Notes re IND ——— RU 38486
Rat and Monkey 26 week studies

Clinical Signs: Increased salivation was a common sign in both rats and monkeys with high dose monkey also showing an increased incidence of vomiting.

Mortality: Not apparently drug related. None in monkeys.

Body Weights: Some decreases in both species especially males.

Food and Water Consumption: Food utilization efficiency lower for rats and some reductions for high dose monkeys. Some increases seen in rat water consumption and some reduction seen in monkeys.

Electrocardiogram: Some decreases in heart rates seen in both species at various times.

Hematology: Although platelet counts for rats were higher at various times for rats they were lower for high dose monkeys at wks 6 and 24. Some decrease in Thrombotest times in rats. Some increases in neutrophils seen in rats were not evident in monkeys.

Blood Chemistry: Sporadic findings in the rat study were in general not consistent with the findings in the monkey study.

Urinalysis: Protein excretion associated with increased specific gravity was greater than controls in rats and electrolyte excretion was decreased in monkeys.

Organ Weights: Liver, adrenals and kidney wts. were increased in both rats and monkeys. In the rat male and female sex organs showed some decreases over controls and female pituitary weights showed some increases.

Gross Pathology: Findings were not consistent from one species to another. They ranged from enlarged pituitaries, adrenals and thyroids and decreased prostates, seminal vesicles and testes, thickened mammary glands and a slight increase in hydronephrosis in rats to dark adrenals, small subscapular foci in the kidneys and a few cysts or dilatations in a few of each group in monkeys.

Histopathology: Sex organs were affected in both species. Spermatogenesis was reduced, corpora lutea were absent, endometrial glands were dilated and there was a change in keratinization of the cervix-vaginal areas. Mammary glands showed a distention of acini and ducts in rats and an increased development without increased secretion in monkeys. Livers showed some hepatocyte enlargement in rats and an increase in brown pigment in monkeys. Adrenals showed some loss of distinction and increases in width between the different zones. Diffuse hyperplasia of the pars anterior seen female rats was not reported for monkeys. Rat kidneys showed an increase in basophilic dilated tubules while in monkeys the incidence of cortical scaring and cysts was increased.

CC:

With regard to the rat study, hematological changes appeared to be attributable to the antiprogesterone component of the drug while the various minor clinical chemistry alterations appear to be the result of antiglucocorticoid activity. There were no observable renal differences between the 5 mg/kg males and the controls. The sponsor indicates that the renal lesions seen in females at all doses and the males at 25 or 125 mg/kg bore resemblance to those of spontaneous progressive glomerulonephrosis, which may reflect a premature aging due to overdosage with the test drug. This may or may not be

true however, it appears that in the rat they were compound related. The occurrence of prominent hemosiderosis in over half of the females at 125 mg/kg, also showing a marginal anemia, would appear to be related to drug administration. Treatment-related changes, in females included an increased occurrence of cornified cells in vaginal smears, decreased uterine and ovarian weights, increased adrenal cortical widths, diffuse hyperplasia in the pars anterior, an absence of corpora lutea, reduced uterine endometrial stroma, absence of uterine pseudo-stratified columnar epithelium and increased incidence of distended mammary acini and ducts.

Low dose male rats showed a reduced prostatic colloid.

A variety of changes were induced in monkeys receiving 5, 15 and 45 mg/kg RU 38486 for 26 weeks which were not seen in control animals. Overall effects appeared to be related to various minor disturbances of metabolic processes which were modulated by glucocorticoid hormones and/or modification of tissues due to unphysiological estrogen/progesterone balance. All treated groups showed an increase in the incidence of brown pigment in the hepatocytes which may or may not be due to an increased metabolic activity caused by RU 38486. Although the incidence and severity of the changes did not increase with increasing dosage, the significance of the histopathological findings of areas of cortical scarring, cortical cysts and increased incidence of subcapsular foci of fibrosis of the kidneys is unclear. Some of the changes were also observed in the controls.

Findings with the low dose of RU 38486 (5 mg/kg) were more or less confined to cessation of menstrual activity with consequent physiological changes in the histological appearance of the reproductive organs for females and decreased spermatogenesis in one male. Pharmacological effects were in general increased at higher doses.

There were no unexpected findings and observed effects were considered predictable consequences of pharmacological suppression of glucocorticoid and progesterone activity. It would appear that the overall effects were related to minor metabolic disturbances modulated by glucocorticoid hormone and the result of unphysiological estrogen/progesterone balance on various tissues.

College of Physicians & Surgeons of Columbia University | New York, N.Y. 10032

DEPARTMENT OF PHARMACOLOGY
Telephone (212) 305-8778

630 West 168th Street
Fax (212) 305-8780

March 21, 1994

US FDA
5600 Fishers Lane, Room 14B04
Rockville, MD 20857

Re: Preclinical rat and rabbit studies of RU-486, in conjunction with Mr. Larry Lader

Dear

I am writing to confirm our telephone discussion of February 14th in which we discussed doses of RU-486 to be utilized in our planned preclinical studies of RU-486. I thank you for your time and interest and greatly appreciate your assistance with this matter. As you may recall, the compound to be utilized for these studies will be synthesized by an FDA-approved contracting laboratory in collaboration with Dr. David Horne of the Chemistry Department at Columbia University. My role will be to guide the planning, conduct and reporting of the preclinical studies in an effort to obtain an IND to study the use of RU-486 as an abortifacient.

Based on our conversation, it is our plan to contract to conduct the following studies, at the dosages listed:

1. A 14-day rat study at doses of 0, 8, 40 and 200 mg/kg/day.

2. A 24-day dog study at doses of 0, 4, 20 and 100 mg/kg/day.

3. A segment II pilot study in rats at 0, 8, 40 and 200 mg/kg/day. The objective of this study is to find a dose which would cause some rat fetuses to be aborted and some retained throughout gestation.

4. A segment II main study in rats at, tentatively, 0, 8, 40 and 200 mg/kg/day.

5. A segment II pilot study in rabbits at 0, 8, 40 and 200 mg/kg/day. The objective of this study is to find a dose which would cause some rabbit fetuses to be aborted and some retained throughout gestation.

6. A segment II main study in rabbits at, tentatively, 0, 8, 40 and 200 mg/kg/day.

If you perceive any basic flaw or deficiency in our preclinical study plan, I would greatly appreciate a response, as the costs associated with the synthesis of the compound and the studies themselves are extraordinarily high. My direct telephone number is 212-305-8368; my fax number is 212-305-8780. Thanks again.

Sincerely,

Joseph H. Graziano, Ph.D.
Professor of Pharmacology (in Pediatrics)
and Public Health (in Environmental Sciences)
Head, Division of Environmental Sciences

cc: Mr. Larry Lader
Dr. David Horne

Not a Report or Record

I N T E R O F F I C E M E M O R A N D U M

Date:
From: [redacted]

Dept:
Tel No:

TO: See Below

Subject: Pre-IND RU-486\Larry Lader

NOTICE OF FORTHCOMING MEETING

DATE: Thursday, March 31, 1994
TIME: 10:00 AM - 11:00 AM
PLACE: C\R 13B-39

Purpose: Dr. Lader is initiating pre-IND studies usung RU-486 imported from the United Kingdom. The Division suggested this meeting to discuss protocol for pre-clinical studies as well as projections for clinical studies.

Background: Dr. Lader has already gained media coverage [redacted] for his clinical studies on RU-486. He intends to import [redacted] of the drug from either [redacted] or [redacted] in the UK. This he plans to use for both pre-clinical and clinical studies. He has discussed some of the pre-clinical protocol with [redacted], but he has not addressed several issues (GMPs of labs, capability for scale-up, data on drug purity, stability, etc.).

Distribution:

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

CC:

Teleconference Meeting Minutes

Date: September 14, 2000 **Time:** 1:00 – 2:00 PM **Location:** Parklawn; 17B-43

NDA 20-687 **Drug:** Mifepristone 200 mg

Indication: induction of abortion

Sponsor: Population Council

Type of Meeting: Status

Meeting Chair:

Minutes Preparer:

FDA Attendees:

Office of Evaluation III (ODEIII; HFD-103)
Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
, DRUDP (HFD-580)
–, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Division of Drug Review and Evaluation II (DDREII; HFD-440)
- Regulatory Health Project Manager, DDREII (HFD-440)
Regulatory Management, DDREII (HFD-440)
v (Epidemiology), DDREII (HFD-440)
Project Management Staff, DRUDP (HFD-580)
- Regulatory Project Manager, DRUDP (HFD-580)

External Lead: Nancy Buc

Meeting Objective: To discuss the Information Request Letters sent September 13 and 14, 2000.

Discussion:

Labeling

- the Agency accepts the manner in which the sponsor is using the trademark symbol and the capitalization of the name "Mifeprex"
    - all CAPS and when used for the first time in any document
    - the second appearance the first letter capitalized with the trademark and an asterisk

indicating the trademark belongs to Danco

- anytime after that it will be first letter capitalized with the asterick

- the sponsor is reviewing the addition of the phrase "with a terminal half-life of 18 hours" in the Distribution section of the label
- the sponsor agrees to the removal of the section on [redacted] the **WARNINGS** section of the label
- in the **PRECAUTIONS** section of the label, the sponsor will respond to the elimination of the phrase [redacted] and replaced with "qualified physician"
- in the **PRECAUTIONS** section, Information for the Patient subsection [redacted] has been deleted
- replaced **PATIENT INFORMATION** with Medication Guide wherever it is used throughout the label
- in the **PRECAUTIONS** section, Drug Interaction subsection, the sponsor agrees with the deletion of the first paragraph and the replacement wording provided for by the biopharmaceutics reviewer
- in the **PRECAUTION** section, Carcinogenesis, Mutagenesis, Impairment of Fertility subsection, the sponsor agrees to the change of the word [redacted] to genotoxic and also the elimination of sentence [redacted]
- in the **PRECAUTIONS** section, Teratogenic Effects subsection, heading Human Data, the sponsor will provide the Agency with the correct numbers of patients since May 2000, and agrees with the number changes the Agency made
- the sponsor agrees with the changes made to Table 2 to update the numbers
- in the **OVERDOSAGE** section the sponsor will provide the Agency with a reponses to changing the [redacted] to "acute lethal dose"
- in the **DOSAGE AND ADMINSTRATION** section the sponsor will change the last sentence to match bullet number 3 of the **PHYSICIAN AGREEMENT**
- in the **DOSAGE AND ADMINSTRATION** section, Day One: Mifeprex Administration subsection should read as follows: "Patient must read the Medication Guide and read and sign the PATIENT AGREEMENT"
- in the **DOSAGE AND ADMINSTRATION** section, Day 3 : Misoprostol Administration subsection, the sponsor agrees to the suggested changes in both paragraphs
- in the **DOSAGE AND ADMINSTRATION** section, Day 14: Post-Treatment Examination subsection, the sponsor agrees with the proposed changes
- in the **HOW SUPPLIED** section the sponsor agrees with the proposed changes [redacted]

PATIENT AGREEMENT

- the sponsor was not prepared to discuss the changes faxed to them in the September 14, 2000 Information Request letter

ORDER FORM

- the sponsor agrees to the addition of a date line for the date of signature

PRESCRIBER AGREEMENT

- the sponsor agrees with the addition of the numeric digits following the "1-877-4 Early Option" phone number
- the sponsor agrees with the change of [redacted] to "administration" in the last paragraph

- the sponsor will add the distributors name, address, phone number, fax number, and website to the end of this document

Phase 4 Commitments

- the sponsor needed clarification of the term "Emergency intervention"; the Agency defined it as medically necessary intervention (i.e. heavy bleeding)
- the sponsor will need to respond with the commitment to perform the Phase 4 studies in a submission to the NDA
- [redacted]
- the sponsor will need to address adding the language from the most recent European label as a contraindication for inharitant porphiera in the label

Action Items:

- the sponsor must to submit the revised label, agreement to Subpart H, and the commitment to perform studies
- meeting scheduled for September 15, 2000 at 11:00 AM to discuss the remaining issues
- fax meeting minutes to the sponsor within 30 days

Minutes Preparer **Concurrence, Chair**

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL **Date:** 04-Aug-1999 02:22pm
From: [redacted]

Dept: HFD-580 PKLN [redacted]
Tel No: [redacted] FAX 301-827-4267

TO: See Below
Subject: List of 580 attendees to be included in meetings on Misoprostol

[redacted]

At the most recent meeting with the ODE, [redacted] requested that an internal meeting be set up between HFD-180 and HFD-580 to discuss the most recent changes on the misoprostol labeling (I am sure that either [redacted] will follow-up with you on the specifics).

The following is the list of 580 attendees that should be included in such a meeting:

[redacted]

Please let me know if you need anything further.

[redacted]

Distribution:

TO: [redacted]

CC:
CC:
CC:
CC:
CC:
CC:

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 7/23/99 4:19:13 PM
From: [redacted]
To: See Below
Subject: More on mifepristone/misoprostol

Dear colleagues:

Please keep dispute resolution in mind as the issues that are mentioned in [redacted] e-mail evolve. That is, if Searle disagree with decisions on this issue made by the Division, and want to appeal, then this is subject to the dispute resolution process. This is being tracked under FDAMA.

The dispute resolution process is described in the Draft Guidance for Industry: "Formal Dispute Resolution: Appeals Above the Division Level" (Issued 3/1999, Posted 3/18/1999). This draft guidance is available on the CDER Web site (it's a draft FDAMA guidance).

[redacted] kindly reminded me of this in a phone conversation this afternoon.

Thank you.

