From:
Sent: Thursday, September 28, 2000 11:16 AM
To:

Cc:
Subject: RU 486

Greetings!

This is to let you know that FDA has just announced the approval of the drug, MIFEPREX (mifepristone), for terminating a pregnancy in the early stages (49 days or less since last menstrual period began). I have attached a copy of the press release for your information.

Agency staff have agreed on a comprehensive roll out strategy to communicate with all of our external audiences about this approval. If you or your staff receive inquiries, you may direct them to FDA's website, http://www.fda.gov/cder/drug/infopage/mifepristone, or refer them to the designated contact below. The website contains the FDA press release, approval letter, package insert, medguide and other information on mifepristone. Please do not answer calls or emails directly.

Calls From:	Refer To:	
Health Professionals/Consumers	OTCOM	888-INFO-FDA
		301-827-4570
Print Media (Includes Trade Press)		301-827-6250
		301-827-6242
Broadcast Media		301-827-3417
Members of Congress/Staff		301-827-0087
Other Government Officials	FDA Exec Sec	301-827-4450

E-Mails should be forwarded to: druginfo@cder.fda.gov

Please forward this information to anyone else on your staff who may receive inquiries.

Thanks,

, FDA Executive Secretariat

NDA 20-687

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

Dear **[Redacted]**:

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

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

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

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

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

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

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

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

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex™.
- Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, give her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well.
- Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an ongoing pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure.
- Must report any hospitalization, transfusion or other serious events to the sponsor or its designate.
- Must record the Mifeprex™ package serial number in each patient's record.

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

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

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

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

1. A cohort-based study of safety outcomes of patients having medical abortion under the care of

physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention. Previous study questions related to age, smoking, and follow-up on day 14 (compliance with return visit) will be incorporated into this cohort study, as well as an audit of signed Patient Agreement forms.

2. A surveillance study on outcomes of ongoing pregnancies.

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

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

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

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

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

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

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

Sincerely,

[Redacted]

Director
Office of
Drug
Evaluation III
Center for
Drug
Evaluation
and Research

Electronic Mail Message

Date: 9/28/00 4:36:02 PM
From:
To:
Subject: A bunch of RU-486 e mails

I saved up several of 'em.

Electronic Mail Message

Date: 9/28/00 12:45:21 PM
From:
To:
Subject: FWD: RU-486

Another RU-486 e mail.

Electronic Mail Message

Date: 9/28/00 10:55:20 AM
From:
To:
Subject: FWD: Do You Believe In God?

Yet another RU-486 e mail.

Electronic Mail Message

Date: 9/28/00 10:33:02 AM
From:
To:
Subject: FWD: RU486 complaint

Another RU-486 e mail.

Electronic Mail Message

Date: 9/27/00 2:23:06 PM
From:
To:
Subject: FWD: RU-486

Another RU-486 e mail.

Electronic Mail Message

Date: 9/27/00 5:17:00 PM
From: [redacted]
To: [redacted]
Subject: Web Address, etc.

The web address will be (it doesn't exist now):
http://www.fda.gov/cder/drug/infopage/mifepristone

the email address for the Drug Info Branch is druginfo@cder.fda.gov
Their phone number is 1-888-463-6332

Electronic Mail Message

Date: 9/27/00 1:46:49 PM
From:
To:
Subject: FWD: Script folks may use re: RU 486 telephone calls

Please let [redacted] now about this.

Electronic Mail Message

Date: 9/27/00 11:52:59 AM
From:
To: See Below
Subject: France Experience

In today's session, one question was:

What percentage of abortions in France are medical, if overall the total numbers did not change?

The total number of abortions in France has remained stable at around 180,000 per year. Currently, about 33% of these are medical using mife and misoprostol.

When the above medical regimen was first approved, during that first year, about 10% of abortions were done medically and 90% were surgical.

Electronic Mail Message

Date: 9/26/00 10:23:25 AM
From:
Subject: Electronic version of my consults

E L E C T R O N I C M A I L M E S S A G E

Date: 28-Sep-2000 12:52pm EDT
From:
Dept:
Tel No:

TO:

Subject: Re: RU 486

ty. very useful. it was particularly helpful in coordination on other Department issues.

-----Original Message-----
From:
[mail
Sent: Thursday, September 28, 2000 11:52 AM

Subject: RE: RU 486

The web page is now live.
http://www.fda.gov/cder/drug/infopage/mifespristone

Electronic Mail Message

Date: 9/26/00 9:41:55 PM
From: Dancogrp (Dancogrp@aol.com)
To: (
To:
Subject: Prescriber's Agreement/Order Form

As discussed with Nancy Buc, we have attached the Prescriber's Agreement/Order Form that was submitted on September 22.

9/21/00

ORDER FORM

To order MIFEPREX™ (Mifepristone) Tablets, 200 mg, just follow the 7 steps below.

