failed. One woman in Group 1 was thought to have aborted after a single dose of misoprostol but was seen on day 51 with an incomplete abortion requiring surgical evacuation of the uterus. One woman in Group 2 had a collapsed gestational sac 24 hours after receiving misoprostol. This sac remained at the two-week and five-week follow up visits. She continued to experience intermittent bleeding and requested surgical evacuation. The pathology report for both of the women who had surgical evacuation of the uterus showed chorionic villi.

Information on cramping and bleeding after the first dose of misoprostol is presented in Table 2. Information on the duration of vaginal bleeding and spotting was available for 37 (88%) and 38 (86%) women in Groups 1 and 2, respectively. Total vaginal bleeding lasted 17 (SD9) days and 17 (SD10) days, respectively. Only one woman had vaginal bleeding that soaked two sanitary towels in one hour for two consecutive hours; this occurred in the woman who aborted after the mifepris-

Table 1. Characteristics of the women. Values are given as n (%) or mean [SD].

	Group 1 ($n = 42$)	Group 2 ($n = 44$)
Age (years)	26 [6]	25 [7]
Gravidity		
1	7 (17)	11 (25)
2	11 (26)	13 (30)
3	10 (24)	7 (16)
4	8 (19)	2 (5)
>5	6 (14)	11 (25)
Mean (SD)	3 [1]	3 [3]
Parity		
1	17 (40)	18 (41)
2	12 (29)	11 (25)
3	8 (19)	8 (18)
>4	5 (12)	7 (16)
Mean (SD)	1 [1]	1 [1]
Marital status		
Single	33 (79)	33 (75)
Married	7 (17)	5 (11)
Divorced or separated	2 (5)	6 (14)
Prior termination of pregnancy	20 (48)	22 (50)
Body surface area (m^2)	1.80 [0.2]	1.80 [0.2]
Gestational age (days)	44 [4]	43 [5]

Table 2. Cramping and bleeding after misoprostol. Values are given as mean (SD). Women in Group 1 received a second dose of misoprostol 400 μg orally if the abortion had not occurred within 24 hours of the initial dose. Data for bleeding and cramping for Group 1 are only for the first dose of misoprostol. Women in Group 2 received only a single dose of misoprostol.

	Group 1 ($n = 42$)	Group 2 ($n = 44$)
Onset of bleeding (h)	3.8 (3.0)	2.7 (2.5)
Onset of cramping (h)	2.9 (2.8)	1.4 (1.4)
Total days of bleeding	16.9 (9.2)	17.0 (10.2)

tone without using misoprostol. Her bleeding subsided during the third hour and no intervention other than telephone contact was required. No women required a blood transfusion.

Side effects are presented in Table 3. The incidence of vomiting, bleeding and spotting in women who received misoprostol on the same day was significantly less compared with women who received misoprostol 48 hours after the mifepristone. Otherwise, there was no difference between the groups in their side effects. There was no statistical difference in side effects after misoprostol between the groups, including after the repeat dose of misoprostol when needed for the women in Group 1. The overall rate of nausea, vomiting or diarrhoea during the medical abortion process (after either or both medications) for women using the standard regimen was 68%, 36%, and 20%, respectively. One significant complication was a tubo-ovarian abscess occurring nine days after the administration of misoprostol and a successful abortion. The woman responded well to treatment with seven days of intravenous antibiotics followed by seven days more of oral antibiotic therapy.

Analgesia was not required at any time by 8 of 42 (19%) and 11 of 44 (25%) women in Groups 1 and 2, respectively ($P = 0.7$); all of these women aborted successfully. All o. the remaining women used only oral medication; 24% and 28% ($P = 0.9$) of women in Groups 1 and 2, respectively used narcotics for pain relief.

DISCUSSION

This is the first published trial to evaluate the use of mifepristone and a prostaglandin analogue on the same day for medical termination of pregnancy. Clearly, after treatment with mifepristone 600 mg, the administration of misoprostol 400 μg orally on the same day is not as effective at causing abortion within the first 24 hours compared with the standard time interval of 48 hours between medications.

Only 5% of women had any bleeding within six to eight hour after mifepristone, and that was only spotting. In the standard treatment group, 52% of women experienced bleeding during the 48 hours between the drugs. This rate is consistent with the 55% rate reported by Spitz *et al.*[5] after 600 mg mifepristone and the 48% rate reported by Schaff *et al.*[12] in 933 women after mifepristone 200 mg. Thus, bleeding during the 48-hour standard interval appears to occur in approximately half of the women after using mifepristone and usually begins more than eight hours after the mifepristone.

In the French study of Peyron *et al.*[4], mifepristone 600 mg followed in 36 to 48 hours by misoprostol 400 μg orally in women up to 49 days gestation, resulted in nausea, vomiting and diarrhoea being reported by 43%, 17% and 14%, of the women, respectively. In contrast, the women in our study reported these side effects in 68%, 36%, and 20%, respectively; these rates are nearly

Table 3. Side effects after treatment with mifepristone 600 mg and misoprostol 400 μg orally for early abortion. Values are given as *n* (%) or RR with (95% CI).

	Mifepristone			Misoprostol[a]				
	Group 1	Group 2	RR[b]	Group 1		RR[b]	Group 2	RR[c]
	$n = 42$	$n = 44$		1st dose $n = 42$	2nd dose $n = 18$		$n = 43$	
Nausea	18 (43)	21 (48)	0.90 (0.56, 1.43)	23 (55)	3 (17)	2.90 (1.00, 8.41)	18 (42)	1.31 (0.84, 2.05)
Vomiting	2 (5)	12 (27)	0.17 (0.04, 0.73)	5 (12)	2 (11)	1.07 (0.23, 5.02)	6 (14)	0.85 (0.28, 2.58)
Diarrhea	0	1 (2)	0.98 (0.93, 1.02)	15 (36)	4 (22)	1.57 (0.60, 4.08)	8 (19)	1.92 (0.91, 4.04)
Cramping	13 (31)	20 (45)	0.68 (0.39, 1.19)	39 (93)	16 (89)	1.04 (0.87, 1.26)	35 (81)	1.14 (0.97, 1.35)
Dizziness	7 (17)	11 (25)	0.67 (0.29, 1.56)	12 (29)	3 (17)	1.71 (0.55, 5.35)	8 (19)	1.54 (0.70, 3.37)
Spotting	2 (5)	23 (52)	0.09 (0.02, 0.36)	–	–	–	–	–
Bleeding	10 (24)	18 (41)	0.59 (0.46, 0.76)	32 (90)	18 (100)	0.90 (0.82,1.00)	43 (100)	0.90 (0.82, 1.00)
Headache	6 (14)	9 (20)	0.70 (0.27, 1.79)	5 (12)	3 (17)	0.71 (0.19, 2.68)	8 (19)	0.64 (0.23, 1.80)
Warmth/chills	10 (24)	10 (23)	1.05 (0.49, 2.26)	12 (29)	5 (28)	1.03 (0.42, 2.49)	13 (30)	0.95 (0.49, 1.83)

[a] One woman in Group 2 aborted after mifepristone and did not receive misoprostol. Data was missing for one of the 19 women in Group 1 who received a second dose of misoprostol.

[b] Relative risk and 95% confidence intervals; 1st dose versus 2nd dose.

[c] Relative risk and 95% confidence intervals of 1st dose of misoprostol in Group 1 compared to Group 2.

identical to those reported in the American study by Spitz *et al.*[5] (61%, 26%, and 20%, respectively). Thus, either French women have a lower rate of side effects from medical termination of pregnancy or do not report side effects when they occur.