[redacted]

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

NDA 19-268

AUG 15 1997

G.D. Searle & Co.
Attention: Mr. Robert Bogomolny
Legal Council
4901 Searle Parkway
Skoki, IL 60077

Dear Mr. Bogomolny:

Please refer to your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, Cosmetic Act for Cytotec (misoprostol) Tablets.

We also refer to the meeting between representatives of your firm and FDA on August 28, 1996.

As requested, a draft copy of our minutes of that meeting is enclosed. We plan to finalize these minutes on September 30, 1997.

If you have any questions, please contact ——— Consumer Safety Officer, at ———

Sincerely,

/S/ 8-13-97

———

———

Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE
August 28, 1996 draft meeting minutes

cc:
Original NDA 20-687 (HFD-180/ NDA19-268)
HFD-580/Div. Files
HFD-580/CSO/ ———
HFD-580/ ———
HFD-580 ——— 8.12.97/searle.gc

GENERAL CORRESPONDENCE (MINUTES SENT)

Printed by [redacted]

Electronic Mail Message

Date: 28-Sep-2000 05:31pm
From: STIKA, CATHERINE S
catherine.s.stika@chi.monsanto.com
Dept:
Tel No:

O: [redacted]

ubject: FW: the RU decision

ops, I thought your email address would follow the same format as [redacted]
ate

-----Original Message-----
From: STIKA, CATHERINE S
Sent: Thursday, September 28, 2000 4:24 PM
To: [redacted]
Subject: the RU decision

To all

My Searle office is in the midst of the the drug info phone group for the old Searle product line. Do you have any idea of how crazy it has been here today? I just got called over to read their internal email that the

[redacted]

I think the current Cytotec patent extends until 2002. I was talking to

[redacted]

I cant wait to get home and watch the news.

Cate Stika

Electronic Mail Message

Date: 9/15/00 3:25:01 PM
From: [redacted]
Subject: Misoprostol "stat" FOI request

1) 25 unduplicated cases of uterine rupture with misoprostol received by FDA between 11/1/97 [redacted] document covered cases through 10/31/97) to present. 17 of these were from ten literature articles.
2) [redacted]

MIFEPRISTONE NDA

STATUS

Brief Summary of Publicly Available Information

- The sponsor, The Population Council, Inc., initially submitted an NDA for Mifepristone (RU-486) in March 1996.

- The NDA contained the results of two large clinical trials performed in the European Union and preliminary data from an on-going U.S. trial in support of the indication: Medical termination of intrauterine pregnancy through 49 days' gestational age. (Pregnancy is dated from the first day of the last menstrual period).

- The NDA was reviewed on a 6-month regulatory clock, and issues were presented and discussed at an open advisory committee meeting in July 1996. The sponsor received an approvable letter on September 18, 1996, which conveyed the conclusion that the drug, used under specific conditions, was found safe and effective for the indication.

- The letter also outlined various deficiencies that required response before the application could be approved, including a list of chemistry and manufacturing controls requirements as well as label modifications and postmarketing surveillance commitments.

- The advisory committee discussion included recommendations for labeling, postmarketing surveillance, and a well-controlled distribution system for the drug. The committee also requested the opportunity to review the final U.S. study report once available.

Brief Summary of Non-Public Information

Printed by [redacted]

Electronic Mail Message

ensitivity: COMPANY CONFIDENTIAL

Date: 30-Jul-1996 02:13pm
From: [redacted]

Dept: HFD-180 PKLN [redacted]
Tel No: [redacted] FAX t-

O: [redacted]

C: [redacted]
C: [redacted]

ubject: Cytotec/RU-486 Labeling Meeting with Searle

f it is at all possible, the ODE III [redacted] would ike to attend this meeting. Please call [redacted] secretary [redacted] when scheduling the meeting. Thanks.

APPEARS THIS WAY
ON ORIGINAL

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 30-Jul-1996 03:21pm
From: [redacted]

Dept: HFD-580 PKLN
Tel No: [redacted] FAX 301-827-4267

TO: See Below
Subject: Cytotec meeting with Searle

Hi there,

The meeting with Searle to discuss the impact of the Mifepristone label on them and their Misoprostol label has been scheduled for August 28, 1996, at 1:30 in the Chesepeake room on the 3rd floor of the Parklawn building.

If you have any questions, please contact [redacted] at [redacted]

Distribution:

TO: [redacted]	(FDAEM)	[redacted]
TO: [redacted]	(FDAEM)	[redacted]
TO: [redacted]	(FDAEM)	[redacted]
TO: [redacted]		[redacted]
TO: [redacted]		[redacted]
TO: [redacted]		[redacted]
TO: [redacted]		[redacted]
TO: [redacted]		[redacted]
TO: [redacted]		[redacted]
TO: [redacted]		[redacted]

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 10/8/99 10:59:09 AM
From: [redacted]
Subject: FWD: draft agenda for the RU486 meeting today.

I noticed you weren't cc'd.

[redacted]

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 10/8/99 10:51:26 AM
From: [redacted]
Subject: draft agenda for the RU486 meeting today.

Hi:

I put together a quick draft of an agenda for the 1:00 meeting on RU486.

If you want to make any additions, call me [redacted]

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 10/8/99 11:05:46 AM
From: [redacted]
Subject: Re: FWD: draft agenda for the RU486 meeting today.

>I noticed you weren't cc'd.
>
> [redacted]

Whoops, sorry I didn't copy you. Here is an additional document I just sent [redacted] FYI.

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 3/18/99 9:25:50 AM
From: [redacted]
To: [redacted]
To: [redacted]
To: [redacted]
Cc: [redacted]
Subject: Re: FWD: Re: Cytotec/Arthrotec Labeling Supplements for Uterine R

[redacted]

Yes, go ahead with the sign-off, etc. I have seen [redacted] e-mail and I also called her this morning for additional clarification. I'll fill you in when I see you. Thank you.

[redacted]

...

*
*
*
*
*
*
* Attached is the HFD-580 medical officer's reply to your concerns about the
* effect of the Cytotec/Arthrotec changes on the RU-486 labeling. I've finalized
* the labeling, approval letter, the letter with comments on the "Dear Doctor"
* letter, and the marked-up draft talk paper for [redacted] signature. I will
* forward copies of them to you and the Press Office before sending them to
* Searle. Should I go ahead with this after [redacted] signs off?

APPEARS THIS WAY
ON ORIGINAL

Printed by [redacted]

Electronic Mail Message

ensitivity: COMPANY CONFIDENTIAL

Date: 18-Mar-1999 09:25am
From: [redacted]

Dept: HFD-103 PKLN [redacted]
Tel No: [redacted] FAX 301-480-3761

'O: [redacted]
'O: [redacted]
'O: [redacted]

:C: [redacted]

ubject: Re: FWD: Re: Cytotec/Arthrotec Labeling Supplements for Uterine R

[redacted]

'es, go ahead with the sign-off, etc. I have seen [redacted] e-mail
ınd I also called her this morning for additional clarification. I'll
:ill you in when I see you. Thank you.

[redacted]

'**

'
'
'
'
'
'
* Attached is the HFD-580 medical officer's reply to your concerns about
the
* effect of the Cytotec/Arthrotec changes on the RU-486 labeling. I've
finalized
* the labeling, approval letter, the letter with comments on the "Dear
Doctor"
* letter, and the marked-up draft talk paper for [redacted]
signature. I will
* forward copies of them to you and the Press Office before sending them
to
* Searle. Should I go ahead with this after [redacted] signs off?

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 3/16/99 2:15:58 PM
From: [redacted]
To: [redacted]
Subject: FWD: Cytotec/Arthrotec Labeling Supplements for Uterine Rupture

[redacted]

FYI. As we discussed.

[redacted]

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 3/16/99 2:16:43 PM
From: [redacted]
To: [redacted]
Subject: FWD: RE: Cytotec/Arthrotec Labeling Supplements for Uterine Rupture

FYI.

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 3/17/99 7:48:07 AM
From: [redacted]
Subject: RE: Cytotec/Arthrotec Labeling Supplements for Uterine Rupture

With regard to your question about the current status of RU-486, the application remains approvable. <

>

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 3/18/99 8:56:20 AM
From: [redacted]
To: [redacted]
Subject: FWD: Re: Cytotec/Arthrotec Labeling Supplements for Uterine R

FYI.

APPEARS THIS WAY
ON ORIGINAL

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 16-Mar-1999 01:26pm
From: [redacted]
Dept: HFD-580 PKLN [redacted]
Tel No: [redacted] FAX 301-827-4267

TO: [redacted]

CC: [redacted]
CC: [redacted]
CC: [redacted]

Subject: RE: Cytotec/Arthrotec Labeling Supplements for Uterine Rupture

With regard to your question about the current status of RU-486, the application remains approvable.

APPEARS THIS WAY
ON ORIGINAL

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 01-Oct-1996 08:23am
From: [redacted]

Dept: HFD-580 PKLN [redacted]
Tel No: [redacted] FAX 301-827-4272

TO: See Below
Subject: meeting minutes from discussion with Searle (cytotec)

On September 9, 1996, I sent each of you a copy of the draft meeting minutes from our meeting with Searle in which we discussed the cross labeling issues regarding their product (Cytotec) and RU-486.

We agreed at the meeting to send the sponsor a copy of the draft meeting minutes once they had been signed off by everyone here. If you have received this E-mail, I have not yet received your comments.

I would like to get these minutes final typed as quickly as possible. Please review them and return them to HFD-580 [redacted] before October 14. If you are unable to locate your copy please call me at [redacted] and I will send you another copy right away.

Thank you for your attention

[redacted]

Distribution:

TO: [redacted]
TO:
TO:
TO:
TO:
TO:
TO: [redacted] (FDAEM) [redacted]

APPEARS THIS WAY
ON ORIGINAL

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE:

FROM: _____ Postmarketing Safety Evaluator
Reports Evaluation Branch, HFD-735

THROUGH: _____ /S/ 6/16/98
Division of Pharmacovigilance and Epidemiology, HFD-730

TO: _____
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

TO: _____
Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Monitored Adverse Reaction Report: Misoprostol (Cytotec®)
Uterine rupture and selected serious events associated with use during pregnancy

Background and Introduction

Two MedWatch direct reports of uterine rupture and recent literature reports of serious adverse events occurring during use of misoprostol (Cytotec®, Searle) were received and led to a review of similar events. The FDA Spontaneous Reporting System was searched for these reports.

Misoprostol (Cytotec®, Searle, U.S.) is a synthetic prostaglandin E1 analog. It was approved for use in the U.S. as a 200mcg (0.2mg) tablet on December 27, 1988 and a 100mcg (0.1mg) tablet was approved September 21, 1990. The U.S. approved indication for use is prevention of NSAID (nonsteroidal anti-inflammatory drugs, including aspirin)-induced gastric ulcers in patients at high risk of complications of gastric ulcers.

The recommended adult oral dose of Cytotec for the prevention of NSAID-induced gastric ulcers is 200 mcg four times daily with food. If this dose cannot be tolerated, a dose of 100 mcg can be used. Cytotec should be taken for the duration of NSAID therapy as prescribed by the physician. Cytotec should be taken with a meal, and the last dose of the day should be at bedtime. Adjustment of the dosing schedule in renally impaired patients is not routinely needed, but dosage can be reduced if the 200-mcg dose is not tolerated.

Misoprostol also has the expected actions of a prostaglandin on the uterus. Misoprostol produces uterine contractions and may endanger pregnancy by causing partial or complete expulsion of uterine contents and produce increased uterine bleeding as well. These clinical pharmacodynamic actions have been the basis for off-label uses such as cervical ripening, induction of labor at term, and induction of abortion. These clinical pharmacodynamic actions have been the basis for off-label uses such as cervical ripening, induction of labor at term, and induction of abortion[1,2,3,4,5,6,7]. No NDA supplements with formal clinical

[1] Sanchez-Ramos L, Kaunitz AM, Wears RL, Delke I, Gaudier FL. Misoprostol for cervical ripening and labor induction: a meta-analysis. Obstet Gynecol 1997 Apr; 89(4):633-42.

[2] Gottschall DS, Borgida AF, Mihalek JJ, Sauer F, Rodis JF. A randomized clinical trial comparing misoprostol with prostaglandin E2 gel for preinduction cervical ripening. Am J Obstet Gynecol 1997 Nov; 177(5):1067-70.

[3] Bauer TA, et al. Vaginal misoprostol for term labor induction. Annal Pharmacother 1997 Nov; 31:1391-3.

[4] Gold M, Luks D, Anderson MR. Medical options for early pregnancy termination. Am Fam Phys 1997 Aug: 533-8.

[5] Grimes DA. Medical abortion in early pregnancy: a review of the evidence. Obstet Gynecol 1997 May; 89 (5 part 1):790-6.

trials have been submitted by the original NDA sponsor for any of these uses, however.

The manufacturer has included extensive warnings and precautions concerning these uterine stimulatory effects in pregnancy in the current product labeling for Cytotec® . These extensive warnings are excerpted in Attachment #1.

Pharmacologically Related U.S. Products

Another prostaglandin E, dinoprostone or PGE2, is approved for obstetrical uses in the United States. Specifically, these products are Prostin E2® 20mg vaginal suppositories (Pharmacia & Upjohn), Prepidil® gel for endocervical application (Pharmacia & Upjohn), and Cervidil® 10mg vaginal insert (Forest Pharmaceuticals).