1. Select quantities of Mifeprex* (Mifepristone) Tablets, 200 mg; NDC 64875-001-03

_____ pkg./each 3 tablets Mifeprex
_____ box/12 pkgs. Mifeprex

2. Billing Information

Bill to Name _____
Address _____
City _____ State _____ ZIP _____
Phone _____ Fax _____
Attention _____ Purchase Order #_____

3. Shipping information. Check if same as above.

Ship to Name _____
Address _____
City _____ State _____ ZIP _____
Phone _____ Fax _____
Attention _____ Purchase Order #_____

4. Additional site locations

I will also be prescribing Mifeprex at these additional locations:

Name	**Address**	**City**	**State**	**Zip**	**Phone#**
	Fax#				

(Any additional sites may be listed on an attached sheet of paper.)

5. Request additional materials:

.Medication Guide
.Patient Agreement
.State Abortion Guidelines

6. Establishing Your Account (required only with first order)

Each facility purchasing Mifeprex is required to be included in your account information (see #4) before the distributor can ship the product. Read the Prescriber's Agreement on the reverse of this order form and sign below.
By signing below, you acknowledge receipt of the Prescriber's Agreement and agree that you meet these qualifications and that you will follow these guidelines for use.

Print Name_____

Signature_____

Medical License # _____

Date_____

7. Fax this form to a distributor(s) of your choice below.

Distributor A	**Distributor B**
Address	**Address**
Phone	**Phone**
Fax	**Fax**

* Mifeprex is a trademark of Danco Laboratories, LLC

MIFEPREX™
(Mifepristone) Tablets, 200 mg

PRESCRIBER'S AGREEMENT

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

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

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

Under Federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex. The prescribing information is attached to this letter, and is also available by calling our toll free number, 1-877-4 Early Option (1-877-432-7596), or logging on to our website, www.earlyoptionpill.com.

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

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

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

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

Training in the administration of mifepristone is very important. A full range of training materials and opportunities with continuing medical education (CME) credit is readily available through Danco Laboratories' website, www.earlyoptionpill.com and our toll free number, 1-877-4 Early Option (1-877-432-7596). Please read the attached page, "Training Opportunities" to identify which program is most appropriate for you.

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

RFC-822-headers:
Received: from cdswss1.cder.fda.gov
("port 1118"@cdswss1.cder.fda.gov [150.148.150.21])
by mail.cder.fda.gov (PMDF V6.0-24 #42130)
with SMTP id <01JUN6RAUDWA934SWT@mail.cder.fda.gov>; Tue,
26 Sep 2000 21:42:04 -0400 (EDT)
Received: from 205.188.157.41 by cdswss1.cder.fda.gov with SMTP
(WorldSecure Server SMTP Relay(WSS) v4.3); Tue, 26 Sep 2000 21:40:05 -0400
Received: from imo-d09.mx.aol.com ([205.188.157.41])
by ocswall01 via smtpd (for cdswss1.cder.fda.gov [150.148.150.21])
with SMTP; Wed, 27 Sep 2000 01:36:47 +0000 (UT)
Received: from Dancogrp@aol.com by imo-d09.mx.aol.com (mail_out_v28.15.)
id t.c8.ab69e61 (4446); Tue, 26 Sep 2000 21:41:15 -0400 (EDT)
X-Mailer: AOL 5.0 for Windows sub 120
X-Server-Uuid: 00796fd4-893e-11d3-8ed3-0008c75df4f2
X-WSS-ID: 15CF907F428464-01-01

Electronic Mail Message

Date: 9/26/00 9:39:52 PM
From: Dancogrp (Dancogrp@aol.com)
To:
To:
Subject: package insert

As discussed with Nancy Buc, we have attached the package insert, including the Medication Guide and PATIENT AGREEMENT, that was submitted on September 26.

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 191-196°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_2. 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; i*n 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**
Total	**42**	**40**	**82**

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

Animal Data

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

Nonteratogenic Effects

The indication for use of Mifeprex in conjunction with misoprostol is for the termination of pregnancy through 49 days' duration of pregnancy (as dated from the first day of the last menstrual period). These drugs together disrupt pregnancy by causing decidual

necrosis, myometrial contractions and cervical softening, leading to the expulsion of the products of conception.

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The treatment procedure is designed to induce the vaginal bleeding and uterine cramping necessary to produce an abortion. Nearly all of the women who receive Mifeprex and misoprostol will report adverse reactions, and many can be expected to report more than one such reaction. About 90% of patients report adverse reactions following administration of misoprostol on day three of the treatment procedure. Those adverse events that occurred with a frequency greater than 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 mifepristone was administered in single doses greater than threefold that recommended for termination of pregnancy. If a patient ingests a massive overdose, she should be observed closely for signs of adrenal failure.

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

DOSAGE AND ADMINISTRATION

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

Day One: Mifeprex Administration

Patients must read the Medication Guide and read and sign the PATIENT AGREEMENT before Mifeprex is administered.

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

Day Three: Misoprostol Administration

The patient returns to the 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)

Please review the Training Opportunities provided with your Prescriber's Agreement, visit our website at www.earlyoptionpill.com, or call us at 1-877-4 Early Option (1-877-432-7596) for information about where to obtain materials or attend programs.