Similarly, use of narcotic drugs in the French studies is different to that reported in the United States. Peyron *et al.*[4] reported that 81% of women experienced cramping and only 16% requested any pain relief, which consisted of a non-opiate analgesic. In the American trial reported by Spitz *et al.*[5], 29% of women received a narcotic analgesic. Women in both of these trials were required to remain in the office for four hours after misoprostol for observation. In contrast, the women in our study used the misoprostol at home, a practice that has been well-documented in the medical literature to be safe and effective[12–14]. Still, the use of narcotics was approximately the same as that reported in American women who remain under observation[5]. Overall, the use of narcotic analgesics is more prevalent in the United States compared with France.

Studies using mifepristone 200 mg followed in 48 hours by misoprostol 800 μg vaginally appear to result in higher rates of complete abortion and more rapid expulsion compared with oral misoprostol[12,15]. Thus, it is possible that a regimen with vaginal misoprostol may hold promise for same day treatment. Since a same-day regimen is desirable from the woman's point of view and has fewer side effects (especially bleeding), vaginal misoprostol given on the same day as mifepristone deserves investigation.

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Medical abortion as an alternative to vacuum aspiration: first experiences with the "abortion pill" in The Netherlands.

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Medical abortion as an alternative to vacuum aspiration: first experiences with the 'abortion pill' in The Netherlands

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ABSTRACT

Objective To establish to what extent medical abortion is desired as a supplement to existing care provision in The Netherlands and to establish the (dis)advantages of medical abortion versus surgical vacuum aspiration.

Methods The research project began in November 1999 and ended in September 2000. In two abortion clinics, the clients were asked to answer some questions about their expectations (before treatment) and their experiences with the treatment (at the post-treatment check-up). At the post-treatment check-up, the clients were also asked to fill out the Hopkin's Symptom Checklist (HSCL) which is an objective measure for the psychological and physical well-being of the clients during the previous week.

Results One hundred and thirty-one clients who chose medical abortion and 131 clients who chose surgical vacuum aspiration participated in the study. The failure rate was 3.3% for medical abortion and 1.5% for surgical vacuum aspiration. Of the medical abortion clients, 80.2% reported they were satisfied with this treatment and 68.1% said they would choose the same treatment procedure in the future. For vacuum aspiration, these figures were 92.9% and 83.2%, respectively.

The most reported advantage of medical abortion was the fact that it was a pill, and no surgical procedures were necessary. The most reported disadvantages of medical abortion were the amount of blood loss and insecurity concerning the time of abortion.

Conclusions Medical abortion seems to be a good supplement to the existing care provision in The Netherlands and should be offered in other clinics.

KEY WORDS Medical abortion, Comparative study

INTRODUCTION

Mifepristone (Mifegyne®), also known as the 'abortion pill', was developed by the French professor, Emil-Etienne Baulieu, and was introduced onto the French market in 1989 by the pharmaceutical company, Roussel Uclaf, under the name of RU 486. Within the same year, the Medicines Evaluation Board

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in The Netherlands proposed a registration request for RU 486. Several months later, Roussel decided not to continue with further distribution of mifepristone, due to pressure from the pro-life movement in several countries. Registration procedures in The Netherlands were also halted. In the years following, RU 486 was eventually introduced in a few countries: Great Britain in 1991 and Sweden in 1992[1]. At the end of 1998, a request for mifepristone was proposed to the European Community, and, since the end of 1999, mifepristone has been available on the Dutch market.

Mifepristone is an antiprogestin, which can cause spontaneous abortion within the first weeks of pregnancy. In France, the use of mifepristone is limited to the period up to 49 days after the first day of the last menstrual period (in other words, until 3 weeks late) and, in Great Britain and Sweden, up to 63 days (5 weeks late). Mifepristone acts as a competitive blockade against progesterone (a hormone necessary for sustaining pregnancy) which, in turn, causes the uterine lining to shed. Simultaneously, mifepristone heightens the sensitivity of the myometrium, which is necessary for the contraction effects of prostaglandin during pregnancy. The substance itself does not work as a prostaglandin; it is combined with a small dose of a prostaglandin[2], for example, misoprostol. This is a synthetic form of prostaglandin E_1 analog which is stable at room temperature. It can be administered orally (buccally or sublingually) and vaginally, and has a half-life of approximately 90 min. Misoprostol stimulates uterine contractions and has a softening effect on the cervix. Dangerous side-effects have not been reported and the gastrointestinal side-effects are relatively mild[3]. Therefore, in addition to the fact that it is less expensive than other prostaglandins, such as gemeprost, misoprostol is becoming more popular in gynecological procedures.

The procedure developed in France, and most used, is carried out as follows[4–6]. On the first day of treatment, the woman is administered 600 mg mifepristone (three tablets of 200 mg) in an abortion clinic or hospital. On the third day (48 h after the first administration), the woman returns to the clinic or hospital and is administered 400 µg misoprostol (in the form of pills or vaginal suppositories). Thereafter, she stays 4–6 h in the clinic or hospital for observation. Most clients (approximately 61%) have an abortion within this time-period; others have an abortion at home within the following 24 h. Between days 10 and 12, the woman must return to the clinic or hospital for a follow-up. In the situation where an abortion has not taken place, vacuum aspiration is performed during the follow-up visit.

Some studies report giving a lower dosage of mifepristone[7–9] or giving a second administration of 400 µg misoprostol[5,10–12]. There are also publications which suggest that administration of misoprostol on day 2 or day 4 is equally successful[13].

The reported successful cases using such procedures vary from 95.4% to 98.7% in France[4–6,10,12], 94.8% in the UK[14], 77–92% in the United States[15] and 97.3% in Austria[11]. The success of cases seems to be dependent on the pregnancy duration: the mifepristone–misoprostol combination seems to be most suitable for the termination of pregnancies of a duration of < 49 days of amenorrhea[8,15].

Dutch physicians do not have much experience with medical abortion. The organization of Dutch abortion services, compared to other western countries, is unique. In other countries, specialists in hospitals usually carry out the termination of pregnancies. The procedure is often carried out under general anesthesia with a pregnancy duration usually more than 7 weeks. It is also not unusual that the patient stays for one to several days in the hospital. Treatment in The Netherlands for termination of pregnancy is easily accessible and not unnecessarily medicalized. Almost 90% take place in abortion clinics where the vacuum aspiration procedure is carried out, usually under local anesthesia[16]. After a resting period, the woman is able to return home. The percentage of complications is extremely low (0.3%)[16]. The question to be answered is to what extent is medical abortion, or treatment with the abortion pill, a viable and desired supplement to the Dutch health-care system and what are the advantages and disadvantages of this method of pregnancy termination in comparison to the vacuum aspiration method? The Netherlands Institute for Social Sexological Research (NISSO), in collaboration with two abortion clinics (Stimezo Den Haag and MR'70 in Amsterdam), carried out research looking at the experiences with medical abortion from November 1999 until

December 2000. Within this article, the results from this research will be discussed.

METHODS

The Medical Ethics Testing Committee approved the research protocol; however, as a consequence of the Medical–Scientific Research with People Act, the review committee put the following restriction into place. Women aged 16–17 years were only allowed to participate if they had written permission signed by both parents.

The research took place from November 1999 until December 2000. Participants were recruited from the two abortion clinics working in collaboration with this project. All the clients who met the research criteria and who qualified for the medical abortion treatment were included (Tables 1 and 2). These clients were then asked to choose between the medical and vacuum aspiration treatment (with or without intravenous sedation). Beforehand, they received neutral information about the different methods. The women who chose to participate in this project were asked prior to the treatment and at the follow-up visit to answer several questions. For example, participants were asked what their expectations were of the chosen method before and after treatment. The Hopkin's Symptom Checklist (HSCL) was also used during the follow-up visit. This questionnaire was used as an objective measurement device for the psychological and physical well-being of the clients during the previous week. The HSCL uses three scales. The first scale measures the complaints concerning the psychoneurological state, the second scale measures physical health and the third scale measures psychological and physical health[17].