Prostin E2® suppositories are approved for termination of pregnancy from the 12th through the 20th gestational week, evacuation of the uterine contents in the management of missed abortion or intrauterine fetal death up to 28 weeks of gestational age, and management of nonmetastatic gestational trophoblastic disease (benign hyatidiform mole). Uterine rupture appears in the labeling for Prostin E2®, as well as a GENERAL PRECAUTION concerning use with caution in patients with compromised (scarred) uteri. This product has been used extensively to extemporaneously compound a cervical and vaginal gel for other obstetric purposes, particularly cervical ripening prior to labor induction at term[9,10].

Prepidil® gel has the approved indication of ripening an unfavorable cervix in pregnant women at or near term with a medical or obstetrical need for labor induction. Uterine rupture appears in this product label as well as a CONTRAINDICATION for use in patients in whom oxytocic drugs are generally contraindicated or where prolonged contractions of the uterus are considered inappropriate, such as cases with a history of cesarean section or major uterine surgery, among others.

Cervidil® vaginal insert is a polymeric slab contained within a polyester pouch of retrieval system, part of which is also a long tape. This product is designed to deliver dinoprostone at approximately 0.3mg/hr and can be removed at the conclusion of therapy or in the event of an adverse reaction. This product is indicated for the initation and/or continuation of cervical ripening in patients at or near term in whom there is a medical or obstetrical indication for the induction of labor. uterine hyperstimulation is a labeled event. A similar contraindication to use in patients with history of C-section or major uterine surgery also appears in this product label.

Medical Literature

MEDLINE was searched for any citation indexed to "misoprostol" from 1985 through 1997. A total of 1042 citations were retrieved using this strategy, approximately 200 of which concerned obstetric and gynecologic use or effects of misoprostol. Citations and/or abstracts were reviewed for potential cases of serious adverse events[11]. Six (6) citations were most relevant to this review, all of which had previously been reported to the SRS by the manufacturer.

Selection of Cases

The FDA Spontaneous Reporting System (SRS) database was searched for reports of serious gynecologic events occurring during the use of misoprostol. This search was conducted using the COSTART terms listed in the table on the following page, based upon the frequency at which they occurred in the entire database of misoprostol SRS reports.

A total of 220 reports were obtained with this search strategy as of 10/31/97, 48 of which had a serious outcome, and 7

[6] Wiebe ER. Abortion induced with methotrexate and misoprostol: a comparison of various protocols. Contraception 1997; 55:159-63.

[7] Yapar EG,et al. Second trimester pregnancy termination including fetal death:comparison of five different methods. Eur J Obstet Gynecol 1996; 69:97-102.

[8] Nishioka FY. Prostaglandin E2 preparations for preinduction cervical ripening: pharmacy considerations. J Reprod Med 1993; 38(1 suppl):83-8.

[9] Bernstein EP. Therapeutic considerations for preinduction cervical ripening with intracervical prostaglandin E2 gel. J Reprod Med 1993; 38(1 supp l):73-7.

[10] Gauger LJ. Extemporaneous preparation of a dinoprostone gel for cervical ripening. Am J Hosp Pharm 1983 Dec; 40(12):2195-6.

[11] Reports of congenital anomalies were not included in this report.

were fatalities.[12] The number of reports per COSTART term is indicated with each COSTART term, followed by the number with a serious outcome (Ser) and the number with a fatal outcome. All reports with at least one of the COSTARTs which appear shaded below were retrieved and reviewed. And, with the exception reports of congenital anomalies, any report with a Serious or Fatal outcome was also retrieved and reviewed. These reports were then screened for unexpected and/or severe outcome were included. ***A total of 17 unduplicated cases are summarized by this review.***

COSTART	Reports: Tot/Ser/Fatal	COSTART	Reports: Tot/Ser/Fatal	COSTART	Reports: Tot/Ser/Fatal
ABORTION	13/6/1	HEM VAGINAL	47/4/0	PREGN UNINTEND	4/0/0
ANOMALY CONGEN	30/27/3	LABOR ABNORM	1/0/0	STILLBIRTH	1/1/0
CERVIX DIS	1/0/0	MENORRHAGIA	25/1/0	UG DIS	4/0/0
DYSMENORRHEA	15/0/0	MENS DIS	11/1/0	UTER DIS	4/1/1
FETAL DIS	2/2/0	METRORRHAGIA	40/0/0	UTER RUPT	7/5/0
HEM PREGN	7/2/0	PAIN PELVIC	13/0/0	UTER SPASM	5/1/0
HEM UTER	40/2/0	PREGN DIS	7/4/0		

[12] Note that these numbers may include duplicate cases and overlap may exist since up to 4 COSTARTs may be listed per report. Reports received since 11/1/97 were not included in this review, due to the AERS database conversion and implementation process.

Summary of cases

This series was comprised of 17 cases, which are summarized below and detailed specifically as Attachment #2. Redacted copies of these 17 cases are also included as Attachment #3.

Uterine rupture cases (n=10)

A total of ten (10) individual cases of uterine rupture were reported to the SRS. The country of origin of each report and number of cases were US (5), Brazil (3), Scotland (1), and South Africa (1). Five cases were literature reports.
The age of the patients where stated was 26 years old (n=2), 27, 34, 35. Age was not stated in 5 cases. Three patients were known to have a history of uterine surgery and/or previous delivery by C-section.

The stated indication for use of misoprostol was pregnancy termination/induction of abortion (n=7), cervical "ripening" and induction of labor (n=3). The doses of misoprostol employed for pregnancy termination/induction of abortion were 100mcg, 400mcg, and 1200mcg vaginal. Dose was unknown in 4 cases. Two reports stated that patients were on other medications dinoprostone, mifepristone. Among these patients, 6 of 7 required hospitalization or extended stay of hospitalization. One outcome was unknown. Three patients required surgery: 2 hysterectomies, 1 surgical repair of the uterine wall.

The dose of misoprostol employed for cervical ripening and induction of labor was 2-25mcg vaginal doses 3-4 hours apart in 2 cases. Dose was unknown in 1 case. No other medications were listed. Among these patients, 2 of 3 were hospitalized. One outcome was unknown. Two patients required hysterectomies, one of which also resulted in 1 fetal death, 1 surviving infant.

Other serious events (n=7)

A variety of other serious events occurred. The country of origin of these reports was U.S. (6) and Singapore (1). Two overdoses were reported with primary symptoms being hyperthermia, acidosis, fetal death. Three termination of pregnancy/abortion reports resulted in severe hemorrhage and one abortion in which a 23-week old fetus was alive and subsequently expired. One patient was given misoprostol for prophylaxis of postpartum hemorrhage and developed severe hyperthermia (800mcg oral). Another patient was given misoprostol for cervical ripening/induction of labor at 41 weeks gestation. In this case, amniotic fluid embolism, maternal and fetal death occurred.

Discussion

This review summarizes cases of uterine rupture and other serious adverse events associated with off-label use during pregnancy that have been reported to the FDA Spontaneous Reporting System in which misoprostol (Cytotec®) was considered the suspect drug. Based upon a review of indications for use from NDTI, a significant proportion of misoprostol prescribing in patients in the child-bearing age range (15 - 44 y.o.) is for gynecologic and obstetric uses. The medical literature describes this pattern of use.

Although the manfacturer of this product, Searle, U.S.,

/S/

Concur:

/S/

Group Leader

/S/

APPEARS THIS WAY
ON ORIGINAL

cc: HFD-180
HFD-180
HFD-730
HFD-733
HFD-735

Attachment #1: Relevant excerpts from Cytotec® (misoprostol) tablets current product labeling (Revision date 8/8/95)

DESCRIPTION

****

* CONTRAINDICATIONS AND WARNINGS *
* Cytotec (misoprostol) is contraindicated, *
* because of its abortifacient property, in *
* women who are pregnant. (See Precautions.) *
* Patients must be advised of the *
* abortifacient property and warned not to *
* give the drug to others. Anecdotal reports, *
* primarily from Brazil, of congenital *
* anomalies and reports of fetal death *
* subsequent to misuse of misoprostol as an *
* abortifacient have been received. Cytotec *
* should not be used in women of childbearing *
potential unless the patient requires *
* nonsteroidal anti-inflammatory drug (NSAID) *
* therapy and is at high risk of *
* complications from gastric ulcers *
* associated with use of the NSAID, or is at *
* high risk of developing gastric ulceration. *
* In such patients, Cytotec may be prescribed *
* if the patient *
* --has had a negative serum pregnancy test *
* within 2 weeks prior to beginning therapy. *
* --is capable of complying with effective *
* contraceptive measures. *
--has received both oral and written *
* warnings of the hazards of misoprostol, the *
* risk of possible contraception failure, and *
* the danger to other women of childbearing *
potential should the drug be taken by *
* mistake. *
* --will begin Cytotec only on the second or *
third day of the next normal menstrual *
* period. *

APPEARS THIS WAY
ON ORIGINAL

ACTIONS/CLINICAL PHARMACOLOGY:

PHARMACOKINETICS:

PHARMACODYNAMICS:

UTERINE EFFECTS: Cytotec has been shown to produce uterine contractions that may endanger pregnancy. (See Contraindications and Warnings.) In studies in women undergoing elective termination of pregnancy during the first trimester, Cytotec caused partial or complete expulsion of the uterine contents in 11% of the subjects and increased uterine bleeding in 41%.

CONTRAINDICATIONS:

****

* CONTRAINDICATIONS AND WARNINGS *
* Cytotec (misoprostol) is contraindicated, *
* because of its abortifacient property, in *

* women who are pregnant. (See Precautions.) *
* Patients must be advised of the *
* abortifacient property and warned not to *
* give the drug to others. Cytotec should not *
* be used in women of childbearing potential *
* unless the patient requires nonsteroidal *
* anti-inflammatory drug (NSAID) therapy and *
* is at high risk of complications from *
* gastric ulcers associated with use of the *
NSAID, or is at high risk of developing *
* gastric ulceration. In such patients, *
* Cytotec may be prescribed if the patient *
* --has had a negative Serum pregnancy test *
* within two weeks prior to beginning *
* therapy. *
* --is capable of complying with effective *
* contraceptive measures. *
* --has received both oral and written *
* warnings of the hazards of misoprostol, the *
* risk of possible contraception failure, and *
* the danger to other women of childbearing *
* potential should the drug be taken by *
* mistake. *
* --will begin Cytotec only on the second or *
* third day of the next normal menstrual *
* period. *

WARNINGS:

APPEARS THIS WAY
ON ORIGINAL

****
* CONTRAINDICATIONS AND WARNINGS *
* Cytotec (misoprostol) is contraindicated, *
* because of its abortifacient property, in *
* women who are pregnant. (See Precautions.) *
* Patients must be advised of the *
* abortifacient property and warned not to *
* give the drug to others. Anecdotal reports, *
* primarily from Brazil, of congenital *
* anomalies and reports of fetal death *
* subsequent to misuse of misoprostol as an *
* abortifacient have been received. Cytotec *
* should not be used in women of childbearing *
potential unless the patient requires *
* nonsteroidal anti-inflammatory drug (NSAID) *
* therapy and is at high risk of *
* complications from gastric ulcers *
* associated with use of the NSAID, or is at *
* high risk of developing gastric ulceration. *
* In such patients, Cytotec may be prescribed *
* if the patient *
* --has had a negative serum pregnancy test *
* within 2 weeks prior to beginning therapy. *
* --is capable of complying with effective *
* contraceptive measures. *
* --has received both oral and written *
* warnings of the hazards of misoprostol, the *
* risk of possible contraception failure, and *
* the danger to other women of childbearing *
* potential should the drug be taken by *

* mistake. *
* --will begin Cytotec only on the second or *
* third day of the next normal menstrual *
* period. *
****

PRECAUTIONS:

INFORMATION FOR PATIENTS: Cytotec is contraindicated in women who are pregnant, and should not be used in women of childbearing potential unless the patient requires nonsteroidal anti-inflammatory drug (NSAID) therapy and is at high risk of complications from gastric ulcers associated with the use of the NSAID, or is at high risk of developing gastric ulceration. Women of childbearing potential should be told that they must not be pregnant when Cytotec therapy is initiated, and that they must use an effective contraception method while taking Cytotec.

See boxed CONTRAINDICATIONS AND WARNINGS.

Patients should be advised of the following:

Cytotec is intended for administration along with nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, to decrease the chance of developing an NSAID-induced gastric ulcer.

Cytotec should be taken only according to the directions given by a physician.

If the patient has questions about or problems with Cytotec, the physician should be contacted promptly.

THE PATIENT SHOULD NOT GIVE CYTOTEC TO ANYONE ELSE. Cytotec has been prescribed for the patient's specific condition, may not be the correct treatment for another person, and may be dangerous to the other person if she were to become pregnant.

The Cytotec package the patient receives from the pharmacist will include a leaflet containing patient information. The patient should read the leaflet before taking Cytotec and each time the prescription is renewed because the leaflet may have been revised.

Keep Cytotec out of the reach of children.

SPECIAL NOTE FOR WOMEN: CYTOTEC MUST NOT BE USED BY PREGNANT WOMEN. CYTOTEC MAY CAUSE MISCARRIAGE. MISCARRIAGES CAUSED BY CYTOTEC MAY BE INCOMPLETE, WHICH COULD LEAD TO POTENTIALLY DANGEROUS BLEEDING, HOSPITALIZATION, SURGERY, INFERTILITY, OR MATERNAL OR FETAL DEATH.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: There was no evidence of an effect of Cytotec on tumor occurrence or incidence in rats receiving daily doses up to 150 times the human dose for 24 months. Similarly, there was no effect of Cytotec on tumor occurrence or incidence in mice receiving daily doses up to 1000 times the human dose for 21 months. The

APPEARS THIS WAY
ON ORIGINAL

mutagenic potential of Cytotec was tested in several In Vitro assays, all of which were negative.