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.

9/21/00

Mifeprex satisfaction/recommendation claims

"Women are highly satisfied with Mifeprex."
"96 percent of women in clinical studies would recommend Mifeprex to others."

Each of these claims was evaluated with a single question. A single question is inadequate to assess patient satisfaction with treatment or likelihood to recommend to others. These types of patient-based assessments should be evaluated in studies using validated instruments that address all relevant determinants of satisfaction or willingness to recommend. For example, patients should be asked about the specific, relevant aspects of treatments with which they were satisfied, e.g., onset of action, adverse effects, route of administration, etc.

Sept 25, 12000

Electronic Mail Message

Date: 9/25/00 2:00:15 PM
From:
To: See Below
Subject: Medication Error Consult

Good afternoon,

The sign off date is 9/22/00.

Electronic Mail Message

Date: 9/25/00 8:23:09 AM
From: [redacted]
To: [redacted]
To: [redacted]
Cc:
Subject: FWD: Pop Council's September 19, 2000 Submission

FYI....

[redacted] ask you to call Pop Council to clarify when they plan to submit these educational materials?

If not, let me know and we can call today.

[redacted]

Electronic Mail Message

Date: 9/24/00 9:15:00 AM
From:
To:
To:
Cc:
Subject: FWD: FOI and RU486

The commissioner's office has made a determination on confidentiality of reviewers and of the firm. This meeting on Monday is to go over the decision and what needs to be done to implement her decision.

Please attend (either one of you is fine, if the scheduling is conflicted).

Thanks.

Electronic Mail Message

Date: 9/22/00 5:12:13 PM
From:
Subject: FOI and RU486

has asked for a meeting on Monday, Sept. 25 at 2pm with some people from OTCOM to discuss FOI and RU486. She would like you or a project manager from Review to attend, if possible.

It will be in Parklawn, 12B02. Here is the list of attendees so far:

Looks like it will be a crazy week. Sorry for the last minute notice.

Electronic Mail Message

Date: 9/22/00 10:56:21 PM
From: [redacted]
Subject: Re: name changes on RU 486 consults

There is a problem with getting signatures on Monday [redacted] will be out of town and I will be attending a meeting both Monday and Tuesday with NICHD. We will get signatures and the consults off to Repro as soon as possible.

[redacted]

=====

I spoke with [redacted] and she prefers that all three consult send to her at same time. She said it is OK to do it on Monday. I will as[redacted] to print the 1st RU 486 consult and get your and [redacted] signature on Monday. Then I will delivery them together[redacted]

Electronic Mail Message

Date: 9/21/00 8:53:55 AM
From:
To:
To:
Subject: medication guide

I have looked over the latest Medication Guide. The sponsor left off the "s" in the word "medicines" in the paragraph at the end, below the 3 asterisks.

E L E C T R O N I C M A I L M E S S A G E

Date: 21-Sep-2000 03:30pm EDT
From: [redacted]

Dept: HFD-42 PKLN 17B17
Tel No: [redacted] FAX [redacted]

TO: [redacted]

Subject: Mifeprex contact

I spoke with Nancy Buc. She told me that it was [redacted] who disseminated the message that [redacted] was the contact. [redacted] did this because [redacted] declared himself contact in his first letter to [redacted] He has since be supressed. Nancy said there are either 3 contacts or one. I asked for one, so she said that she would be the contact for all materials during the launch phase of the product. As time goes on though, we will probably have to deal with three contacts.

I am faxing the letter to Nancy upon her request.

E L E C T R O N I C M A I L M E S S A G E

Date: 21-Sep-2000 03:30pm EDT
From:

Dept: HFD-42 PKLN 17B17
Tel No:

TO:

Subject: Mifeprex contact

I spoke with Nancy Buc. She told me that it was who disseminated the message that was the contact. did this because declared himself contact in his first letter to He has since be supressed. Nancy said there are either 3 contacts or one. I asked for one, so she said that she would be the contact for all materials during the launch phase of the product. As time goes on though, we will probably have to deal with three contacts.

I am faxing the letter to Nancy upon her request.

Electronic Mail Message

Date: 9/21/00 4:01:10 PM
From:
To:
To:
Tr
To
To:
Subject: FWD: Change in two places in label

Electronic Mail Message

Date: 9/21/00 10:35:02 PM
From:
Subject: FWD: OPDRA consults on RU 486

We are regenerating the consults for you. Med Errors deals with the medication name review. I have forwarded your request to them.

Electronic Mail Message

Date: 9/21/00 10:33:57 AM
From: [redacted]
Subject: FWD: OPDRA consults on RU 486

Dear Med Errors,

Request from [redacted] regarding consult on RU486. Please read and make name changes as per request. DDRE2 will take care of other consult issues. Thanks.

Sandy Arnold of the Population Council asked me to send you the attached, electronic version of the the Labeling document and the Medication Guide.

I may be sending you more than you asked for, but better safe than sorry.