The recruitment of participants was difficult. Approximately one-half of all Dutch abortion clients should, when looking at the pregnancy duration (< 49 days of amenorrhea) qualify for a medical abortion: approximately 10 000 women per year. Ultimately, 283 respondents from the two participating clinics were recruited. One hundred and thirty-one women chose medical treatment, 131 women chose vacuum aspiration with local anesthetic and 21 women chose vacuum aspiration with intravenous sedation. This last group is too small to include in further statistical analysis[18].

The data from the questionnaires were calculated with help of an SPSS program. Differences between the groups were tested using Pearson's χ^2 test and the t test for independent samples (significance level at $p < 0.05$).

RESULTS

Characteristics of the participants

The average age of the patients opting for the abortion pill was 27.7 years, and 30.4 years for the vacuum aspiration clients. The participants as a whole were highly educated, with 73.9% of the abortion pill clients and 73.3% of the vacuum aspiration clients having a minimum of an intermediate-level secondary school diploma. The high level of education can be explained by a selection bias in the clinics and the fact that the majority of women with lower levels of education (immigrants) cannot speak Dutch fluently. Fluent Dutch was included as part of the criteria to participate in the research (Table 1).

Failure rate

During treatment with the abortion pill, eight women (6.1%) discontinued treatment. Of the 123 women who completed treatment with the abortion pill, four received additional vacuum aspiration during the follow-up visit. The failure rate of treatment with the abortion pill within this project was 3.3%. Reasons for vacuum aspiration during the follow-up visit were

Table 1 Inclusion criteria for the research

Singular pregnancy ≤ 49 days of amenorrhea, diagnosed through an echogram
Fluent Dutch
Good health
AWBZ qualified
Aged 16 years or older
Prepared to follow visiting schedule
Prepared to sign 'informed consent'
For clients of 16 or 17 years, permission from parents or legal guardian required

AWBZ, national health insurance for special medical costs

positive pregnancy tests and continued blood loss (this can be the result of an incomplete abortion). Of the 131 women who completed treatment with vacuum aspiration, two required treatment with an additional vacuum aspiration (1.5%).

Motivation for chosen treatment and experiences of advantages and disadvantages

Most of the clients agreed that the most important advantage of medical abortion was that no surgical procedure was required. This was mentioned by almost three-quarters of the women who chose the abortion pill. Further, four out of ten women considered it to be a more natural method and approximately one-third considered it to be an advantage that a doctor would not physically handle them. The fact that taking a series of pills does not involve surgery seemed to be the most frequently mentioned advantage following treatment (Table 3). Other significant advantages mentioned following this treatment method were a greater feeling of control ($t = -2.42$, $p = 0.02$), being fully aware of what was happening ($t = -2.95$, $p < 0.01$) and it is a more natural experience ($t = -2.47$, $p = < 0.05$). Also, for some, it was a comforting idea that the abortion could take place at home ($t = -3.76$, $p < 0.001$). The most important disadvantage of medical abortion, mentioned prior to treatment, was that there was a greater chance of failure after treatment. Almost one-half of the women considered this to be a disadvantage. One-third considered it to be a disadvantage that they were required to come to the clinic several times. One-quarter of the clients mentioned the unreliability of the time-frame in which the abortion would take place and the fact that there could be more blood loss (Table 4). Blood loss was mentioned significantly more after treatment ($t = 3.32$, $p = 0.001$). The amount of blood loss is, therefore, disappointing when compared to what was initially expected. The fact that medical treatment had a greater failure rate than vacuum aspiration was actually mentioned less after treatment ($t = 2.65$, $p = 0.01$). This initial perceived disadvantage was mentioned less after a successful treatment.

Women who chose vacuum aspiration mentioned, both prior and following treatment, that the short procedure time and the fact that a direct result was obtained were the most important advantages (Table 5). Pain was mentioned as the most important disadvantage prior to treatment (65.4%) and pain was again mentioned as the most important disadvantage

Table 2 Exclusion criteria

Adrenal gland disease or use of corticosteroids
With respect to misoprostol: severe bronchial asthma, glaucoma, mitral stenosis, sickle cell anemia, hypertension, prostaglandin allergy
History of severe liver, lung or kidney disease
Cardiovascular disease
Coagulation disorder, use of anticoagulation medicine
Intrauterine device insertion
Insulin-dependent diabetic
Unwilling to stop breastfeeding for 1 week
Suspicion of pelvic inflammatory disease
Extrauterine gravidity or threatened abortion
35 years or older + smokes more than 20 cigarettes per day + risk factors
Unwilling or unable to give up the following medications: salicylic acid, anticoagulants, indomethacin, prostaglandin inhibitors (naproxen, etc.), uterotonica, antipsychotics (haldol trilafon)

Table 3 Perceived advantages of the abortion pill, prior to and following treatment

	Before treatment		*After treatment*	
	n	%	*n*	%
Pill, no surgical intervention	93	72.7	71	80.7
It is a more 'natural' way to terminate a pregnancy	53	41.4	46	52.3
No doctors touching my body	39	30.5	33	37.5
Conscious experience	17	13.3	20	22.7
Self-control	15	11.7	21	23.9
Chance that abortion will happen at home, in own environment, is high	14	10.9	19	21.6

Table 4 Perceived disadvantages of the abortion pill, prior to and following treatment

	Before treatment		*After treatment*	
	n	%	*n*	%
Slightly larger chance of failure in treatment	56	45.5	25	28.1
Necessary to come back to the clinic	43	35.0	25	28.1
Not sure when abortion will take place	32	26.0	27	30.3
More blood loss (in comparison to vacuum aspiration)	30	24.4	35	39.3
No disadvantages/no negative experiences	17	13.8	16	18.0
Chance that abortion will take place at home is high	4	3.3	4	4.5

Table 5 Perceived advantages of vacuum aspiration (under local anesthetic), prior to and following treatment

	Before treatment		*After treatment*	
	n	%	*n*	%
Short treatment time	79	62.2	96	85.0
Direct result	72	56.7	72	63.7
Smaller chance of failure	41	32.2	55	48.7
Small chance of or no problems with side-effects such as nausea and diarrhea	27	21.3	25	22.1
Conscious experience	17	13.4	29	25.7

Table 6 Perceived disadvantages of vacuum aspiration (under local anesthetic), prior to and following treatment

	Before treatment		*After treatment*	
	n	%	*n*	%
Pain	85	65.4	64	57.1
Conscious experience	41	31.5	23	20.5
Position on examination table	28	21.5	19	17.0
Surgical intervention	27	20.8	9	8.0
No disadvantages/no negative experiences	13	10.0	21	18.8

following treatment (Table 6). However, pain was mentioned less frequently as a disadvantage following the procedure than prior to it ($t = -1.96$, $p < 0.05$), as was the idea of a surgical procedure ($t = 2.09$, $p < 0.05$) and the fact that it is a conscious experience ($t = 3.59$, $p < 0.001$), following the procedure than prior to the procedure. This means that the actual procedure exceeded prior expectations.

Information sources

Almost half (46.0%) of the clients who chose medical treatment had chosen the participating abortion clinics especially because such a treatment was available. They had made their choice for this treatment based on information they had received from the media. Family practitioners did not play any role.

Through the research, it became clear that the clients did not always receive the correct information concerning medical treatment, resulting in them coming to the clinic with false expectations. During the explanation of the differences between the two methods at the clinic, it became clear that the medical treatment consisted of taking pills and that they would be required to come back to the clinic several times.