Misoprostol, when administered to breeding male and female rats at doses 6.25 times to 625 times the maximum recommended human therapeutic dose, produced dose-related pre- and post-implantation losses and a significant decrease in the number of live pups born at the highest dose. These findings suggest the possibility of a general adverse effect on fertility in males and females.

PREGNANCY: PREGNANCY CATEGORY X. See boxed CONTRAINDICATIONS AND WARNINGS.

NONTERATOGENIC EFFECTS: Cytotec may endanger pregnancy (may cause miscarriage) and thereby cause harm to the fetus when administered to a pregnant women. Cytotec produces uterine contractions, uterine bleeding, and expulsion of the products of conception. Miscarriages caused by Cytotec may be incomplete. In studies in women undergoing elective termination of pregnancy during the first trimester, Cytotec caused partial or complete expulsion of the products of conception in 11% of the subjects and increased uterine bleeding in 41%. Anecdotal reports, primarily from Brazil, of congenital anomalies and reports of fetal death subsequent to misuse of misoprostol as an abortifacient have been received (see Contraindications and Warnings.) If a woman is or becomes pregnant while taking this drug, the drug should be discontinued and the patient apprised of the potential hazard to the fetus.

TERATOGENIC EFFECTS: Cytotec is not fetotoxic or teratogenic in rats and rabbits at doses 625 and 63 times the human dose, respectively.

APPEARS THIS WAY
ON ORIGINAL

NURSING MOTHERS: See Contraindications. It is unlikely that Cytotec is excreted in human milk since it is rapidly metabolized throughout the body. However, it is not known if the active metabolite (misoprostol acid) is excreted in human milk. Therefore, Cytotec should not be administered to nursing mothers because the potential excretion of misoprostol acid could cause significant diarrhea in nursing infants.

ADVERSE REACTIONS

The following have been reported as adverse events in subjects receiving Cytotec:

GYNECOLOGICAL: Women who received Cytotec during clinical trials reported the following gynecological disorders: spotting (0.7%), cramps (0.6%), hypermenorrhea (0.5%), menstrual disorder (0.3%) and dysmenorrhea (0.1%). Postmenopausal vaginal bleeding may be related to Cytotec administration. If it occurs, diagnostic workup should be undertaken to rule out gynecological pathology.

PATIENT PACKAGE INSERT:
PATIENT INFORMATION

Read this leaflet before taking Cytotec(R) (misoprostol) and each time your prescription is renewed, because the leaflet may be changed.

Cytotec (misoprostol) is being prescribed by your doctor to decrease the chance of getting stomach ulcers related to the arthritis/pain medication that you take.

Cytotec can cause miscarriage, often associated with potentially dangerous bleeding. This may result in hospitalization, surgery, infertility, or death. DO NOT TAKE IT IF YOU ARE PREGNANT AND DO NOT BECOME PREGNANT WHILE TAKING THIS MEDICINE.

If you become pregnant during Cytotec therapy, stop taking Cytotec and contact your physician immediately. Remember that even if you are on a means of birth control it is still possible to become pregnant. Should this occur, stop taking Cytotec and contact your physician immediately.

Cytotec may cause diarrhea, abdominal cramping, and/or nausea in some people. In most cases these problems develop during the first few weeks of therapy and stop after about a week. You can minimize possible diarrhea by making sure you take Cytotec with food.

Because these side effects are usually mild to moderate and usually go away in a matter of days, most patients can continue to take Cytotec. If you have prolonged difficulty (more than 8 days), or if you have severe diarrhea, cramping and/or nausea, call your doctor.

Take Cytotec only according to the directions given by your physician.

Do not give Cytotec to anyone else. It has been prescribed for your specific condition, may not be the correct treatment for another person, and would be dangerous if the other person were pregnant.

This information sheet does not cover all possible side effects of Cytotec. This patient information leaflet does not address the side effects of your arthritis/pain medication. See your doctor if you have questions.

Keep out of reach of children.

APPEARS THIS WAY
ON ORIGINAL

Attachment #2: Table of cases included for review (n=17)

Mfr. or FDA#	Year of Event(s)– approx	Country	Event(s)	Age (yrs)	Outcome– maternal	Outcome– fetal	Misoprostol dose	Indication for use
UTERINE RUPTURE CASES (n=10)								
940804-SK733	1993	Brazil	**Uterine perforation**	Unk	Hosp	Unk	Unk	Abortion
940804-SK735	1993	Brazil	**Uterine perforation**	Unk	Hosp	Unk	Unk	Abortion
940804-SK736	1993	Brazil	**Uterine perforation**	Unk	Hosp	Unk	Unk	Abortion
961023-SK024	1995	Scotland	Painful contractions, vaginal bleeding, retained placenta, shock, ~4L blood loss, WBC 14.4, aPTT50s, PT18s, 8-cm **uterine rupture.** Hysterectomy, right salpingo-oophorectomy.	26 yrs.	Hosp, hysterectomy, right salpingo-oophorectomy	**Aborted**	2-600mcg vaginal doses, 6hrs apart	Induce abortion
961022-SK848	1996	US	**Uterine rupture.**	Unk	Unk	Unk	Vaginal	Induce abortion
961022-SK850	1996	US	**Uterine rupture.**	Unk	Unk	Unk	Vaginal	Induction of labor
970714-SK994	1996	US	Uterine hyperstimulation resistant to terbutaline rx, **15-cm rupture of posterior uterine wall,** 2L blood loss, fetal bradycardia, hysterectomy w/left salpingo-oophorectomy. Post-op vaginal cuff cellulitis, ileus.	34 yrs.	Hosp, hysterectomy, left salpingo-oophorectomy. Mother, infant d/c 8 days later.	Survived	2-25mcg doses, vaginal ~3 hrs apart	Cervical ripening, induction of labor.
970529-SK651	1997	South Africa	**Ruptured uterus** which required abdominal hysterectomy, 4 units blood.	27 yrs.	Hosp. life-threatening. Hysterectomy.	Unk	400mcg vaginal	Induce abortion
MedWatch 74036	1997	US	**Uterine rupture** on posterior wall, fetus & placenta in abdominal cavity. Emergency C-section w/fetal death.	35 yrs.	Hosp, emergent C-section, hysterectomy	Death	2-25mcg doses, vaginal ~4 hrs apart	Cervical ripening, induction of labor
MedWatch 75822	1997	US	Abdominal pain w/o contractions noted on monitor, vaginal bleeding, **uterine rupture.**	26 yrs.	Hosp, surgery.	N/A	2-50mcg vaginal	Induction of labor, 2° to fetal demise

Other Rx	Medical Hx	Narrative of events/Other information	Literature citation
Unknown	Unk	Demographic review of 102 women.	Coelho HL, et al. Misoprostol: the experience of women in Fortaleza, Brazil. Contraception 1994; 49:101-10.
Unknown	Unk	Demographic review of 102 women.	Coelho HL, et al. Misoprostol: the experience of women in Fortaleza, Brazil. Contraception 1994; 49:101-10.
Unknown	Unk	Demographic review of 102 women.	Coelho HL, et al. Misoprostol: the experience of women in Fortaleza, Brazil. Contraception 1994; 49:101-10.
Mifepristone (RU486) 200mg oral 48 hrs prior, per protocol.	18 weeks gestation. 2 previous vaginal deliveries, one possible spontaneous abortion @5weeks.	Patient received 2 doses, then developed painful uterine contractions ~4hrs following 2nd dose misoprostol. Rx diamorphine IV. Vaginal bleeding, began w/cervical dilation, fetal head palpable. Bleeding, pain persisted w/further analgesia.	Phillips K, Berry C, Mathers AM. Uterine rupture during second trimester termination of pregnancy using mifepristone and a prostaglandin. Eur J Obstet Gynecol 1996; 65:175-6.
Prostin given prior	Unk	Same physician reported 2 cases of uterine rupture. Follow-up attempt unsuccessful.	N/A
Unknown	Unk	Same physician reported 2 cases of uterine rupture. Follow-up attempt unsuccessful.	N/A
Terbutaline	39 weeks gestation. 3 previous vaginal deliveries, D&C 1st trimester spont abortion.	Patient received 2 doses, then developed tachysystole, hyperstimulation w/o cervical dilation. Fetal bradycardia occurred ~5hrs after 2nd dose. vaginal bleeding noted w/fetal head, 2cm dilation. Infant delivered, resuscitated. Uterine rupture tx.	Bennett BB. Uterine rupture during induction of labor at term with intravaginal misoprostol. Obstet Gynecol 1997; 89(5 part 2): 832-3.
None	20 weeks gestation. Hx C-section 10yrs prior.	Ruptured uterus occurred 6 hours following dose.	N/A
Not stated	Gestatnl diabetes, Hx C-section.	Event may have occurred in several minutes when off monitor & moving to L&D. Uterine tissue showed intact C/S scar in anterior wall w/large rupture of posterior wall which was noted to contain multiple transmural fibroids.	N/A
Not stated	38.4 wks gestation. Hx C-section.		N/A

OTHER CASES w/SEVERE OUTCOME (n=7)								
900122-SK323 and 900122-SK545	1990	US	Overdose, malignant hyperthermia, lactic acidosis, abortion, CPK inc (~6000 peak), vaginal hemorrhage, uterine tetanic contractions. Fetal death, abortion.	18/19 yrs	Hosp. Sx resolved after 6 hours	**Death.** Diffuse ecchymosis noted on autopsy.	6000mcg, oral	Possible suicide attempt (not pt's med)
900105-SK567	1990	US	Severe vaginal bleeding, pelvic pain, cervical effacement, D&C	37 yrs.	Recovered. D&C performed since fetal tissue at cervix.	**Aborted**	1200mcg oral	Induce abortion
900522-SK586	1990	US	Abortion induced at 23 weeks @home, per mother fetus "drew a breath". Both transported to hospital where fetus pronounced dead.	Unk	Hosp, assume recovered	**Death**	Unknown oral dose	Induce abortion
MedWatch 22753	1994	US	Hemorrhage, Hgb 4.5. Surgery required.	32 yrs.	Hosp, surgery required	Unk	Unk	Induce abortion
950707-SK495	1995	US	Overdose, shaking, chills, cramping of abdomen & extremities, tetanic uterine contractions, emesis, confusion, hyperthermia, hypotension, metabolic acidosis, CPK ~3000, fibrinogen 553-327mg/dL, impending DIC, fetal death.	25 yrs	Hosp, emergent C-section. Sx resolved ~15hrs. following OD.	**Death,** small subarachnoid hem on autopsy.	6000mcg vaginal & 600mcg oral	?Induce, shorten duration of labor.
970527-SK452	1997	US	Sudden collapse, seizures, respiratory arrest, death (maternal & fetal). Autopsy showed "Amniotic fluid embolism".	33 or 41 yrs	Death	**Death**	100mcg vaginal	Cervical ripening, induction of labor
971113-SK133	1997	Singapore	Malignant hyperthermia (peak 41.9C rectal), tachycardia, CPK inc first postnatal day (4715IU/L). No myoglobinuria noted.	20 yrs.	Recovered w/cooling 3 hrs, 40mins. Discharged 3rd postnatal day.	N/A	800mcg oral	Prophylaxis post-partum hemorrhage

Stelazine 8mg	31 weeks gestation	Pt intentionally ingested misoprostol, Stelazine in possible suicide attempt. Seen in ER 2 hours later w/uterine contractions, vaginal bleeding, absent fetal heart tones. Aborted fetus, developed hypoxia, lactic acidosis, inc CPK, hyperthermia (105.8).	Bond GR, Van Zee A. Intentional misprostol (Cytotec) overdosage in pregnancy. Vet Hum Toxicol 1990; 32(4):352 and Overdosage of misoprostol in pregnancy. Am J Obstet Gynecol 1994; 171:561-2.
Advil, vitamins listed. Miso belonged to relative.	10/11 weeks gestation. Normal exam, fetal heartbeat detected at initiation of hosp visit.	Patient took misoprostol in a.m. to induce abortion. Changed her mind couple hrs later, went to hospital. Normal exam in a.m., vaginal bleeding began 12N. Mid-afternoon sx worsened, was admitted. D&C performed ~1a.m.	
None	23 weeks gestation. No other info.	Coroner's office report.	
Mifepristone (RU486)--not available in US?	Unknown	Minimal info provided.	
Tox screen neg	36 weeks gestation	Self-adminstered 2 slurries of tabs crushed in vaginal lubricant. Between initial 20 & next 10 tab vaginal doses, had mild contractions, noted fetal movt. Presented to ER 3 hrs later. Fetal heart tones not detected. C-section. Patient required intubation.	Ford M et al. Acute intravaginal misoprostol toxicity with fetal demise (NACCT abstract). J Toxicol Clin Tox 1996; 34(5): 570 and Austin J et al. Acute intravaginal misoprostol toxicity with fetal demise. J Emerg Med 1997; 15(1):61-64.
Unknown	41 wks+ gestation. NPMH of significance, NKA. Nonsmoker, no ETOH.	Pt given misoprostol for cervical ripening, induction of labor. Experienced gradual onset of labor w/rupture of membranes ~6.5hrs later. At 10hrs, sudden collapse w/sz, resp arrest, death. Fetal death. Autopsy noted "Amniotic fluid embolism".	N/A
None	Postpartum period of normal delivery @41 weeks gestation. Previously healthy.	Within 13 minutes of oral intake, developed chills, rigors. Temperature axillary 36.8C, temp & BP nl. Warmed but chills continued. 90 mins later became restless, disoriented w/temp 41.9C rectal, pulse 180. Cooling measures brought temp to 37.3C ~3.75hrs.	Seng Chong Y et al. Severe hyperthermia following oral misoprostol in the immediate postpartum period. Obstet Gynecol 1997; 90(4 part 2):703-4.