If this is not the right document, please call me at (202) 736-3613.

Assistant to Nancy L. Buc

Electronic Mail Message

Date: 9/21/00 1:47:58 PM
From:
To:
To:
Subject: My office memo is being revised

Again I'm receiving comments on my memo from GC and I will be revising it accordingly.

Thus, it may not be until next week I get to the final final final version...

Electronic Mail Message

Date: 9/21/00 1:44:23 PM
From:
To:
To:
To:
Cc:
Subject: Phase 4 committment for final protocols

I asked Nancy Buc if Pop Council can get the final phase 4 protocols to us in 6 months. I told her that we would put in our approval letter the time deadline for submission of the two protocols and that if there is a problem with 6 months to let us know now.

Printed by

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 01-Mar-2000 05:52pm
From:

Dept: HFD-320 MPN1 273
Tel No:

TO:

Subject: FWD: Re: FWD: Re: Mifepristone from

Please see me on this.

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 24-Jun-1999 09:26am
From: [redacted]
Dept: HFD-580
Tel No: FAX t-

TO: See Below
Subject: FDA funding bill in Congress

House passed the FDA funding bill, 246-183, on June 8th.

Coburn (R-OR) RU-486 amendment agreed to, 217-214. The amendment prohibits any funds in the bill from being used by FDA for the testing, development, or approval (including approval of production, manufacturing, or distribution) of any drug for the chemical inducement of abortion. Those opposed to the amendment claimed it would eliminate FDA testing, development, or approval of any drug that could possibly cause miscarriage, and, therefore, research on such diseases as cancer would be jeopardized. Coburn contended that the language would do no such thing, that it clearly only applies to drugs whose sole purpose is abortion.

The bill citation for the relevent amendment is is HR 1906, Title VII, section 742, page 72.

On May 26, the Administration sent a letter strongly opposing the potential FDA, RU 486 amendment. I'm not sure if this will lead to a veto threat.

The Senate version of this bill (S.1323) does not a similar provision. Floor action was supposed to start Monday, but has been delayed due to Sen. Dorgan (D-ND) introducing a Patient Bill of Rights amendment (on behalf of Sen. Daschle (D-SD)). As a result, Sen. Lott pulled the bill.

If this restriction is not added to the Senate bill, it could still be included in conference (that's where a joint House and Senate committee resolve differences between their respective bills. Knowing which members are named to the relevant conference committee is key to knowing what the final bill will look like.)

Distribution:

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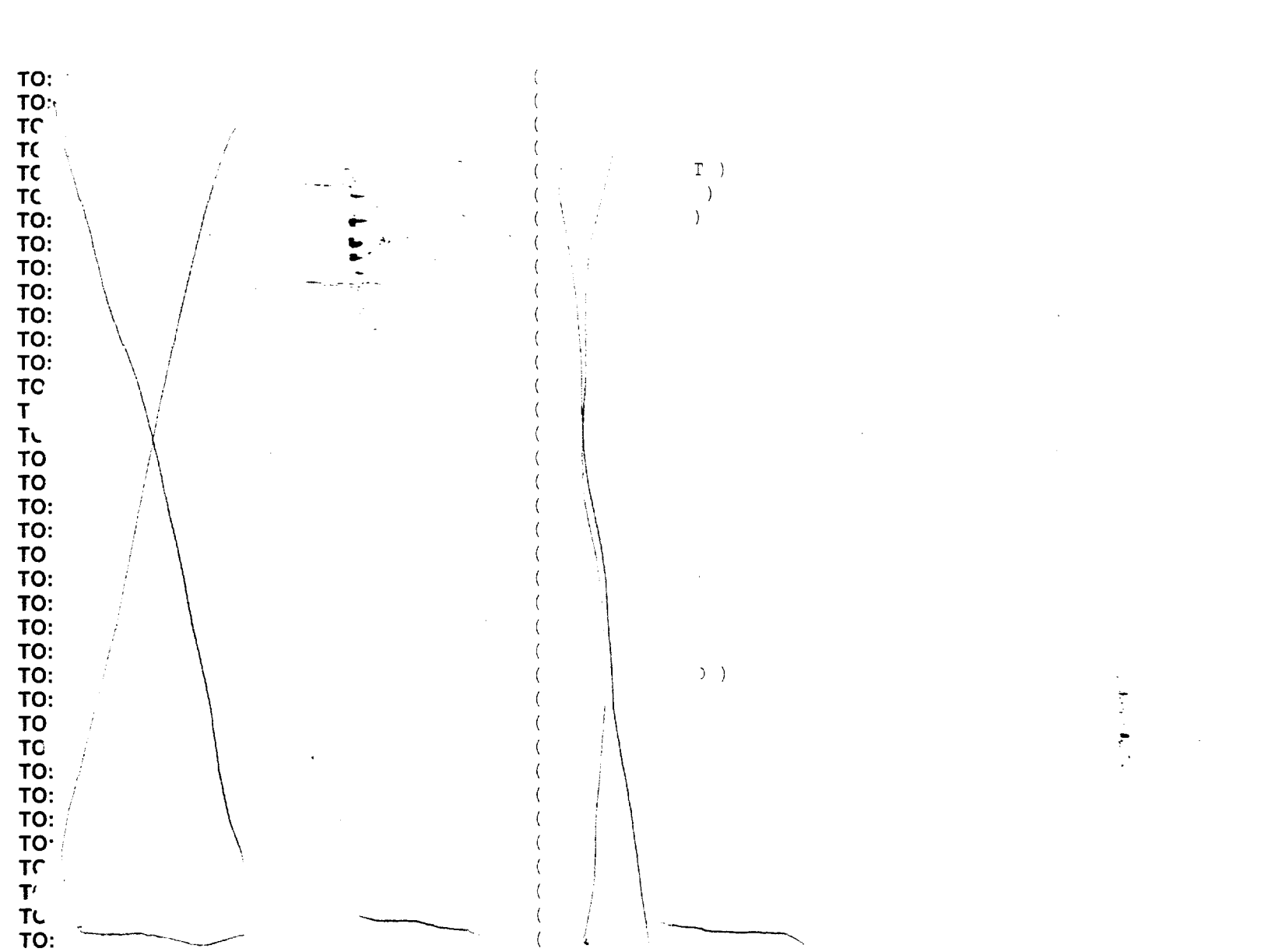