Physical and psychological effects

The abortion pill clients had higher scores especially on the somatic scale: 55.7% of the women scored higher than average. This high score can probably be explained by the side-effects that were experienced from the medication. Examples on this scale include headaches and lower back pain. The differences between the abortion pill and vacuum aspiration clients are significant on the third scale, the total scale, which measures both the psychological and the physical complaints.

Satisfaction rate

Of the women who chose the abortion pill, 80.2% were satisfied with the treatment and 68.1% would opt for this method again, if necessary. With vacuum aspiration, the numbers were, respectively, 92.9% and 83.2% (Tables 7 and 8).

DISCUSSION

Through the research it is evident that the clients regard medical abortion as a positive addition to Dutch public health services. It is clear that the women in both groups were satisfied with the choices they made for treatment. The research encouraged other abortion clinics to start offering medical abortion as well.

Although the abortion pill failure rate (where additional vacuum aspiration was necessary) is higher than with vacuum aspiration, both failure rates (3.3% for medical abortion and 1.5% for vacuum aspiration) are acceptable.

The research does not offer any insight into the use of medical abortion treatment for adolescent girls (under 18 years) and women with lower levels of education, due to the restrictions put in place by the Medical Ethics Testing Committee. Additional insights into the experiences of these groups with the abortion pill could lead to further tightening of criteria used in the selection and screening of clients for the

Table 7 Scale of satisfaction following medical abortion or vacuum aspiration

	Medical abortion		*Vacuum aspiration*	
	n	%	*n*	%
0. Stopped	8	8.3	—	—
1. Absolutely not satisfied	4	4.2	3	2.7
2. Slightly satisfied	7	7.3	5	4.4
3. Satisfied	34	35.4	70	61.9
4. Very satisfied	17	17.7	17	15.0
5. Very much satisfied	26	27.1	18	15.9
Total	96	100.0	113	100.0

Table 8 Number of patients who would choose the same treatment again

	Medical abortion		*Vacuum aspiration*	
	n	%	*n*	%
0. Stopped	8	8.5	—	—
1. No, absolutely not	5	5.3	3	2.7
2. No, I don't think so	5	5.3	7	6.2
3. I don't know	12	12.8	9	8.0
4. Yes, I think so	18	19.1	45	39.8
5. Yes, absolutely	46	48.9	49	43.4
Total	94	100.0	113	100.0

abortion pill, which could lead to formulating standards for responsible qualitative services for these groups.

In relation to the treatment protocol, further research is necessary to look at the possibilities of lower doses of mifepristone and the influences of that on the efficacy of the treatment. At the moment, mifepristone is only registered in The Netherlands as a method for pregnancy termination. In low doses of 10 mg, mifepristone can also be used as a 'late' morning after pill[19–21]. Considering the positive experiences in other countries, it is desirable to research other possibilities for the use of mifepristone in The Netherlands.

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APPENDIX 11.6.

UPDATED LISTING ON ONGOING PREGNANCIES FROM 1987 TO 2002

	MIF ALONE	MIF+ MIS	MIF+ SUL	MIF+ UNK	MIF+ PG	MIF+ GEM	TOTAL
Normal Babies	14	15	2	4	2	5	42
Malformation At Term	0	0	0	0	0	3	3
MALF/ TToP	1	1	0	0	0	5	7
Delayed spont. Abortion	5	1	0	0	0	0	6
TToP UNK	4	6	0	0	2	0	12
TToP Normal Foetus	2	14	1	1	1	0	19
UNK/USNL	3	4	0	2	3	0	12
UNK	22	16	1	5	1	0	45
TOTAL	51	57	4	12	9	13	146

Update on June 30, 2002

LEGENDS

MIF= mifepristone
MIS= misoprostol
SUL= sulprostone
GEM= gemeprost
PG= prostaglandin (unspecified)
UNK= unknown
TToP= Therapeutic Termination of Pregnancy
USNL= Ultrasound Normal (at second or third trimester)
Delayed Spont. Abortion= Delayed Spontaneous Abortion
MALF/TToP= Malformation with Therapeutic Termination of Pregnancy

ONGOING PREGNANCIES

1	N°	Case Number	Date MIF or week of Am.	PG	TERM	DOSE	CAT	TYPE	OUTCOME
1		PMIF0001.87FR$	(b) (6) 5 w	NO		400	TTOPM	Sirenomelia,*	
2	GI	PMIF0002.88FR$	6 w	SUL		600	TTOP	**	NL Foetus
3	2	PMIF0001.89FR	7w	YES		600	TTOP	**	NL Foetus, Male
4	3	PMIF0002.89FR		NO	TERM	600	NL	***	Female
5	5	PMIF0004.90FR		NO		600	TTOP	***	NL Foetus
6	8	PMIF0003.89FR$	End 1989, 6-7 w	NO	TERM	400	NL	Published,Pons,*,***	Male
7		PMIF0001.90UK£	8 w	NO	TERM	600	NL	*	Male
8		PMIF0002.90UK£	8 w	NO	TERM	600	NL	*	Male
9		PMIF0003.90UK£	9 w	NO	TERM	600	NL	*	Female
10	7	PMIF0005.90FR	1990	NO		600	TTOP	At 2 months, U	NL Foetus
11	9	PMIF0006.90FR	(b) (6) 6 w	SUL		600	U	*, ***, SA?	
12	10	PMIF0007.91FR		SUL	TERM	600	NL	*, **	Male
13		MIF0029.91FR/OS	U	U	TERM	600	NL	U	
14		MIF0030.91FR/OS	U	U		600	U	***	NL 2nd semester
15	11	PMIF0008.91FR	1991	NO	TERM	600	NL	*	
16	12	PMIF0009.92FR/RA	U	NO		600	U	***	NL 2nd semester
17	13	PMIF0004.92FR$	CT;47OA	NO		600	U	***	
18	14	PMIF0010.92FR	(b) (6) 7 w, Trinordiol	SUL	TERM	600	NL	*	Female
19		PMIF0002.93UK	8 w	YES		600	U	***	NL 2nd semester
20	15	PMIF0011.92FR/RA	(b) (6), 5 w	YES		600	TTOP	*, ***	7,5
21	16	PMIF0012.93FR	U	MIS		600	TTOP	***	NL Foetus
22	17	PMIF0013.93FR/RA	6/7 w a	MIS		600	U	Lost to FU	NL 2nd semester
23	18	PMIF0014.93FR	U	NO		600	TTOP	***	
24	19	PMIF0015.93FR	(b) (6) 7 w 2 d	MIS		600	U	***	
25		PMIF0003.93UK	U	GEM	TERM	600	ABN	Bilateral talipes, *	
26	20	PMIF0016.93FR/RA	(b) (6) vomits) Twice 3 cp	NO		1200	U	U	
27	21	PMIF0017.93FR	1993	MIS		600	U	U	
28	22	PMIF0018.93FR	U	MIS	TERM	600	NL	*	
29	23	MIF/PG0024.93FR	(b) (6), 5 w	NO		600	SA	*	Bled since MIF, 5 m
30	24	MIF/PG0026.93FR	(b) (6) at 8 w	MIS		600	SA	*	
31	25	MIF0001.94FR$	At 7 w of am	MIS		600	U	Unsure at start	
32		MIF0001.94UK	U	NO		600	U	U	
33	26	MIF/PG9011.93UK£	(b) (6) 9 w 2 d	GEM	TERM	600	ABN	Finger nail defect(3), **	Oral Contraceptive
34		MIF/PG0001.93SE	48 d	GEM	TERM	600	NL	Premature birth/cesarean	DMPA, Male
35	27	MIF0003.94FR	U	YES	TERM	600	NL	**	Male
36	28	MIF0004.94FR	(b) (6)	YES		600	U	**, US NI, Lost to FU	NL 2nd semester
37	29	MIF0005.94FR	6,5 w of a	U		600	U	U	NL 2nd semester
38		MIF0005.94.UK	U	GEM	TERM	600	NL	U	
39	30	MIF/PG0029.93FR	(b) (6) 6 w of am	MIS	TERM		NL	U	Male
40	31	MIF0009.94FR		MIS		600	TTOP	***	NL Foetus, 25 w
41	32	MIF0013.94FR	à 52 d of am.	NO		200	U	*	