Attachment #3: Original case reports (n=17)

APPEARS THIS WAY
ON ORIGINAL

Searle
5200 Old Orchard Road
Skokie, Illinois 60077
Telephone 708 470 6025
Fax 708 967 2032

Robert L. Bogomolny
Corporate Senior Vice President,
General Counsel and Corporate Secretary

September 9, 1996

CONFIDENTIAL
This document Contains Trade Secret
and/or Confidential Commercial Information
Exempt From Public Disclosure
Pursuant to 21 C.F.R. § 20.61 and 21 U.S.C. § 331(j)

Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research (HFD-180)
Food and Drug Administration
Document Control Room 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

Attn: [redacted]

RE: NDA 19-268
Cytotec®

Dear [redacted]

G. D. Searle appreciates the opportunity to have met with you and your colleagues on August 28 to discuss issues related to the inclusion of Cytotec (misoprostol) in the Population Council's pending NDA for mifepristone. We are currently working to develop some of the ideas discussed at that meeting, and plan to pursue those ideas further with FDA in the near future. In the interest of time, however, I am writing now to provide Searle's preliminary views on one of the matters discussed at our meeting, namely the labeling of the pending mifepristone product.

As I noted at the meeting, Searle believes it should have the chance to review the labeling of mifepristone prior to final approval in order to ensure that any references to misoprostol in that labeling are accurate and appropriate, and that Searle's interests in connection with the use of its drug under another sponsor's NDA are protected as much as possible under the circumstances. Accordingly, our request for such a review stands. In advance of that review, however, we wish to set forth here certain elements we believe should be reflected in mifepristone's labeling as it relates to misoprostol. This discussion is without prejudice to Searle's future ability to comment on the labeling of

mifepristone, or to pursue further with FDA other matters raised at the August 28 meeting or any other issue that may arise in connection with the inclusion of misoprostol in the pending mifepristone NDA.

One of our primary concerns about the mifepristone label, as I mentioned at our meeting, has to do with references to misoprostol relating to safety issues such as adverse reactions, warnings, and precautions. As you know, the human safety data base on Cytotec has been developed predominantly on the basis of medium- to long-term use in a patient population that is relatively elderly, with joint disease or other conditions requiring continuing NSAID therapy. Most important, that patient population, with very limited exceptions, has not included women of childbearing age in general, or pregnant women in particular. In contrast, misoprostol together with mifepristone, in a single 400 mcg dose, would be used exclusively in a pregnant female population. As such, the conditions surrounding the use of misoprostol in connection with mifepristone, as contemplated in the Population Council's NDA, are markedly different from the conditions of use reflected in the current Cytotec label.

Therefore, Searle believes that the labeling of mifepristone should not refer to or rely upon Cytotec's labeling for safety information. Indeed, any such cross-reference could be taken as an implied claim that the safety information in Cytotec's label was based on data derived from adequate, well-controlled clinical investigations and/or market experience involving the use of misoprostol as contemplated in the mifepristone label. Such a claim, of course, would not be accurate and might be considered false and misleading.[1] Accordingly, to the extent misoprostol is discussed in the mifepristone labeling, it must be in a self-contained discussion of the relevant warnings, containdications, adverse reactions, and other safety information derived from mifepristone clinical investigations. Such an approach will not only more accurately reflect medical reality, but will also help to avoid the confusion inherent in referring mifepristone users to the label of a drug product (i.e., Cytotec) that contains a black box warning against precisely the use they are planning.

[1] See 21 C.F.R. §201.6(a): "Among representations in the labeling of a drug which render such drug misbranded is a false or misleading representation with respect to another drug...."

As noted above, we may wish to raise other specific issues once we have had a chance to review the current mifepristone draft labeling. In the meantime, we ask that the concerns discussed in this letter be included in FDA's current review of the mifepristone NDA.

Please feel free to call me with any questions.

Sincerely,

Robert L. Bogomolny

cc: [ ]

APPEARS THIS WAY
ON ORIGINAL

RLB\jv

NDA 19-268/S-037

SEP 28 2000

G.D. Searle & Co.
Attention: Mary Jo Pritza
4901 Searle Parkway
Skokie, Illinois 60077

Dear Dr. Pritza:

Please refer to your supplemental new drug application dated August 8, 2000, received August 9, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cytotec (misoprostol) Tablets.

This supplement proposes the following changes to the product labeling: addition of a "Labor and Delivery" subsection to the PRECAUTIONS section and a revision to the "Pregnancy" subsection of the PRECAUTIONS section of the package insert.

We also acknowledge receipt of your facsimiles dated September 22, 2000.

We have completed our review of this supplement and it is not approvable. In addition, it should not have been submitted as a "Changes Being Effected" supplement because some of the items do not strengthen or add to the CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, or ADVERSE REACTIONS already stated in the approved Cytotec labeling (21 CFR 314.70(c)(2)(i). An approved supplement is required for this proposed change prior to distributing the drug product with labeling including this change. Before this supplement may be approved, it will be necessary for you to address the following and submit revised draft labeling:

1. Please remove from the "Labor and Delivery" section all references to the effects of misoprostol use as an abortifacient. The "Labor and Delivery" section required by 21 CFR 201.57(f)(7) is not intended to provide information regarding the use of any drug to induce abortion. Furthermore, you have addressed the abortifacient properties of Cytotec in other sections of your labeling, (e.g., the "Black box", CONTRAINDICATIONS and WARNINGS, CLINICAL PHARMACOLOGY "Uterine effects" subsection, PRECAUTIONS section).

   In addition, the first sentence of the new "Labor and Delivery" section is misleading. The drug mifepristone is now approved in a regimen with misoprostol for termination of pregnancy of 49 days or less.

2. You have added additional information in the "Labor and Delivery" section concerning certain adverse events that were not included in the last approved version of your labeling. The supporting documentation you provided is largely anecdotal in nature and is not sufficient to justify adding them to the label. Furthermore, the second paragraph of the "Labor and Delivery" section does not contain information on when during a pregnancy certain adverse events were reported or which routes of administration were associated with the events. Failure to include this information causes the labeling to be misleading. If there

is additional supporting evidence concerning the use of Cytotec during labor or delivery, please provide it or delete, in your revised draft labeling, these new references to adverse events.

3. To support any revision to the first sentence of the "Pregnancy" subsection of the PRECAUTIONS section, provide supporting data on the number of cases of amniotic fluid embolism which resulted in maternal and fetal death.

To facilitate review of your submission, please provide a highlighted or marked-up copy that shows all of the changes that you are proposing to make to the most recently approved labeling (approved on June 22, 2000).

Finally, please submit your plans to correct the misimpressions that may have been caused by the distribution of the misleading information in the CBE labeling to the health care community.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Distribution of the product with the labeling proposed in this supplemental application is not permitted without prior approval of the application.

If you have any questions, call Alice Kacuba, Regulatory Health Project Manager, at (301) 827-7450.

Sincerely,

SA for LT 9/28/00

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

I talked to —— (OTCOM) again about the calls she's receiving re misoprostol AEs. In order to avoid any misinterpretation we decided on the following for a response:

The caller can obtain copies of AE reports made to the agency through FOI.

One of the sources, listed by regulation, that drug manufacturers have to monitor for reporting purposes is the published literature. The caller could do their own search to learn additional information.

I made a bibliography for the articles you do have in hand (see attached)—most of the work was done so I finished it in case it turns out to be useful to you. This list did not go to OTCOM. ——

/S/
9/29/00

APPEARS THIS WAY
ON ORIGINAL

PUBLISHED LITERATURE RELATED TO ADVERSE EVENTS REPORTED TO FDA FOR MISOPROSTOL

NOTE: This list is NOT all-inclusive of published literature related to use of or adverse events related to misoprostol.

Aguero O, Use of Misoprostol in Obstetrics. Rev Obstet Ginecol Venez. 1996; 56: 67-74.

Bennett BB. Uterine Rupture During Induction of Labor at Term with Intravaginal Misoprostol. Obstetrics & Gynecology. 1997; 89: 832-833.

Bugalho A, Bique G, Machungo F, Bergstrom S. A Comparative Study of Vaginal Misoprostol and Intravenous Oxytocin for Induction of Labour. Gynecol Obstet Invest. 1995; 39: 252-256.

Daisley H. Case Reports: maternal Mortality Following the Use of misoprostol. med Sci law. 2000; 40: 78-82.

Fletcher H, McCaw-Binns A. Rupture of the Uterus With Misoprostol (prostaglandin E1) Used for Induction of Labour. 1998; 18: 184-185.

Gonzalez CH, Marques-Dias MJ, Kim CA, et.al. "Congenital Abnormalities in Brazilian Children Associated With Misoprostol Misuse in First Trimester of Pregnancy" *Lancet.* 1998; 351: 1624-1627.

Jwarah E, Greenhalf JO. Rupture of the Uterus After 800 Micrograms Misoprostol Given Vaginally for Termination of Pregnancy. Brit. J. of Obstetrics & Gynecology. 2000; 107: 807.

Mathews JE, Mathai M, George A. Uterine Rupture in a Multiparous Woman During labor Induction with Oral Misoprostol. Int. J of Gynecology & Obstetrics. 2000; 68: 43-44.

Phillips K., Berry C, Mathers AM. "Uterine Rupture During Second Trimester Termination of Pregnancy Using Mifepristone and a Prostaglandin. European J Obstetrics & Gynecology and Reproductive Biology. 1996; 65: 175-176.

Plaut MM, Schwartz ML, Lubarsky SL. Uterine Rupture Associated with the Use of Misoprostol in the Gravid Patient with a Previous Cesarean Section. Am J Obstet Bynecol. 1999.

Wing DA, Lovett K, Paul RH. Disruption of Prior Uterine Incision Following Misoprostol for Labor Induction in Women with Previous Cesarean Delivery. Obstetrics & Gynecology. 1998; 91: 828-830.

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting by health professionals of adverse events and product problems

CDER Page 1 of 1

Form Approved: OMB No. 0910-0291 Expires 12/31/96
See OMB statement on reverse

FDA Use Only H Pad

Triage unit # 22753

10456778

A. Patient information

1. Patient identifier	2. Age at time of event: / or Date of birth:	3. Sex	4. Weight
— In confidence	32	☐ female ☐ male	____ lbs or ____ kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death ____ (mo/day/yr)
- ☐ life-threatening
- ☒ hospitalization – initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other: ____

3. Date of event (mo/day/yr): 11-30-94

4. Date of this report (mo/day/yr): 1-18-95

5. Describe event or problem

required surgtry - hemorrhage due to chemically-induced abortion

DIVISION OF EPIDEMIOLOGY AND SURVEILLANCE
95 JAN 30 PM 2:27

HEM
ANEMIA HYPOCHROM
ABORTION

6. Relevant tests/laboratory data, including dates

Hgb dropped to a minimum of 4.5

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

REC'D.

JAN 27 1995

MEDWATCH

(2/17/95)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

EX: Mifepristone

#A. Misoprostol

2. Dose, frequency & route used
#1
#2

3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1
#2

4. Diagnosis for use (indication)
#1 Induce an abortion
#2 " "

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
#2 ☐ yes ☐ no ☒ doesn't apply

6. Lot # (if known)
#1
#2

7. Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
#2 ☐ yes ☐ no ☒ doesn't apply

9. NDC # (for product problems only)
- -

10. Concomitant medical products and therapy dates (exclude treatment of event)

-

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

4. Operator of device
- ☐ health professional
- ☐ lay user/patient
- ☐ other: ____

5. Expiration date (mo/day/yr)

6.
model # ____
catalog # ____
serial # ____
lot # ____
other # ____

7. If implanted, give date (mo/day/yr)

8. If explanted, give date (mo/day/yr)

9. Device available for evaluation? (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on ____ (mo/day/yr)

10. Concomitant medical products and therapy dates (exclude treatment of event)

CONFIDENTIAL

E. Reporter (see confidentiality section on back)

1. Name, address & phone #

[redacted]

2. Health professional? ☒ yes ☐ no

3. Occupation: physician

4. Also reported to
- ☐ manufacturer
- ☐ user facility
- ☐ distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☒

Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787 or FAX to: 1-800-FDA-0178

FDA Form 3500 (6/93)

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

BEST POSSIBLE COPY

MIF 008851

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

U.S. REPORTING

SEARLE *Drug Experience Report*

Searle Research and Development

(20)

Approved by FDA on September 17, 1993

MFR report #: 961023-SK024

UF/Case report #:

FDA Use Only

A. Patient information

1. Patient Identifier	2. Age at time of event: 26 Yrs or Date of birth:	3. Sex	4. Weight
--- In confidence		☑ female ☐ male	UNK lbs or ____ kgs

B. Adverse event or product problem

1. ☑ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)

- ☐ death ____ (mm/dd/yy)
- ☐ life-threatening
- ☑ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other: ____

3. Date of event (mm/dd/yy): Unknown

4. Date of this report (mm/dd/yy): NOV 7 1996

5. Describe event or problem

Uterine rupture during second trimester termination of pregnancy using mifepristone and a prostaglandin; K. Phillips, C. Berry, A. M. Mathers; European Journal of Obstetrics & Gynecology and Reproductive Biology 65 (1996): pp. 175-176

A 26-year-old woman was seen with a request for termination of her pregnancy. She estimated that she was about 14 weeks pregnant. Her past obstetric history consisted of one spontaneous vertex delivery at term, one post term induction of labour resulting in spontaneous vertex delivery and one possible spontaneous abortion of 5 weeks gestation at home; curettage of uterine cavity was not performed. She had no history of cervical or uterine surgery. Examination of the abdomen suggested a more advanced pregnancy and gestational age was corrected to 18 weeks following an ultrasound scan. After full counselling the request for termination of pregnancy was agreed (Clause D, Termination of Pregnancy Act, 1991).