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 10-May-1999 03:58pm
From: [redacted]

Dept: HFD-580 PKLN 17B45
Tel No: [redacted]

TO:
TO:

CC:
CC
Subject: FWD: Re: Mifepristone

Please help us figure out exactly what needs to be done for this one! I would assume that the sponsor needs to provide the same info as they would for a DMF, but to the IND. Please let[redacted] know how best to proceed.,

Thanks,

[redacted]

Printed by [redacted]

Electronic Mail Message

Date: [redacted]
From: [redacted]
Dept: HFD-580 PKLN 17B45
Tel No: [redacted]

Subject: FWD: Re: Mifepristone

This is the information that I am getting from [redacted] Please let me know what I should do or who I should be talking to. It seems as though there is more to this than I thought.

[redacted]

Printed by [redacted]

Electronic Mail Message

Date: 06-Jan-2000 11:55am
From: [redacted]

Dept:
Tel No:

TO:
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TO:

Subject: RU-486 REVOLUTION (http: //intranet.tda.gov/clips/web/01062000/r48 6.htm)

<<RU-486 REVOLUTION.htm>>

Printed by [redacted]

Electronic Mail Message

Date: 12-Sep-2000 09:47am
From: [redacted]
Dept:
Tel No:

TO: See Below
Subject: FW: Call List

Here is a long list of interested women's groups. It does not include other federal offices or health professionals. We could also send these two lists to you. Just let us know.

> RU486
>
> Women's Groups
>
> The Feminist Majority - Jennifer Jackman
> phone--703-522-2214 fax--703-522-2219 (fax)
>
> Planned Parenthood Federation of America -- Gloria Feldt
> phone--212-541-7800 fax-- 212-245-1845
>
> National Abortion Rights Action League -- Kate Michelman
> phone--202-973-3000 fax--202-973-3096
>
> National Organization for Women -- Patricia Ireland
> phone-- 202-628-8669 fax--202-785-8576
>
> NOW Legal Defense and Education Fund -- Juliana Grant
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> phone--202-986-2600 fax--202-986-2539
>
> National Women's Law Center -- Marcia Greenberger
> phone--202-588-5180 fax--202-588-5185
>
> American Association of University Women -- Nancy Zerkin
> phone--202-785-7700 fax--202-872-1425
>
> The Society for Women's Health Research -- Phyllis Greenberger
> phone--202-223-7009 fax--202-833-3472
>
> National Women's Health Network -- Cindy Person
> phone--202-347-1140 fax--202-347-1168
>

Church Women United -- Tiffany Heath
phone--202-544-8747 fax--202-544-9133

> National Council of Negro Women -- Jane Smith
> phone--202-383-9134 fax--202-737-0746
>
> National Black Women's Health Project -- Julia Scott
> phone--202-543-9311 fax--202-543-9743
>
> National Asian Women's Health Organization -- Mary Chung
> phone--415-989-9747 fax--415-989-9758
>
> National Asian Pacific Legal Consortium -- Karen Narasaki
> phone--202-296-2300 fax--202-296-2318
>