ONGOING PREGNANCIES

1	N°	Case Number	Date MIF or week of Am.	PG	TERM	DOSE	CAT	TYPE	OUTCOME
42	33	MIF0017.94FR	7,5 w of am	MIS		600	TTOP	Unsure	Foetus unassessable
43	34	MIF0021.94FR	7 w of am	MIS	TERM	600	NL	*	Female
44	35	MIF0022.94FR$	(b) (6) 6 w	MIS	TERM	600	NL	At 3 Mths (Hepatitis..)	Other medical, Fem
45	36	MIF0003.95FR	1995	NO		600	TTOP	*	
46		MIF0003.95UK£	8 w of pregnancy	GEM		600	TTOPM	**,Talipes Equinovares	OC
47	37	MIF0011.95FR	U	U			U	U	
48	38	MIF0005.95FR	(b) (6)	NO		600	U	*	
49	40	MIF0008.95FR	U	MIS		600	TTOP	***	NL Foetus, Male
50	41	MIF0009.95FR	(b) (6), 7 w, in fact 11 w	GEM	TERM	600	NL	*?	
51	42	MIF0012.95FR/RA	7 w of am	YES			TTOP	*	
52	43	MIF0013.95FR	(b) (6)	MIS		600	TTOP	U	
53	44	MIF0015.95FR	6 w	MIS	TERM	600	NL	U	Male
54	45	MIF0019.95FR/RA	mic (b) (6)	NO	TERM	600	NL	***	
55	46	MIF0021.95FR	Beginning (b) (6) 5 w of a.	MIS	TERM	600	NL	*	Female
56	47	MIF0004.96UK	(b) (6) 7 w pregnancy	GEM		600	TTOPM	Acheiria/talipes eq/toes abn/,**	Mandibula hypo
57	48	MIF0005.96FR	Unk, 5.5 w of am	MIS		600	U	*, ***	NL 2nd semester
58	49	MIF0007.96FR/RA	(b) (6)	MIS		600	U	***	
59	50	MIF0003.96SE		GEM		600	TTOPM	Anencephaly, talipes eq	
60	51	MIF0001.97FR		NO		600	NL	***	Female
61		199500383RU(FR)	55 d of am.	MIS		600	TOP	U	NL Foetus
62	52	199710066RDF	6/7 w of am.	NO		600	TOP	*	
63	53	199710097RDF	(4w of preg)	YES			NL	*	
64	54	199710379RDF		NO		600	U	*	
65	55	199710378RDF	11 w	U		600	TTOP	*	NL Foetus
66	56	199710383RDF	U<7 w	U		600	U	U	
67	57	199710467RDF	6 w	MIS		600	TTOP		NL Foetus
68	58	MIF0001.97SE	8 w 4 d	GEM?	TERM	600	ABN	Heart malformation, *	
69	59	S970001UK/MIF1	6-7 w	GEM		200	TTOPM	Cerebellum atrophy, *	
70	61	S980002F/MIF1	6w	MIS	TERM		NL	U	
71		S980001UK/MIF1	9 w	MIS	TERM	200	NL	**	Male NL
72		S980004F/MIF1	7 w	MIS		600	U	***	US NL at 18 w
73		S980005F/MIF1	6-7 w	NO		600?	U	***	
74		S980009F/MIF1	6 w	MIS		?	U		U
75		S980001UK/MIF1	7 w	GEM	TERM	200	NL	***	NL Male
76		S98001UK/MIF1	8 w 1 d	MIS		200	TTOP	**	At 16 w No anomaly
77		S980013F/MIF1	14.5 w	?	?	?	NL	?	NL Male
78		S980014F/MIF1	8 w	?	?	?	NL	?	Female NL
79		S980015F/MIF1	16 w + 2 d	?	?	?	NL	?	NL
80		S980016F/MIF1	9 w + 3 d	MIS		400	NL	?	NL at 31 w
81		S980017UK/MIF1	8-9 w	GEM		200	TTOPM	***, Hydroceph, cleft P.	Cyclopia, Talipes

ONGOING PREGNANCIES

1	N°	Case Number	Date MIF or week of Am.	PG	TERM	DOSE	CAT	TYPE	OUTCOME
82		S980018FR/MIF1	6 w	MIS	TERM	600	NL		Male NL
83		S980020UK/MIF1	13 w	NO	TERM	600	NL	*	NL delivery
84		S990004F/MIF1	7.5 w	MIS	TERM	600	NL	***	Male NL
85		S990005F/MIF1	6.5 w	MIS		600	TTOP	***, US Viable at 14 w	No exam
86		S990006UK/MIF1	14 w	NO	SA	200	SA	*	SA
87		S990009UK/MIF1	8 w	NO		200	NL	*	Male NL
88		S990013UK/MIF1		NO		200		*	
89		S990007F/MIF1	8 w am.	MIS				*	
90		S990008F/MIF1	7 w	MIS					
91		S990015F/MIF1	6 w of pregnancy	NO		600		*? US NI at 17 w	
92		S990016F/MIF1	8 w	NO		600		**, US NI	
93		S990019UK/MIF1	8 w am	MIS		200		*, US, Viable preg	
94		S990020UK/MIF1	8 w 6 days am.	MIS		200		***	NI male baby
95		S990021UK/MIF1	7 w am.	MIS				*	NI baby
96		S990022F/MIF1	7 w am.	PG				15 w US NI	
97		S990023UK/MIF1		NO			TToP	*, Intrauterine death	
98		S990024UK/MIF1	8 w preg.	NO		200		**, US dead foetus, delayed SA	
99		S990025UK/MIF1	8 w Preg	MIS		200			
100		S990026UK/MIF1	21 w preg.	NO		200		*	
101		S990027UK/MIF1	8 w am	MIS		600			
102		S990028UK/MIF1	15 w am	NO		200		*	
103		S990029UK/MIF1	8 w am.	NO		200		*	
104		S990031UK/MIF1	21 w preg	NO			TTOP	*	
105		S990032UK/MIF1	Mosaic	NO		600		*	Left multicystic kidney
106		S990035UK/MIF1$	13-21 w	NO		200		*	NL baby
107		S990036UK/MIF1$	13-21 w	NO		200		*	NL baby
108		S20000001F/MIF1	8 w preg.	NO	TERM	600	NL	Premature birth	NL Male
109		S20000002F/MIF1	4-5 w preg;	MIS		600	TTOP	At 14 w, U	U
110		S20000005F/MIF1	U	MIS		600	TOP	At 12 w	NL Foetus
111		S20000009UK/MIF1	20 w preg.	NO		600	SA	*	SA
112		S20000010UK/MIF1	17-18 w preg.	?		200		*	U
113		S20000011F/MIF1	6-7 w preg.	MIS		600	TOP	At 11 w	U
114		S20000012UK/MIF1	9 w preg.	?		200		*	U
115		S20000016F/MIF1	7 w preg	NO		600	TOP	*	U
116		S20000018UK/MIF1	mid-tremester	?	?	?	?	?	U
117		S20000019UK/MIF1	6 w preg	NO		200	SA	At 7 w	SA
118		S20000020UK/MIF1	15 w preg	?		600		*	U
119		S20000021UK/MIF1	17 w preg	?		200		*	U
120		S20000022UK/MIF1	6-7 w preg	MIS		200	?	?	U
121		S20000023UK/MIF1	12 w preg	NO		200		*	U
122		S20000024S/MIF1	8-9 w preg	GEM		600	TERM	* *	NL baby