She underwent the termination of pregnancy using mifepristone and misoprostol; the procedure was devised from the protocol reported by Thong and Baird. Oral mifepristone (200 mg) is administered under supervision; this is followed 48 h later by misoprostol (600 mcg) vaginally and repeated at 6-h intervals if required. In

(continues...)

6. Relevant test/laboratory data, including dates

Ultrasound:	gestational age 18 weeks.
SURGERY:	emergency removal of placenta.
Laparotomy:	found 8-cm right uterine side wall rupture, with substantial haemorrhage into the broad ligament and abdominal cavity confirmed.

Hysterectomy and right salpingo-oophprectomy performed to control the haemorrhage.

(continues...)

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Past obstetric history consisted of one spontaneous vertex delivery at term, one post term induction of labour resulting in a spontaneous vertex delivery and one possible spontaneous abortion of 5 weeks gestation at home. No history of cervical or uterine surgery.

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#1 MISOPROSTOL

#2

2. Dose, frequency & route used

#1 600.000 MCG Q6H VAG

#2

3. Therapy dates (if unknown, give duration) (from/to or best estimate)

#1 2 DOSES

#2

4. Diagnosis for use (indication)

#1 UNSPECIFIED ABORTION

#2

5. Event abated after use stopped or dose reduced

#1 ☐ yes ☐ no ☑ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)

#1 UNK

#2

7. Exp. date (if known)

#1 UNK

#2

8. Event reappeared after reintroduction

#1 ☐ yes ☐ no ☑ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)

MIFEPRISTONE

G. All manufacturers

1. Contact office - name/address

Dennis P. Miley, M.D.
G.D. Searle and Co.
4901 Searle Parkway
Skokie, Illinois 60077

2. Phone number: (847) 982-8714

3. Report source (check all that apply)

- ☐ foreign
- ☐ study
- ☑ literature
- ☐ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other: ____

4. Date received by manufacturer (mm/dd/yy): OCT 22 1996

5. (A) NDA # 19-268

IND # ____

PLA # ____

pre-1938 ☐ yes

OTC product ☐ yes

6. If IND, protocol #

7. Type of report (check all that apply)

- ☐ 5-day ☑ 15-day
- ☐ 10-day ☐ periodic
- ☑ Initial ☐ follow-up # 0 (Rev No. 0)

8. Adverse event term(s)

UTERINE PERFORATION

9. Mfr. report number

961023-SK024

E. Initial reporter

1. Name, address & phone #

Telephone Nr: Unknown

CONFIDENTIAL

2. Health professional? ☑ yes ☐ no

3. Occupation: MD

4. Initial reporter also sent report to FDA ☐ yes ☐ no ☑ unk

SEARLE Drug Surveillance Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MIF 008852

Adverse Event reports related to Uterine Rupture for Cytotec (misoprostol) [NDA 19-268] from 1985 to September 2000.

Reports from published literature
MedWatch 3189268-X-00-01 (990125-SK821)
MedWatch 3490309-0-00-01 (000405-SK976)
MedWatch 3522918-4-00-02 (000619-SK110)
MedWatch 3188502-X-00-01 (990126-SK156)
MedWatch 3189258-7-00-01 (990126-SK155)
MedWatch 3494592-7-00-01 (000414-SK112)
MedWatch 3521502-6-00-01 (000614-SK250)
MedWatch 3198076-5-00-01 (990209-SK266)
MedWatch 3477116-X-00-01 (000302-SK676)
MedWatch (940804-SK733)
MedWatch (940804-SK735)
MedWatch (961023-SK024)
MedWatch (970714-SK994)

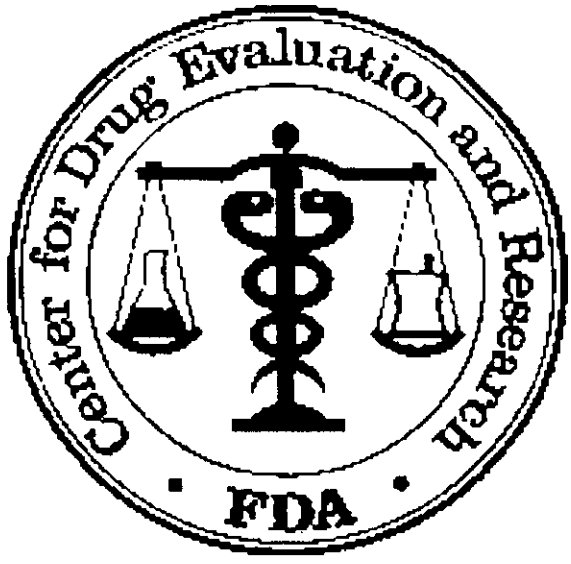
list faxed to 9/18/00

Independent reports
MedWatch 3015209-1-00
MedWatch 3471220-8-00-01
MedWatch 3051561-9-00 (980114-SK161)
MedWatch 3007564-3-00
MedWatch 3535666-1-00-01 (000713-SK605)
MedWatch 3383627-8-00-01 (B0072245A)
MedWatch 3065272-7-00 (80407-SK060)
MedWatch 3477097-9-00-01 (000308-SK953)
MedWatch 3477110-9-00-01 (000303-SK967)
MedWatch 3477108-0-00-01 (000303-SK968)
MedWatch 3477115-8-00-01 (000303-SK965)
MedWatch 3477100-6-00-01 (000303-SK976)
MedWatch 3477103-1-00-01 (000303-SK975)
MedWatch 3477106-7-00-01 (000303-SK972)
MedWatch (961022-SK848)
MedWatch (961022-SK850)
MedWatch (970529-SK651)
MedWatch (74036)
MedWatch (75822)

Follow-up reports
MedWatch 3121134-8-00-01 (980114-SK162)
MedWatch 3454176-3-00-01 (991217-SK980)

FOOD AND DRUG ADMINISTRATION
DIVISION OF GICDP
DOCUMENT CONTROL ROOM 6B-24
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: September 28, 2000



TO:

Name: Mary Jo Pritza

Fax No: 847-982-~~8090~~ 8152

Phone No: 847-982-7831

Location: G. D. Searle & Co.

FROM:

Name: ———

Fax No: ———

Phone No: ———

Location: FDA/PKLN —/HFD-180

This fax is 3 pages long, which includes a 1 page cover sheet and a ——— r

———

DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 19-268/S-031
NDA 20-607/S-005

Food and Drug Administration
Rockville MD 20857

G.D. Searle & Company
Attention: Peter F. East
Associate Director, Regulatory Affairs
4901 Searle Parkway
Skokie, IL 60077

MAY 2 8 2000

Dear Mr. East:

Please refer to your supplemental new drug applications dated October 13, 1998, received October 15, 1998, submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act for Cytotec (misoprostol) Tablets and Arthrotec (diclofenac sodium/misoprostol) Tablets, respectively.

We also refer to your March 9, 2000, submission received March 10, 2000, in response to our Approvable letter dated December 17, 1999. This submission contained a draft "Dear Health Care Practitioner" letter addressing the unapproved use of intravaginal or oral misoprostol in pregnant women for the induction of labor or abortion.

We have reviewed your letter and have the following recommendations:

1. Move the phrase "in women who are pregnant", found in the first sentence of the first paragraph, to just before the phrase "because it can cause abortion" also found in the first sentence of the first paragraph. The sentence should read, "The purpose of this letter is to remind you that Cytotec (misoprostol) administration by any route is contraindicated in women who are pregnant because it can cause abortion." Highlighting, bolding, or bulleting this information would add emphasis and increase clarity.

2. Delete the phrase "in any form and by any route" from the second sentence of the first paragraph.

3. Delete the term "deliberately" from the second sentence of the third paragraph.

4. Change the wording in the fourth paragraph to reflect the wording found in the June 1, 1999, "Dear Health Care Practitioner" letter, as follows:

   "Serious adverse events reported following off-label use of misoprostol in pregnant women include uterine hyperstimulation, rupture or perforation requiring surgical repair, hysterectomy or salpingooophorectomy; amniotic fluid embolism resulting in material and fatal death; severe vaginal bleeding, retained placenta, shock, fetal bradycardia and pelvic pain."

5. Consistently refer to the drug by either the brand name or the generic name throughout the letter.

6. Consult 21 C.F.R. 200.5 for requirements as to the envelope size and IMPORTANT DRUG WARNING caption that must appear on the envelope.

7. Consider revising the letter to reflect Arthrotec Tablets as well as Cytotec Tablets. In addition, target the letter to likely misoprostol prescribers, including rheumatologists, general practitioners, and internal medicine practitioners. You may also consider including physicians likely to assess patients who may have used misoprostol to induce labor or abortion, such as general surgeons and emergency room physicians, as well as those proposed in your submission.

If you have any questions, contact Paul E. Levine, Jr., R.Ph., Project Manager, at (301) 827-7310.

Sincerely yours,

Lilia Talarico

Lilia Talarico, MD
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Electronic Mail Message

Date: 8/2/2000 7:43:33 AM
From: [redacted]
To: See Below
Subject: Pop Council

I called our epidemiologist who is out of the country last night and updated him regarding our meeting yesterday. He had the following comments (see attachment) on the outline of the study reports and the concept of combining objectives 1, 2 and 4.

To: [redacted]
To: [redacted]
To: [redacted]
To: [redacted]
To: [redacted]
To: [redacted]

Hilton
) Perry Parkway
aithersburg, MD 20877

Preprinted Requisition
E-094495

EXPENDITURES FOR ADVISORY COMMITTEE MEETING

Advisory Committee for Reproductive Health Drugs — July 19, 1996
(24-hour hold on one **days)**

CONFERENCE ROOM RENTAL one days at $2400 per day	$2,400.00
[redacted] (2) easels at $10 ea.	$ 20.00
TELEPHONE FOR REGISTRATION TABLE	$ 25.00
TOTAL CONFERENCE ROOM EXPENSES	$2,445.00

[redacted]

ALTBOX	
2X2 C USEL SLIDE PROJECTOR W/REMOTE	
MIC W/PODI ND LIGHT	
FLOOR MIC (2)	
TABLE MICS (10)	
OVERHEAD PROJECTOR	
SCREEN	
LASER POINTER	
MIXERS (16 CH L)	
LAVAL	
PROFESS L AUDIO TECHNICIAN (10 HOURS)	
EX SLIDE PREVIEWERS	

SET UP FEE (**first day only**)	18% x $2,445 = $440.10	$440.10
TOTAL AUDIO VISUAL EXPENSES	$	
TOTAL CONFERENCE RM. EXPENSES	$ 2,885.10	
GRAND TOTAL	$ 2,885.10	

TAX EXEMPT NUMBER - 30005004

SET UP AND SPECIAL INSTRUCTIONS: **(NO ADDITIONAL CHARGE)**

[redacted]

THEATRE STYLE SEATING
WATER STATION - OUTSIDE OF CONFERENCE ROOM OR IN BACK OF ROOM
6' SKIRTED REGISTRATION TABLE IN FOYER WITH TWO CHAIRS

[redacted]

MIF 008858

DEPARTMENT OF
HEALTH AND HUMAN SERVICES
PURCHASE/SERVICE/STOCK REQUISITION

BPA and Call No. _____

REQUISITION NUMBER: F07836
OFFICE CODE/SYMBOL: ACS:HFD-21

TO: DHHS/FDA/DCGM (HFA-13)
REQUEST FOR: ☐ PURCHASE ☐ SERVICE ☐ STOCK ISSUE ☒ RENTAL/LEASE
REQUESTING ORGANIZATION: Food and Drug Administration
CUSTODIAL AREA: CDER
DATE: 09/06/96
OBJECT CLASS: 25.9Z
FOR REFERENCE CALL:
EXTENSION:
APPROPRIATION: 7560600 223200 20
DELIVER TO:
FDA/CDER/ACS
5600 Fisher Lane (HFD-21)
Rockville, MD 20857
CAN: 6-6992862 D-52004
DATE REQUIRED: 07/19/96

ITEM NO.	DESCRIPTION (INCLUDE STOCK NUMBER, MODEL/PART NO., ETC.)	QUANTITY REQUIRED	UNIT OF ISSUE	COST UNIT	COST TOTAL
	Use and reconfiguration of National Narrowcast Network's ISDN line for 7/19/96 Reproductive Health Drugs Advisory Committee Meeting. TITLE OF MEETING: Reproductive Health Drugs Advisory Committee LOCATION: FDA Tech., Center Gaithersburg, MD DATE: July 19,1996 TIME: 8:00am-6:00pm JUSTIFICATION: See attached.	reconfiguration			$143.50
				TOTAL	$143.