> National Coalition of Hispanic HHS -- Jane Delgado
> phone--202-387-5000 fax--202-797-4353
>
> MANA (A National Latina Organization) -- Alma Morales Riojas
> phone--202-833-0060 fax--202-496-0588
>
> National Council of La Raza -- Yanera Cruz Gonzales
> phone -- 202-776-1715 fax-202--776-1792
>
> National Congress of American Indians -- Jo Ann Chase
> phone--202-466-7767 fax--202-466-7797
>
> HADASSAH Department of Women's Health -- Dale Mintz
> phone--212-303-8094 fax--212-303-7486
>
> National Council of Jewish Women -- Ivy Miller
> phone--212-645-4048 fax--212-645-7466
>
> Disability Rights Education and Defense Fund -- Patrisha Wright
> phone--510-644-2555 fax--510-841-8645
>
> Jacobs Institute for Women's Health -- Martha Romans
> phone--202-863-4990 fax--202-488-4229
>
> Alan Guttmacher Institute -- Sara Seims
> phone--212-248-1111 fax--212-248-1951
>
> Business and Professional Women's Foundation -- Gail Schafer
> phone--202- fax--202--861-0298

Distribution:

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Electronic Mail Message

Date: 4/28/00 7:51:17 AM
From: [redacted]
To: [redacted]
Subject: FWD: Environmental information for 20-687

FYI

Electronic Mail Message

Date: 9/20/00 12:11:14 PM
From:
To:
To:
Subject: External Q & A

FYI-attached is the latest revision. Thanks for your input,

Electronic Mail Message

Date: 9/20/00 11:58:54 AM
From:
To:
To:
To:
Subject: DDMAC and Website

I've talked to [redacted]. I learned that [redacted] of DDMAC have already agreed to no action on the website [redacted] is in concurrence. If any action is to be done [redacted] needs to know.

Electronic Mail Message

Date: 9/19/00 10:41:12 AM
From:
To: See Below
Subject: External Q & As

Sorry, I forgot to the the Q & As

To:
To:
To:
Cc:
Cc:
Cc:

Electronic Mail Message

Date: 9/19/00 10:39:09 AM
From: [redacted]
To: See Below
Subject: External Q & As for RU-486 - 9/19

Attached is the latest revision of the proposed External Q&As. These revised Q&As reflects the comments made in yesterday's meeting. Any comments should be forwarded to [redacted] as soon as possible.

[redacted]

To:
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Cc:
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Electronic Mail Message

Date: 9/19/00 10:27:5[illegible] AM
From:
To:
To:
To:
Subject: 9-15-00 Meeting minutes

Here are the meeting minutes. the final minutes will have attached the Medication Guide that the sponsor submitted 9-15-00.

Thanks,

Electronic Mail Message

Date: 9/18/00 4:55:10 PM
From:
To: See Below
Subject: Medication Error Consult

Good Afternoon,

The sign off date is 9/13/2000.

To:
To:
To:
To:
To:
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Electronic Mail Message

Date: 9/18/00 10:33:10 AM
From: [redacted]
Subject: FWD: Re: Pop Council agrees to our proposed studies

fyi

Electronic Mail Message

Date: 9/15/00 10:45:37 AM
From:
To: See Below
Subject: Re: 9-14-00 Meeting Minutes

Please review and respond by 12:00 today.

Thanks,

To:
To:
To:
To:
To:
To:

Electronic Mail Message

Date: 9/15/00 3:46:35 PM
From:
To: See Below
Subject: Agreement on Label, Med Guide, Pt Agreement, Physician's Agreement & Pha

Everyone,

The division and office have reached agreement w/ the Pop Council on all the pieces for drug approval.

The last step is DDMAC review of the promotional materials, to be submitted for review on Monday.

Thanks to all for your help and support.

To:
To:
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Cc:
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Cc:
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Electronic Mail Message

Date: 9/15/00 9:59:06 AM
From:
To: See Below
Subject: 8-8-00 pop meeting minutes

Please review and respond by 12:00 today. Sorry for the short turn around

To:
To:
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Printed by [redacted]

Electronic Mail Message

Date: 15-Sep-2000 11:23am
From: [redacted]

Dept: HFD-800 PKLN 13B31
Tel No: [redacted] FAX [redacted]

Subject: NDA 20-687

[redacted]: I have reviewed the Action Package and concur with the Approval recommendation made by the Chemistry reviewer and the team leader of this NDA.

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 15-Sep-2000 01:30pm
From: [redacted]

Dept: HFD-103 PKLN 13B45
Tel No: [redacted] FAX [redacted]

TO: [redacted]
TO: [redacted]
TO: [redacted]
TO [redacted]

Subject: FWD: NDA 20-687

We have clearance on the mifepristone action package from [redacted]

[redacted]

Printed by

Electronic Mail Message

Date: 14-Sep-2000 08:37am
From:

Dept: HFD-103
Tel No: FAX

Subject: FWD: Stability testing

Printed by

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 14-Sep-2000 09:35am
From: [redacted]

Dept: HFD-580 PKLN 17B45
Tel No: [redacted] FAX [redacted]

TO:
TO:

CC
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CC
Subject: FWD: Stability testing

FYI

Electronic Mail Message

Date: 9/14/00 4:28:52 PM
From: [redacted]
Subject: Internal Q's and A's

Electronic Mail Message

Date: 9/13/00 1:12:40 PM
From:
To:
Subject: FWD: - no subject (01JU4IA0WZHI94DVX1) -

Another RU-486 e mail.