ONGOING PREGNANCIES

1	N°	Case Number	Date MIF or week of Am.	PG	TERM	DOSE	CAT	TYPE	OUTCOME
123		S20000025F/MIF1	?	NO	TERM	600	NL	*	NL Baby
124		S20000026F/MIF1	5 w preg	MIS		600		*	U
125		S20000027F/MIF1	6 w preg	NO		600		*	U
126		S20000028D/MIF1	6 w preg	MIS		600		*	U
127		S20000027F/MIF1	6 w preg	MIS	TERM	600	NL	*	NL Baby
128		S20010003F/MIF1	Date of am (b) (6)	MIS	TERM	600	NL	Delivery by Caesarean section (b) (6)	NL baby boy
129		S20010012UK/MIF1	15 weeks of gestation	NO		200		*	
130		S20010013UK/MIF1	10 weeks gestation	MIS		200		*	
131		S20010014UK/MIF1	First trimester of pregnancy	PG		200		*	
132		S20010015UK/MIF1	8 weeks of gestation	MIS		200		*	
133		S20010016UK/MIF1	First trimester of pregnancy	NO		200		*	
134		S20010017UK/MIF1	First trimester of pregnancy	MIS		200	SA	At 22 weeks	NL
135		S2001023D/MIF1	First trimester of pregnancy	MIS		600	TOP	?	U
136		S2001024D/MIF1	6 weeks of gestation	MIS		600	TOP	?	U
137		S2001025F/MIF1	7 weeks of gestation	MIS		600	TOP	At 9 weeks	U
138		S2001026F/MIF1	First trimester of pregnancy	MIS		600	TOP	?	U
139		S2001027F/MIF1	7 weeks of gestation	MIS		600	TOP	At 9 weeks	U
140		S2001028F/MIF1	6 weeks of gestation	MIS		600	TOP	At 10 weeks	U
141		S2001029F/MIF1	7 weeks of gestation	MIS		600	TOP	At 9 weeks	U
142		S2001031UK/MIF1	17 weeks of gestation	NO		200			U
143		S2001032UK/MIF1	First trimester of pregnancy	MIS		200			U
144		S2001033UK/MIF1	18 weeks of gestation	NO		600			U
145		S2001034UK/MIF1	9 weeks of gestation	NO		200			U
146		S2001035UK/MIF1	10 weeks of gestation	MIS		200			U

Summary table of ongoing pregnancies

Abbreviations: ABN (Abnormality at term), Am or ame (amenorrhea), Cat (Category), GEM (Gemeprost), MIF (Mifepristone), MIS (Misoprostol), NL (Normal), OC (Oral contraceptive). OUT (Outcome), PG (Prostaglandins), SA (Spontaneous abortion), SUL (Sulprotone), TToP (Therapeutic Termination of Pregnancy), TToPM (Therapeutic Termination of Pregnancy with Malformation), U or UNK (Unknown), W (weeks), * (changed her mind), ** (diagnosis error), *** (did not return), TOP (Surgical early termination of pregnancy).

ATTACHMENT 3

(b) (4), (b) (6) M.D.

From: (b) (4), (b) (6)
To:
Sent: Tuesday, April 23, 2002 1:08 PM
Subject: AE report

April 23, 2002

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(b) (4), (b) (6)

Danco Laboratories

Dear (b) (4), (b) (6):

The following is a report of an infection that occurred with an incomplete abortion following treatment with mifepristone and misoprostol.

The patient was a 24 yo G4P2Tab1 black female at 60 days' gestation who received mifepristone 200 mg followed 6 hours later by misoprostol 800 mcg on (b) (6) in an IRB-approved study protocol. She presented for follow-up 24 hours after misoprostol and was noted, by transvaginal ultrasound examination, to have expelled the gestational sac. Her endometrial lining was 19.2 mm. She was scheduled as per the protocol for a follow-up evaluation on (b) (6)

She called our office on study day 5 ((b) (6)) with complaints of malodorous vaginal discharge. She was seen that day (on the weekend) in our office by a study investigator. Her exam revealed malodorus necrotic tissue in the cervical os and her uterus was 8 weeks size and non-tender. Her bleeding was scant at that time. She was afebrile. Transvaginal ultrasound examination failed to demonstrate an easily identifiable endometrial stripe. The pregnancy tissue was removed from the cervical os using ring forceps and a suction aspiration using MVA and a 7 mm cannula was performed. Tissue was obtained which was sent for pathologic examination. After the aspiration, the patient was observed for 30 minutes and had an uneventful immediate post-operative course. She was discharged with doxycycline 100 mg bid and flagyl 500 mg bid for 7 days. She was instructed to keep her scheduled follow-up visit.

The final pathology report demonstrated necrotic villi with chronic and acute inflammation, numerous colonies of coccoid bacteria were present.

She did not return for her visit as scheduled or otherwise despite numerous phone calls and registered letters. She finally called our office back on (b) (6) stating she was pregnant again and wanted to schedule an appointment for a medical abortion. She never showed for that appointment.

As this was not a serious adverse event, the infection was not reported to

the IRB.

Please let me know if you need any further information.

(b) (4), (b) (6)

[redacted]

4/24/2002

(b) (4), (b) (6) **M.D.**

(b) (4), (b) (6)

From: (b) (4), (b) (6)
To:
Sent: Monday, May 13, 2002 4:41 PM
Subject: AE report

May 13, 2002

(b) (4), (b) (6)

Danco Laboratories

Vaginal Protocol

Dear (b) (4), (b) (6)

The following is a report of an infection that occurred with an incomplete abortion following treatment with mifepristone and misoprostol.

The patient was a 19 yo G1P0 white female with IDDM at 36 days' gestation who received mifepristone 200 mg on (b) (6) to be followed 24 hours later by misoprostol 800 mcg in an IRB-approved study protocol. She presented on (b) (6) prior to her scheduled follow-up visit because of a fever of 101.9 with chills and sweats. She had normal amounts of bleeding and cramping after insertion of the misoprostol and was having light bleeding at the time of her visit. On examination, hertemperature was 98.8 degrees and her uterus and adnexa were non-tender. Transvaginal ultrasound examination demonstrated what appeared to be a collapsed gestational sac. Given her fever and ultrasound findings, a a suction aspiration using MVA and an 8 mm cannula was performed. Tissue was obtained which was sent for pathologic examination. After the aspiration, the patient was observed for 30 minutes and had an uneventful immediate post-operative course. She was discharged with ciprofloxacin 500 mg bid and flagyl 500 mg bid for 7 days. She was instructed to keep her scheduled follow-up visit.. She returned as per the protocol for a follow-up evaluation on (b) (6) and had no complaints at that time.

The final pathology report demonstrated decidua and endometrial fragments. No acute inflammation or pregnancy tissue was evident. Thus, the diagnosis of infection and incomplete abortion was made totally on clinical grounds at the time of the patient's visit.

As this was not a serious adverse event, the infection was not reported to the IRB.

Please let me know if you need any further information.

(b) (4), (b) (6)

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5/13/2002

(b) (4), (b) (6) M.D.