I certify that the property/services requested are required for Government business, and are not available from excess or current stock.*
FUNDS AVAILABLE: Director, ACS /S/ DATE 9/6/96

REQUESTED BY (Signature): /S/
Deputy Director, ACS
DATE: 9/6/96
RECOMMEND APPROVAL (Signature/Title)*
DATE:

RECEIVING OFFICIAL - I certify that the quantities indicated in the "Quantity Required" column above have been received in total or as annotated.
RECEIVING OFFICIAL (Signature/Title)
DATE:

APPROVED BY (Signature): /S/
Director, ACS
DATE: 9/6/96
PROPERTY MANAGEMENT OFFICER (Signature)*
DATE:

ORDER NO. (PO, DO, FEDSTRIP, ETC.)
ORDER DATE:
VOUCHER NO.
VOUCHER DAT

NATIONAL
NARROWCAST
NETWORK℠
FRIENDSHIP STATION, P.O. BOX 9597, WASHINGTON, D.C. 20016
PHONE: (202) 966-2211 FAX: (202) 966-1770

Invoice Date: August 26, 1996

ACS/ORM,CDER
FDA
5600 Fishers Lane -- HFD-21
Rockville, MD 20857

INVOICE #: 6082609
(156BA5N)

NAME	DATE	HEARING(S)	UNITS	FEE
	7/19/96	FDA/Reproductive Health Drugs	8	$
			5	$

SUBTOTAL

SUBTOTAL $143.50
DC SALES TAX $ 00.00

****
$143.50
****

PLEASE REFERENCE INVOICE NUMBER WITH PAYMENT

** PAYABLE UPON RECEIPT

** INTEREST ON OVERDUE BILLS 1.25% PER MONTH

... we thank you for your patronage. Please call us whenever there's a Washington event you'd like to hear on Hearings-On-The-Line®.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date September 6, 1996

From [redacted] Advisors and Consultants Staff

Subject Requisition for Narrowcast Network

To [redacted]

Office of Facilities, Acquisitions and Central Services, HFA-512

On July 19, 1996, the Reproductive Health Drug Advisory Committee held a meeting at the FDA Technical Center. Due to the the large public interest in the meeting an overflow room was reserved at the Hilton Hotel in Gaithersburg, Maryland. Since a large number of people requested time to speak it was necessary to change the agenda for the meeting. As originally planned the meeting was scheduled to finish at 5:30 p.m. However, the meeting ran later and ended after 6:30 p.m.

At the meeting we learned the company responsible for the broadcasting the video from the FDA Technical Center to the Hilton Hotel had been able to reserve a satellite transponder only until 6:00 p.m. The company was unable to obtain additional time on a transponder because of the Olympics beginning that day.

Faced with the prospect that the overflow room would be disconnected from the meeting, I contacted Hearings-On-The-Line, a private firm that was already at the meeting and providing the audio services of the meeting to its subscribers. I learned that the firm could arrange for the audio to be sent to the overflow room beginning at 6:00 p.m. or at any time we wished. The estimated cost given was about $100 but could have been more, depending on how long the meeting lasted. I then spoke to [redacted] Office of Facilities, Acquisitions and Central Services. [redacted] was at the meeting to oversee the technical support and to respond to any last minute problems. I explained the situation to [redacted] and asked if it would be acceptable to request Hearings-On-the-Line to provide audio services to the overflow room. [redacted] indicated that would be fine and we preceded.

During the afternoon of the meeting there was a severe thunderstorm which interrupted the satellite transmission. During the interruption of the transmission, we utilized the audio provided by Hearings-On-The-Line until the satellite transmission was restored. Again, at 6:00 p.m., the audio services were used until the end of the meeting. The total cost of the audio service provided was $143.50.

/S/

[redacted]

MIF 008861

REGULATORY TV/VIDEO SERVICE

Preliminary Telecast Order Form

1. ***Bill To:*** Name and Title

Company FDA, ORM, ACS, HFD-21

Address 5600 Fishers Lane

City, State, Zip, Country Rockville MD 20857-1000

Phone ____ FAX ____

2. ***Site Receiving Telecast***

Company FDA c/o Gaithersburg Hilton

Address 620 Perry Parkway

City, State, Country Gaithersburg MD

Transmission options: (Check one) [X] KU-band satellite [ ] Videoconference

Contact(s) *(Only individuals named herein will be provided coordinates for accessing the satellite or videoconference transmission.)*

Phone ____ FAX ____

After Hours Phone (Office and/or Home) N/A

3. ***Request***

A. **Advisory Committee** Reproductive Health

Meeting Date 19 July 96

B. **Coverage Desired** [X] One Day [ ] Two Days [ ] Three Days

4. ***Payment*** (U.S. Dollars Only. Payable to F-D-C Reports, Inc. Maryland residents add 5% sales tax)

[X] Invoice me (purchase order # optional) # 7560600

[ ] American Express [ ] Mastercard [ ] Visa

(Account Number) (Exp. Date)

/S/ 7-5-96

(Signature) (Date)

(more)

5. Agreement

I have reviewed and understand the "Conditions of Sale" below and the various charges described in the Regulatory TV price list. I agree to abide by the "conditions of sale" herein and to pay the applicable charges incurred in response to this order.

/S/ (Signature)

7-5-96 (Date)

Conditions of Sale

Regulatory TV telecasts (Telecasts) of FDA advisory committee meetings are sold by F-D-C Reports, Inc. (Seller) under the following conditions:

1. Telecasts may contain copyrighted material. Federal law [Title 17 USC, Sections 501 and 506] provides severe civil and criminal penalties for unauthorized reproduction, distribution and exhibition of copyrighted works. Criminal copyright infringement is investigated by the FBI and may constitute a felony with a maximum penalty of up to five years in prison and/or a $250,000 fine. In addition, state law provides severe civil penalties for the misappropriation of Seller's Telecasts, including monetary damages.

2. Telecasts are for the internal viewing by the purchasing organization at the site specified on the order form. Viewing at unauthorized sites is strictly prohibited. Viewing by any non-employee of the purchasing organization is prohibited without the permission of the Seller.

Videotape Duplication Rules

3. Telecasts are not to be recorded or duplicated in any manner by the Purchaser, except under the following terms: a) Purchaser is authorized to make one video recording of the Telecast for internal use only by the purchasing organization; b) additional copies of the recording can be purchased from the Seller under the prices and terms specified in the F-D-C Regulatory TV/Video Service price list ("Additional-copy Rates") and "Conditions of Sale;" or c) Purchaser obtains written authorization from the Seller to make additional copies directly at a charge specified by the Seller. Resale or an exchange of any kind of these recordings with organizations or individuals outside the purchasing organization is strictly prohibited.

4. In the event of a complete disruption of the Telecast, or cancellation by the Seller, Seller is liable only for the refund of paid orders.

Purchaser can also choose to receive videotape recordings of such meetings within five business days after the meeting. Purchaser will be billed at the current prices for F-D-C Regulatory TV/Video Service recordings of FDA advisory committee meetings.

5. In the event of a partial interruption of the Telecast, Seller will make every effort to provide Purchaser with a videotape recording of the interrupted portions of the Telecast to be available within two business days after the date of the Telecast. Seller will also, at its sole discretion, consider adjustments to the Purchaser's charges for the Telecast.

Seller is not responsible for problems with Purchaser's reception of the Telecasts (Contact Seller for procedures for assistance with reception problems.)

6. Although the Seller believes that the information contained in the Telecasts are an accurate and complete record of the public portions of the FDA advisory committee meetings, no guarantee is offered to that effect. The Seller does not assume any liability for the accuracy and comprehensiveness of the information presented.

7. Prices are subject to change without notice, including due to satellite availability.

8. Purchaser's Preliminary Order is valid until ten business days prior to the Telecast date. Purchaser can cancel a Preliminary Order at any time during the valid period. After that date, Purchaser can convert the Preliminary Order to a Firm Order for the Telecast. Cancellation of a Firm Order is at the sole discretion of the Seller.

Mail or FAX form to:
Lori Hardin, F-D-C Reports, Inc.

Signs

DATE: 7/2/96

TO: _____

_____

_____

_____

_____

FROM: _____

Food and Drug Administration
Advisors and Consultants Staff
5600 Fishers Lane
HFD-9, Room 8B-45
Rockville, MD 20857

Facsimile no: 3/9108

Phone number: _____

Phone number: _____

Facsimile no: _____

No. of pages 1
(not including cover)

PLEASE CALL IMMEDIATELY IF RE-TRANSMISSION IS NECESSARY.

Thank You!

☆U.S. GOVERNMENT PRINTING OFFICE:1993—357-864

FDA REQUEST FOR GRAPHIC SERVICES

VISUAL INFORMATION SERVICES BRANCH
5600 Fishers Lane Rm. 9-67, Rockville, MD 20857
PHONE # [redacted] FAX # [redacted]

YOUR NAME: [redacted]

PHONE # [redacted] FAX # [redacted]

OTHER CONTACT:

PLEASE, If submitting a Disk, you Must:
- Submit a 3½" **HD** (High Density) **copy** of your original disk.
- **Label** your disk (your name, file name & program job was created in)
- Submit **only the necessary file(s)**
- **Include paper copies** of all enclosed files

PLEASE LABEL HD

DATE IN: 7/2/96 DATE DUE: ASAP 7/10/96

CENTER/OFFICE: CDER/ACS

MAIL CODE: HFD-21

PROJECT TITLE: Adv. Cmte. for Reproductive Health Drugs — July 19, 1996

CAN #: 6-6992304

Authorized Signature for Approval/Title:

TO BE FILLED OUT BY VISB STAFF WITH REQUESTER

GENI JOB # _____ DISK # _____ MAC DISK # _____ RECEIVED BY _____ ARTIST _____

SLIDES

	Quantity	Set(s)
☐ PHOTO		
☐ GENI		
☐ MAC		
☐ VENDOR CREATES		
☐ *DISK IMAGING		

VUGRAPHS

	Quantity	Set(s)
☐ PHOTO		
☐ GENI		
☐ MAC		
☐ VENDOR CREATES		
☐ *DISK IMAGING		

PHOTOGRAPHY

☐ **35mm PROCESSING**
_____ Roll(s)

☐ **B/W PRINT(S)**
Quantity: Size:

☐ **COLOR PRINT(S)**
Quantity: Size:

GRAPHICS

Quantity	Size	
2	easel	☒ Poster(s)
		☐ Cover Design
		☐ Brochure
		☐ Lino - Paper Pos.
		☐ Lino - Film Pos.
		☐ Lino - Film Neg.
		☐ Other: *See Special Instructions

ART/FRAMING SERVICES

Quantity	
	☐ Nameplate(s)
	☐ Name Tags/Badges
	☐ 8½ x 11 Canon Copies
	☐ 11 x 17 Canon Copies
	☐ *Framing (Custom)
	☐ *Framing (In-House)

GERBER GRAPHICS

Quantity	Size	
		☐ Banner(s)
		☐ Sign(s)
		☐ Flip Chart(s)
		☐ Other: _____

*SPECIAL INSTRUCTIONS: Hi [redacted] the signs you made were great. I need a duplicate of the same signs.

Signs should read:

All personal belongings and packages are subject to inspection.

Picture ID must be shown before entering meeting.

MIF 008865

CONTRACTOR: CALL NO. DUE DATE: PRODUCTION

DEPARTMENT OF
HEALTH AND HUMAN SERVICES
PURCHASE/SERVICE/STOCK REQUISITION

REQUISITION NUMBER: F08008

BPA and Call No. BPA 90243
CALL #17

OFFICE CODE/SYMBOL: ACS:HFD-21

TO: DHHS/FDA/ACS/DAN/PROC (Rm 5101)

REQUEST FOR: ☐ PURCHASE ☒ SERVICE ☐ STOCK ISSUE ☐ RENTAL/LEASE

REQUESTING ORGANIZATION	CUSTODIAL AREA	DATE	OBJECT CLASS
Food and Drug Administration	CDER	07/12/96	25.2P

FOR REFERENCE CALL	EXTENSION	APPROPRIATION
		7560600 223200 20

DELIVER TO:
FDA/CDER/ACS
1901 Chapman Avenue, Rm 200, HFD-21
Rockville, MD 20852

SJA 6.25

CAN: 6-6992862 D-51764

DATE REQUIRED: GT 7/19/96 JUN 24

RECEIVED
JUN 24 8 30 AM '96
OD-DIV. OF ACQUISITION MANAGEMENT, ASG

ITEM NO.	DESCRIPTION (INCLUDE STOCK NUMBER, MODEL/PART NO., ETC.)	QUANTITY REQUIRED	UNIT OF ISSUE	UNIT COST	TOTAL
	Transcription services for a meeting of an FDA/CDER Advisory Committee meeting, Rquest is made for: (1) An original-4 per page, ONE SIDE (2) A hard copy-1 per page, doublespaced, ONE SIDE (3) 3-1/2" diskett-1 per page with WP60 Compatibility, KEY WORD INDEX (4) Tapes EIGHT DAY DELIVERY!!! DELIVER TO ATTENTION VENDOR: PLEASE PROVIDE INVOICE WITH TRANSCRIPT MEETING: Reproductive Health Drugs Advisory Committee. PLACE: FDA Technical Center 16071 Industrial Drive Gaithersburg, MD DATE: July 19,1996 TIME: July 19;9:00am-5:00pm OPEN The contractor must have been approved by FDA for access to "Priveleged Information" and must be certified as being capable to receive and protect such information according to the requirements set forth in 21 CFR 20.90 (Disclosure to Contractor). SOURCE: C.A.S.E.T. ASSOCIATES 10201 Old Lee Highway Suite 180 Fairfax, VA 22030 Contact:Debra Gilliam Phone:703/352-0091 /S/ 6/24 ENTERED	1	EA	2000.00	2000.00

$ 3.50/PAGE
$ 12.50/DISK
$ 3.50/MASTER TAPE

RECEIVED
JUN 24 2 47 PM '96
OD-DIV. OF ACQUISITION MANAGEMENT, ASG

NOT To Exce

I certify that the property/services requested are required for Government business, and are not available from excess or current assets.*

FUNDS AVAILAB: /S/ SGE Programs Officer — DATE: 6/21/96 — TOTAL: 2000.00

REQUESTED BY (Signature): /S/ Cmte. Mgmt. Asst. — DATE: 6/21/96

RECEIVING OFFICIAL - I certify that the quantities indicated in the "Quantity Required" column above have been received in total or as annotated.