Printed by

Electronic Mail Message

Date: 13-Sep-2000 05:46pm
From:

Dept: HFD-103 PKLN 13B45
Tel No: FAX

Subject: Stability testing

stopped by to say that the Office in ONDC concurs with the ..n stability for mifepristione.

Electronic Mail Message

Date: 9/13/00 2:20:53 PM
From: [redacted]
Subject: Re: Population Council Meeting on 9-14-00

This is the package sent to the sponsor 9-13-00. Please have this for the meeting on 9-14-00 to discuss with the sponsor.

Electronic Mail Message

Date: 9/13/00 2:20:53 PM
From:
To: See Below
Subject: Re: Population Council Meeting on 9-14-00

This is the package sent to the sponsor 9-13-00. Please have this for the meeting on 9-14-00 to discuss with the sponsor.

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Electronic Mail Message

Date: 9/13/00 2:20:53 PM
From:
Subject: Re: Population Council Meeting on 9-14-00

This is the package sent to the sponsor 9-13-00. Please have this for the meeting on 9-14-00 to discuss with the sponsor.

Electronic Mail Message

Date: 9/13/00 5:56:42 PM
From:
Subject: FWD: Re: Population Council Meeting on 9-14-00

Electronic Mail Message

Date: 9/13/00 10:05:50 AM
From:
To: See Below
Subject: updated timeline

Attached is an updated timeline. Please let me know of any changes or updates.

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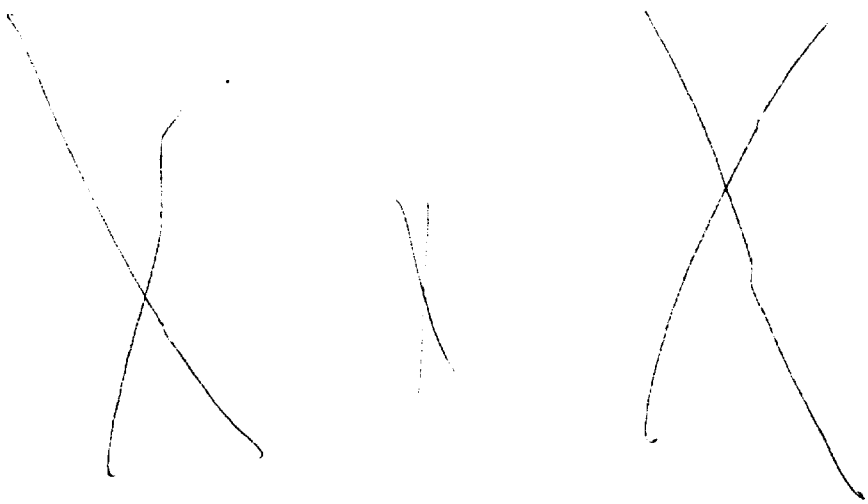

Electronic Mail Message

Date: 9/13/00 10:05:50 AM
From: [redacted]
To: See Below
Subject: updated timeline

Attached is an updated timeline. Please let me know of any changes or updates.

[redacted]

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Printed by [redacted]

Electronic Mail Message

Date: 12-Sep-2000 09:47am
From: [redacted]
Dept:
Tel No:

TO: See Below
Subject: FW: Call List

Here is a long list of interested women's groups. It does not include other federal offices or health professionals. We could also send these two lists to you. Just let us know.

> RU486
>
> Women's Groups
>
> The Feminist Majority - Jennifer Jackman
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>
> National Abortion Rights Action League -- Kate Michelman
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>
> National Organization for Women -- Patricia Ireland
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> phone--202-588-5180 fax--202-588-5185
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> National Congress of American Indians -- Jo Ann Chase
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> Disability Rights Education and Defense Fund -- Patrisha Wright
> phone--510-644-2555 fax--510-841-8645
>
> Jacobs Institute for Women's Health -- Martha Romans
> phone--202-863-4990 fax--202-488-4229
>
> Alan Guttmacher Institute -- Sara Seims
> phone--212-248-1111 fax--212-248-1951
>
> Business and Professional Women's Foundation -- Gail Schafer
> phone--202- fax--202--861-0298

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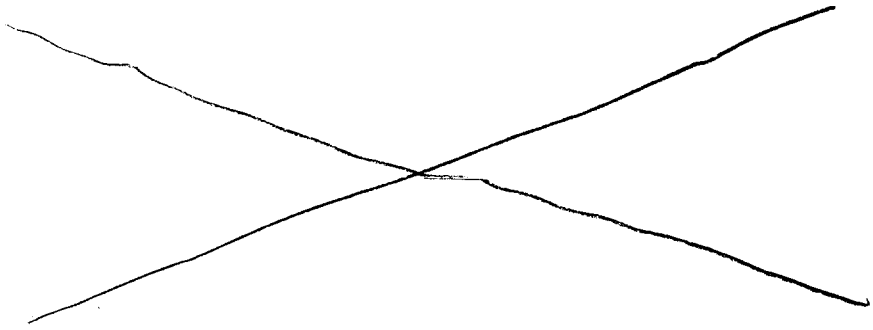