From: (b) (4), (b) (6)
To:
Sent: Wednesday, June 12, 2002 11:01 AM
Subject: AE report

June 12, 2002

(b) (4), (b) (6)

> Danco Laboratories
>
> Dear (b) (4), (b) (6)
>
> The following is a report of an infection that occurred with an incomplete
> abortion following treatment with mifepristone and misoprostol.
>
> The patient was a 27 yo G5P2Tab1Sab1 black female with IDDM at 51 days'
> gestation who received mifepristone 200 mg on (b) (6) to be
> followed 6-8 hours later by misoprostol 800 mcg in an IRB-approved study
> protocol. She presented on (b) (6) for a follow-up examination as per
> the study protocol. The ultrasound examination revealed a moderate
> amount of intrauterine clot (endometrial lining 17 mm) and no gestational
> sac. No further treatment was indicated at this time and she returned for
> another scheduled follow-up on (b) (6). The participant stated she
> had intercourse after her first follow-up visit with a condom. She had
> noted severe back pain and passage of large clots in the preceding two
> days. The ultrasound examination revealed a large amount of clot and
> blood in the uterine cavity. She was afebrile, her uterus was non-tender,
> and no cervical motion tenderness was present.
>

Because of the unusual ultrasound findings, the subject was asked to return for another follow-up visit on (b) (6). At that time, the participant had noted heavier bleeding with clots over the preceding two days. Her temperature was 99.5F, her cervix had malodorous clot presect which was removed with a ring forceps. The ultrasound examination showed a 27 mm clot in the cavity. The physician evaluating the patient felt that the clot in the os was necrotic tissue and she performed a D&C and treated her for an infection with ciprofloxacin and metronidazole.

The woman returned for a follow-up evaluation on (b) (6) at which time she was afebrile and without significant complaints. She had only taken the antibiotics for one day because they caused diarrhea. Her pelvic examination was benign and a transvaginal ultrasound demonstrated an endometrial lining of 5 mm.

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> The final pathology report demonstrated blood clot and degenerating
> chorionic villi with bacterial colonies (predominantly cocci), gestatinal
> endometrium and implantation site. Thus, the diagnosis of infection and

> incomplete abortion was confirmed.
>
> As this was not a serious adverse event, the infection was not reported to
> the IRB.
>
> Please let me know if you need any further information.
>
>
> (b) (4), (b) (6)
>
>
>
>
>
>
>

6/12/2002

(b) (4), (b) (6)

RECEIVED
(b) (4), (b) (6)
OCT 21 2002
(b) (4), (b) (6)

October 17, 2002

(b) (4), (b) (6)

Dear (b) (4), (b) (6)

Enclosed is a copy of an adverse experience report submitted to our IRB for a woman enrolled in our current mifepristone trial. A copy of this report has been sent to all of the study centers for submission to their local IRBs.

Please let me know if you have any questions about the content of this report.

Sincerely,

(b) (4), (b) (6)

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MOD STUDY

MEMORANDUM

Date: October 14, 2002

To: Study sites (b) (4), (b) (6)

From: (b) (4), (b) (6)

RE: Adverse experience report from (b) (4), (b) (6)

Attached is a serious adverse experience report that was submitted to the (b) (4), (b) (6) IRB. I have reviewed the report and concur with the findings as outlined in the cover letter from (b) (4), (b) (6)

Please submit a copy of this report to your local IRB.

MOD STUDY

(b) (4), (b) (6)

October 11, 2002

(b) (4), (b) (6)

RE: Mifepristone and Misoprostol for Abortion up to 63 Days' Gestation: A Multicentered Randomized C(b) (4), (b) (6)ison of Misoprostol Administration 6-8 Hours vs. 24 Hours Following Mifepristone ((6)22-024)

I am writing to provide the IRB with follow-up information regarding the serious adverse event that occurred in our ongoing trial. The IRB was initially notified upon the subject's hospitalization on (b) (6)

Subject # (b) (6) was admitted to the hospital for intravenous antibiotics for presumed endometritis. The endometritis developed after the subject had an outpatient D&C for an incomplete abortion and heavy bleeding. Outpatient treatment with oral antibiotics was unsuccessful, so the subject was hospitalized for 2 ½ days to receive intravenous antibiotics. She remained afebrile and clinically well throughout her admission. The subject was discharged on oral antibiotics to complete a 14 day course. Since her hospital discharge on (b) (6), she has continued to do well.

Incomplete abortion, heavy bleeding requiring D&C, and infection are known risks of medical abortion as stated in the consent form and protocol. The risk of infection from a D&C is also stated in the protocol and consent document. Given the time course, this subject's infection most likely resulted from uterine instrumentation rather than the medications administered for the medical abortion or the regimen used within the protocol. This adverse experience does not alter the risk-benefit ratio of the protocol.

This infection and hospitalization has been reported to the study sponsor, (b) (4), (b) (6) Please contact me if you have any questions or concerns regarding the above event.

Sincerely,

(b) (4), (b) (6)

Principal Investigator

CC: (b) (4), (b) (6) Study Sponsor

(b) (4), (b) (6)

(b) (4), (b) (6) IRB Appendix J Advers01.doc

(b) (4), (b) (6) RB Adverse Event Form

A. Protocol Information

Event occurred within IRB#:	Event occurred within Manufacturer Protocol #:	Event occurred within Other Associated Protocol #:	FDA-IND#:
(b) (4), (b) (6) 22-024			57,890

Protocol Title: Mifepristone and Misoprostol for Abortion up to 63 Days' Gestation: A Multicentered Randomized Comparison of Misoprostol Administration 6-8 Hours vs. 24 Hours Following Mifepristone

PI Name/Address/Phone #: (b) (4), (b) (6)

Study Size and Enrollment:
# of subjects to be enrolled at (b) (4), (b) (6) 300 in Entire Study:1200
# of subjects enrolled to date at (b) (4), (b) (6) 173 in Entire Study:344

Investigational Drug Names: Misoprostol 800 µg vaginally; Mifepristone 200 mg orally

B. Adverse Event Information

Date of Event (b) (6)

Subject ID #: (b) (6)

Event Report:
☐ Initial
☒ Follow-up

(b) (4), (b) (6)
☐ External Site

Classification (check all that apply):
☐ Death
☒ Serious
☐ Unexpected
☐ Increased Frequency

Causality:
☐ Remote
☐ Possible
☐ Probable
☒ Highly Probable

Nature of Event (Please describe a brief description):
Subject developed post-procedural endometritis after undergoing a D&C for an incomplete abortion and heavy bleeding after her medical abortion. The D&C took place on study day #5. Fevers developed on day #8. Oral antibiotics were started on day #8. Due to persistent fevers on study day #11, she was admitted for intravenous antibiotics. She received 48 hours of intravenous antibiotics and remained afebrile throughout her 2 ½ days admission. After discharge, she completed a 14 day course of antibiotics as an outpatient and remained well.

C. Recommendations

Is the event listed in the current sponsor protocol or investigational brochure?	☒ Yes ☐ No
Is the event listed in the current, most recently approved IRB summary protocol?	☒ Yes ☐ No
Is the event listed in the current, most recently approved IRB informed consent form?	☒ Yes ☐ No

If answered "No" to any questions above, are changes necessary to address increased monitoring or to provide new information to the subject?
☐ Yes, *please attach a modification request form and protocol/consent with changes highlighted to this report.*
☐ No, please explain:

Signature of Principal Investigator: (b) (4), (b) (6)	Date: 10/11/02
Name of individual who prepared this report: (b) (4), (b) (6)	Date: 10/11/02

Notes by IRB Office Staff:

(b) (4), (b) (6) IRB Date Stamp:

ATTACHMENT 4

1.6.2 Auxiliary Raw materials and Suppliers

Code Number	Name	Supplier
(b) (4)		

Code Number	Name	Supplier
(b) (4)		

ATTACHMENT 5

LONG TERM STABILITY STUDIES (1)

LOT No. (b) (4)

TESTS	SPECIFICATIONS	RESULTS & TEST DATES				
		99. 01.07	99.02.09	99.03.10	99.04.09	99.07.14
(b) (4)						

ENVIROMMENTAL CONDITIONS: (b) (4)

PACKING: (b) (4)

Tabulated by (b) (4), (b) (6)

Date: January 16th,2002

Reviewed by (b) (4), (b) (6)

Date: January 18th,2002

LONG TERM STABILITY STUDIES (2)

LOT No. (b) (4)

TESTS	SPECIFICATIONS	RESULTS & TEST DATES				
		99.10.16	00.01.16	00.07.13	01.01.13	02.01.14
(b) (4)						

ENVIROMMENTAL CONDITIONS: (b) (4)

PACKING: (b) (4)

Tabulated by (b) (4), (b) (6)

Date: January 16th,2002

Reviewed by (b) (4), (b) (6)

Date: January 18th,2002

LONG TERM STABILITY STUDIES (1)

LOT No. (b) (4)

TESTS	SPECIFICATIONS	RESULTS & TEST DATES				
		99.01.15	99.02.25	99.03.22	99.04.16	99.07.14
(b) (4)						

ENVIROMMENTAL CONDITIONS: (b) (4)

PACKING: (b) (4)

Tabulated by (b) (4), (b) (6)

Date: January 16th,2002

Reviewed by (b) (4), (b) (6)

Date: January 18th,2002

LONG TERM STABILITY STUDIES (2)

LOT No. (b) (4)

TESTS	SPECIFICATIONS	RESULTS & TEST DATES				
		99.10.16	00.01.16	00.07.13	01.01.13	02.01.14
(b) (4)						

ENVIROMMENTAL CONDITIONS: (b) (4)

PACKING: (b) (4)

Tabulated by (b) (4), (b) (6)

Date: January 16th,2002

Reviewed by (b) (4), (b) (6)

Date: January 18th,2002

LONG TERM STASBILITY STUDIES (1)

LOT No. (b) (4)

TESTS	SPECIFICATIONS	RESULTS & TEST DATES				
		99.01.20	99.02.22	99.03.24	99.04.22	99.07.28
(b) (4)						

ENVIROMMENTAL CONDITIONS: (b) (4)

PACKING: (b) (4)

Tabulated by (b) (4), (b) (6)

Date: January 16th,2002

Reviewed by (b) (4), (b) (6)

Date: January 18th,2002

LONG TERM STABILITY STUDIES (2)

LOT No. (b) (4)

TESTS	SPECIFICATIONS	RESULTS & TEST DATES				
		99.10.16	00.01.16	00.07.13	01.01.13	**02.01.14**
(b) (4)						

ENVIROMMENTAL CONDITIONS: (b) (4)

PACKING: (b) (4)

Tabulated by (b) (4), (b) (6)

Date: January 16th,2002

Reviewed by (b) (4), (b) (6)

Date: January 18th,2002

LONG TERM STABILITY STUDIES (1)

LOT No. (b) (4)

TESTS	SPECIFICATIONS	RESULTS & TEST DATES				
		00. 01.21	00.03.03	00.04.03	00.05.07	00.08.09
(b) (4)						

ENVIROMMENTAL CONDITIONS: (b) (4)

PACKING: (b) (4)

Tabulated by (b) (4), (b) (6)

Date: March 1st, 2002

Reviewed by (b) (4), (b) (6)

Date: March 2nd, 2002

LONG TERM STABILITY STUDIES (2)

LOT No. (b) (4)

TESTS	SPECIFICATIONS	RESULTS & TEST DATES				
		00.11.06	01.02.06	01.08.10	**02.02.28**	/ /
(b) (4)						

ENVIROMMENTAL CONDITIONS: (b) (4)

PACKING: (b) (4)

Tabulated by (b) (4), (b) (6)

Date: March 1st, 2002

Reviewed by (b) (4), (b) (6)

Date: March 2nd, 2002

LONG TERM STABILITY STUDIES (1)

LOT No. (b) (4)

TESTS	SPECIFICATIONS	RESULTS & TEST DATES				
		00.04.06	00.05.07	00.06.07	00.07.05	00.10.11
(b) (4)						

ENVIROMMENTAL CONDITIONS: (b) (4)

PACKING: (b) (4)

Tabulated by (b) (4), (b) (6)

Date: April 16th, 2002

Reviewed by (b) (4), (b) (6)

Date: April 17th ,2002

LONG TERM STABILITY STUDIES (2)

LOT No. (b) (4)

TESTS	SPECIFICATIONS	RESULTS & TEST DATES				
		01.01.13	01.04.10	01.10.05	02.04.14	/ /
(b) (4)						

ENVIROMMENTAL CONDITIONS: (b) (4)

PACKING: (b) (4)

Tabulated by (b) (4), (b) (6)

Date: April 16th, 2002

Reviewed by (b) (4), (b) (6)

Date: April 17th, 2002

LONG TERM STABILITY STUDIES (1)

LOT No. (b) (4)

TESTS	SPECIFICATIONS	RESULTS & TEST DATES				
		00. 05.31	00.07.14	00.08.17	00.09.14	00.12.13
(b) (4)						

ENVIROMMENTAL CONDITIONS: (b) (4)

PACKING: (b) (4)

Tabulated by (b) (4), (b) (6)

Date: June 13th, 2002

Reviewed by (b) (4), (b) (6)

Date: June 13th, 2002

CMC SECTION: Drug Substance
Mifepristone (b) (4)

LONG TERM STABILITY STUDIES (2)

LOT No. (b) (4)

TESTS	SPECIFICATIONS	RESULTS & TEST DATES				
		01.03.12	01.06.11	**01.12.13**	**02.06.12**	/ /
(b) (4)						

ENVIROMMENTAL CONDITIONS: (b) (4)

PACKING: (b) (4)

Tabulated by (b) (4), (b) (6)

Date: June 13th, 2002

Reviewed by (b) (4), (b) (6)

Date: June 13th, 2002

LONG TERM STABILITY STUDIES (1)

LOT No. (b) (4)

TESTS	SPECIFICATIONS	RESULTS & TEST DATES				
		00.05.31	00.07.14	00.08.17	00.09.14	00.12.15
(b) (4)						

ENVIROMMENTAL CONDITIONS: (b) (4)

PACKING: (b) (4)

Tabulated by (b) (4), (b) (6)

Date: June 13th, 2002

Reviewed by (b) (4), (b) (6)

Date: June 13th, 2002

LONG TERM STABILITY STUDIES (2)

LOT No. (b) (4)

TESTS	SPECIFICATIONS	RESULTS & TEST DATES				
		01.03.12	01.06.11	01.12.13	02.06.12	/ /
(b) (4)						
ENVIROMMENTAL CONDITIONS (b) (4)						
PACKING: (b) (4)						

Tabulated by (b) (4), (b) (6)

Date: June 13th, 2002

Reviewed by (b) (4), (b) (6)

Date: June 13th, 2002

LONG TERM STASBILITY STUDIES (1)

LOT No. (b) (4)

TESTS	SPECIFICATIONS	RESULTS & TEST DATES				
		00.05.31	00.07.14	00.08.17	00.09.14	00.12.16
(b) (4)						

ENVIROMMENTAL CONDITIONS: (b) (4)

PACKING: (b) (4)

Tabulated by (b) (4), (b) (6)

Date: June 13th, 2002

Reviewed by (b) (4), (b) (6)

Date: June 13th, 2002

LONG TERM STABILITY STUDIES (2)

LOT No. (b) (4)

TESTS	SPECIFICATIONS	RESULTS & TEST DATES			
		01.03.15	01.06.11	01.12.13	02.06.12
(b) (4)					

ENVIROMMENTAL CONDITIONS: (b) (4)

PACKING: (b) (4)

Tabulated by (b) (4), (b) (6)

Date: June 13th, 2002

Reviewed by (b) (4), (b) (6)

Date: June 13th, 2002