Electronic Mail Message

Date: 9/12/00 4:41:51 PM
From: [redacted]
To: [redacted]
Subject: Sorry for the delay. Make any changes that you want. I am also faxing to

Electronic Mail Message

Date: 9/12/00 4:41:51 PM
From: [redacted]
Subject: Sorry for the delay. Make any changes that you want. I am also faxing to

Printed by [redacted]

Electronic Mail Message

Date: 12-Sep-2000 04:41pm
From: [redacted]
Dept: HFD-440 PKLN 15B23
Tel No: [redacted] FAX [redacted]

Subject: Sorry for the delay. Make any changes that you want. I am also faxing to [redacted] now

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 19-Sep-2000 08:02am
From: [redacted]

Dept: HFD-440 PKLN 15B18
Tel No: [redacted] FAX :

TO: [redacted]

Subject: Re: OPDRA attendance is NOT necessary at PopCouncil on Tues AM..... [redacted]

Printed by

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 11-Sep-2000 03:28pm
From:

Dept: HFD-580 PKLN 17B30
Tel No: FAX

TO:

CC:
CC:
Subject: Mifepristone: Spitz article

109 women over age 35 were included in the P.C. sponsored U.S. studies of women of up to 49 days gestational age. The Spitz article is a report of the U.S. studies in which he says that the (efficacy) outcomes were unrelated to age (AND OTHER VARIABLES). No DATA IS INCLUDED ON THIS SUBJECT IN THE ARTICLE. I calculate that complete abortion occurred in 92.6% of women less than age 35 and in 88.7% of women over age 35.

Table 10 (Continued)
Success Rates and 95% Confidence Limits by Patient Characteristics
Complete Expulsion (Success)
[Efficacy Evaluable Patients]

Gestational Age Group [1]: ≤49 Days (Group 1)

Variable	Successes/Total N	Incidence Rate (%)	Confidence Limits (95%)
All Patients	372 / 407	91.40	88.14, 93.86
AGE (years)			
<20	26 / 27	96.30	79.11, 99.81
20-24	102 / 108	94.44	87.81, 97.72
25-29	117 / 128	91.41	84.80, 95.42
30-34	82 / 92	89.13	80.49, 94.38
>35	45 / 52	86.54	73.60, 93.97
RACE			
AFRICAN AMERICAN	46 / 52	88.46	75.87, 95.22
CAUCASIAN	266 / 291	91.41	87.43, 94.25
EAST ASIAN	14 / 14	100.00	73.24,100.00
HISPANIC	39 / 43	90.70	76.95, 96.98
OTHER	7 / 7	100.00	56.09,100.00
BODY MASS INDEX (kg/m^2)			
NORMAL (≤25)	253 / 277	91.34	87.22, 94.26
OVERWEIGHT (25-30)	79 / 86	91.86	83.42, 96.39
OBESE (>30)	40 / 44	90.91	77.42, 97.05
GRAVIDITY			
1	194 / 207	93.72	89.26, 96.47
2	74 / 79	93.67	85.21, 97.65
3	50 / 51	98.04	88.21, 99.90
4+	54 / 70	77.14	65.28, 85.99
PARITY			
0	217 / 231	93.94	89.82, 96.52
1	68 / 73	93.15	84.07, 97.45
2	58 / 66	87.88	76.96, 94.25
3+	29 / 37	78.38	61.34, 89.58
NUMBER OF PREVIOUS SPONTANEOUS ABORTIONS			
0	319 / 345	92.46	89.02, 94.92
1	43 / 49	87.76	74.54, 94.92
2+	10 / 13	76.92	45.98, 93.84
NUMBER OF PREVIOUS ELECTIVE ABORTIONS			
0	187 / 200	93.50	88.90, 96.35
1	115 / 125	92.00	85.41, 95.88
2+	70 / 82	85.37	75.44, 91.89
DAYS OF AMENORRHEA (PATIENT ESTIMATE)			
< 36 days	2 / 4	50.00	9.19, 90.81
36 to <43 days	78 / 84	92.86	84.53, 97.06
43 to ≤49 days	189 / 206	91.75	86.90, 94.97
50 to ≤56 days	71 / 79	89.87	80.50, 95.21
57 to ≤63 days	26 / 28	92.86	75.04, 98.75
>63 days	6 / 6	100.00	51.68,100.00

[1] Amenorrhea group was assigned by the investigator based on the final assessment of duration of amenorrhea.

Data:

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Table 10 (Continued)
Success Rates and 95% Confidence Limits by Patient Characteristics
Complete Expulsion (Success)
[Efficacy Evaluable Patients]

Gestational Age Group [1]: ≤49 Days (Group 1)

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PARITY			
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>63 days	6 / 6	100.00	51.68,100.00

[1] Amenorrhea group was assigned by the investigator based on the final assessment of duration of amenorrhea.

Data:

\166b\saspgms\tables\succ1.SAS 25APR97:08:53