RECOMMEND APPROVAL (Signature/Title)* — DATE — RECEIVING OFFICIAL (Signature/Title) — DATE

APPROVED BY (Signature): /S/ SGE Programs Officer — DATE: 6/21/96 — ORDER NO. (PO, DO, FEDSTRIP, ETC.) — ORDER DATE

PROPERTY MANAGEMENT OFFICER (Signature)* — DATE — VOUCHER NO. — VOUCHER DATE

HHS - 393 (Rev. 4/81)

MIF 008866

National Narrowcast Network, L.P.

Box 9597, Friendship Station
Washington, D.C. 20016
(202)966-2211 or Fax (202)966-1770

Hearings-On-The-Line® Service Agreement {Separate form should be submitted for each authorized user.}

NAME: _____

POSITION: _____ ACS, ORM, CDER, FDA

ORGANIZATION: HFD-21

ADDRESS: 5600 FISHERS LANE

CITY: ROCKVILLE STATE: MD ZIP: 20857

PHONE: _____ FAX: _____

I DO want to use National Narrowcast Network's **Hearings-On-The-Line®**. Please provide me with my personal **H-O-T-Line℠** authorization code, and instructions on how to tune in to Congressional hearings live at my desk or from any phone. I understand that the regular charge for each hearing is $20 for the first 10 minutes or part and $15 for each additional 10 minutes or part, plus any additional taxes, and that I personally and my organization will be responsible for any charges to this code. If I do not pay the bills for my usage promptly, I authorize National Narrowcast Network, L.P., or its agents, after notice to me, to charge my VISA account for the overdue amounts, Acct. Name MASTER CHARGE Acct. # _____ {if I do not have a VISA account I will make other arrangements with NNN}. Interest on overdue bills will be 1.25% per month. I understand that the cost of the **Hearings-On-The-Line®**. service does not include the cost of the calls I make to connect to **H-O-T-Line℠**.

I understand that while **Hearings-On-The-Line®**. will do its best to provide coverage of scheduled hearings, this service is necessarily subject to last minute changes in schedules, locations, availability for coverage, and witnesses, and to other technical interruptions or last minute circumstances which may cause non-transmission of a particular hearing, and that National Narrowcast Network, L.P. does not guarantee that a particular hearing will occur, will be available for transmission, or will in fact be transmitted to subscribers. I agree that neither National Narrowcast Network, L.P., nor its agents or affiliates, will have any liability whatsoever, except for refund of any amount paid in advance, for any failure to carry any hearing.

I also understand that the charges above are for direct use of the **Hearings-On-The-Line®**. service by the authorized person and do not authorize re-transmission in any manner, other than listening on an existing telephone extension at the same location as the authorized person. I understand that any other use, including re-transmission or re-broadcast in any manner, will entail substantial additional charges, for which I and my organization will be responsible. I am authorized to bind my organization to this agreement. _____

Date: 7/19/96 Signed: /S/ _____
{Mother's full birth nam .or identification verification:

First..... Middle..... Last.....

Send to: ***Hearings-On-The-Line®***., Box 9597, Friendship Station, Washington, D.C. 20016; or FAX to 202-966-1770

Presenting:
Hearings-On-The-Line® -- Your H-O-T Line℠ to Congress & Federal Agencies

GAITHERSBURG Marriott WASHINGTONIAN CENTER

INTEROFFICE MEMO

Date: July 2, 1996

To: Brian Sepanik

From: _____
Executive Meeting Manager

Subject: FDA Confidentiality

Copies: Distribution

For security reasons, the attached list of FDA guests cannot be identified to outside persons.

The guests have been advised to identify themselves as part of the FDA Group and understand that upon check-in on Thursday, July 18th, the front desk associate will ask if they wish their name be changed to an alias.

The associate will then change the name of the person registered, however the PMS account number should remain the same so that the charges can be routed to the appropriate guest.

If you have any questions, please see me.

Distribution:
_____ (FDA)
K. Wishard
K. Summerlin

APPEARS THIS WAY
ON ORIGINAL

Advisory Committees; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). This notice also summarizes the procedures for the meeting and methods by which interested persons may participate in open public hearings before FDA's advisory committees.

FDA has established an Advisory Committee Information Hotline (the hotline) using a voice-mail telephone system. The hotline provides the public with access to the most current information on FDA advisory committee meetings. The advisory committee hotline, which will disseminate current information and information updates, can be accessed by dialing 1–800–741–8138 or 301–443–0572. Each advisory committee is assigned a 5-digit number. This 5-digit number will appear in each individual notice of meeting. The hotline will enable the public to obtain information about a particular advisory committee by using the committee's 5-digit number. Information in the hotline is preliminary and may change before a meeting is actually held. The hotline will be updated when such changes are made.

MEETING: The following advisory committee meeting is announced:

Advisory Committee for Reproductive Health Drugs

Date, time, and place. July 19, 1996, 9 a.m., FDA Technical Center, 16071 Industrial Dr., Gaithersburg, MD. Attendees should allow time to proceed through security procedures. Admission to the facility by public participants will be available on a first come, first serve basis, and will be limited to approximately 200, the number of seats available to the public in the conference room. There will be an overflow room with both audio and video link to the meeting. The overflow room is located at the Hilton Hotel, 620 Perry Pkwy., Gaithersburg, MD.

Type of meeting and contact person. Open committee discussion, 9 a.m. to 1:30 p.m.; open public hearing, 1:30 p.m. to 3:30 p.m., unless public participation does not last that long; open committee discussion, 3:30 p.m. to 5 p.m.; Philip A. Corfman, Center for Drug Evaluation and Research (HFD–580), Food and Drug Administration, 5600 Fishers Lane, rm. 14B–04, Rockville, MD 20857, 301–443–3510, FAX 301–443–9282, or e-mail july19@cder.fda.gov. Information concerning the meeting is available from FDA Advisory Committee Information Hotline, 1–800–741–8138 (301–443–0572 in the Washington, DC area), Advisory Committee for Reproductive Health Drugs, code 12537. Please call the hotline for information concerning any possible changes.

General function of the committee. The committee reviews and evaluates data on the safety and effectiveness of marketed and investigational human drugs for use in the practice of obstetrics, gynecology, and related specialties.

Agenda—Open public hearing. Interested persons may present data, information, or views, orally or in

Electronic Mail Message

Date: 9/22/00 1:21:47 PM
From: [redacted]
To: [redacted]
Subject: cytotec

[redacted]

I talked to [redacted] and added two more points which I have attached

[redacted]

- The first paragraph in the Labor and Delivery may produce misinformation. A fair clinical discussion of the numerous prospective randomized studies and/or position of organizations such as ACOG have not been included in this section to balance out the second two paragraphs which stress adverse events.

  21 CFR 201.57

  (7) ..... Shall describe the available information about the effect of the drug on the mother and the fetus.....

- The first paragraph does not strengthen a contraindication, warning, precaution (314.70)

- The first paragraph could be misleading if mifepristone is approved for use in termination of pregnancy in conjunction with misoprostol.

- The second two paragraphs are accurate. The word off-label may not be necessary in the first sentence of the second paragraph.

- The change from case to cases of amniotic fluid embolism is acceptable if this has been substantiated from an accurate case reporting.

- Our changes for the submitted labeling are shown below. In addition consideration should be given for balanced information from prospective randomized trials.

[redacted] (HFD-580)

[redacted] (HFD-580)

[redacted] (HFD-580)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

AUG 18 1997

Robert L. Bogomolny
General Counsel
Searle
5200 Old Orchard Road
Skokie, IL 60077

Re: NDA 19-268, Cytotec®

Dear Mr. Bogomolny:

This letter responds to your letter of April 23, 1997. We understand your concerns regarding the proposed use of Searle's drug Cytotec® (misoprostol) as part of an abortifacient regimen with the drug mifepristone under the Population Council's pending NDA, which, as a matter of public record, has been designated "approvable." *See* Sara Silver, "Abortion Pill Move to U.S. in Jeopardy," *Associated Press* (June 12, 1997). It is the policy of the Center for Drug Evaluation and Research to encourage a company that recommends use of its product in conjunction with another's to consult regarding appropriate usage and labeling.

As with all NDAs designated "approvable," issues remain to be resolved before the Population Council's drug can be fully approved. Recent media reports indicate the nature of some of these issues. *Id.; see also* John Sullivan, "Another Delay in Store for French Abortion Pill on U.S. Market," *The New York Times* A16 (June 13, 1997); Caryle Murphy, "Abortion Pill's U.S. Sponsor Suing Hungarian Drug Firm," *The Washington Post* A3 (June 12, 1997).

In response to your previous requests, we enclose a copy of the FDA's minutes for the August 28, 1996 meeting between FDA and Searle. We apologize for the delay in providing these minutes and invite your comments.

Sincerely yours,

/S/

Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL

MIF 008872

Robert L. Bogomolny

cc:
HFD-1
HFD-2
HFD-5
HFD-7 HFD-7/R, HFD-7/C
HFD-180
HFD-580

j:\ searle\423respo.lt2
Prepared: HFD-7: 06/19/97;8/11/97
Reviewed:HFD-7 8/11/97

/S/ 8/12/97
/S/ 8/15/97
/S/ 8/16/97

APPEARS THIS WAY
ON ORIGINAL

********** Entire Monograph **********

06/19/97 14:49:17

Cytotec
Searle

DESCRIPTION:

****
*
* CONTRAINDICATIONS AND WARNINGS
* Cytotec (misoprostol) is contraindicated,
* because of its abortifacient property, in
* women who are pregnant. (See Precautions.)
* Patients must be advised of the
* abortifacient property and warned not to
* give the drug to others. Anecdotal reports,
* primarily from Brazil, of congenital
* anomalies and reports of fetal death
* subsequent to misuse of misoprostol as an
* abortifacient have been received. Cytotec
* should not be used in women of childbearing
* potential unless the patient requires
* nonsteroidal anti-inflammatory drug (NSAID)
* therapy and is at high risk of
* complications from gastric ulcers
* associated with use of the NSAID, or is at
* high risk of developing gastric ulceration.
* In such patients, Cytotec may be prescribed
* if the patient
* --has had a negative serum pregnancy test
* within 2 weeks prior to beginning therapy.
* --is capable of complying with effective
* contraceptive measures.
* --has received both oral and written
* warnings of the hazards of misoprostol, the
* risk of possible contraception failure, and
* the danger to other women of childbearing
* potential should the drug be taken by
* mistake.
* --will begin Cytotec only on the second or
* third day of the next normal menstrual
* period.
*
****

Cytotec oral tablets contain either 100 mcg or 200 mcg of misoprostol, a synthetic prostaglandin E1 analog.
Misoprostol contains approximately equal amounts of the two diastereomers presented below with their enantiomers indicated by (+/-):
Click here to view chemical structure(s).
$C_{22}H_{38}O_5$: M.W. = 382.5
(+/-) methyl 11alpha, 16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate
Misoprostol is a water-soluble, viscous liquid.
Inactive ingredients of tablets are hydrogenated castor oil, hydroxypropyl

methylcellulose, microcrystalline cellulose, and sodium starch glycolate.

ACTIONS/CLINICAL PHARMACOLOGY:

PHARMACOKINETICS: Misoprostol is extensively absorbed, and undergoes rapid de-esterification to its free acid, which is responsible for its clinical activity and, unlike the parent compound, is detectable in plasma. The alpha side chain undergoes beta oxidation and the beta side chain undergoes omega oxidation followed by reduction of the ketone to give prostaglandin F analogs.

In normal volunteers, Cytotec (misoprostol) is rapidly absorbed after oral administration with a Tmax of misoprostol acid of 12 +/- 3 minutes and a terminal half-life of 20-40 minutes.

There is high variability of plasma levels of misoprostol acid between and within studies but mean values after single doses show a linear relationship with dose over the range of 200-400 mcg. No accumulation of misoprostol acid was noted in multiple dose studies; plasma steady state was achieved within two days.

Maximum plasma concentrations of misoprostol acid are diminished when the dose is taken with food and total availability of misoprostol acid is reduced by use of concomitant antacid. Clinical trials were conducted with concomitant antacid, however, so this effect does not appear to be clinically important.

Mean +/- SD	Cmax(pg/ml)	AUC(0-4) (pg.hr/ml)	Tmax(min)
Fasting	811 +/- 317	417 +/- 135	14 +/- 8
With Antacid	689 +/- 315	349 +/- 108*	20 +/- 14
With High Fat Breakfast	303 +/- 176*	373 +/- 111	64 +/- 79*

* Comparisons with fasting results statistically significant, $p<0.05$.

After oral administration of radiolabeled misoprostol, about 80% of detected radioactivity appears in urine. Pharmacokinetic studies in patients with varying degrees of renal impairment showed an approximate doubling of T1/2, Cmax, and AUC compared to normals, but no clear correlation between the degree of impairment and AUC. In subjects over 64 years of age, the AUC for misoprostol acid is increased. No routine dosage adjustment is recommended in older patients or patients with renal impairment, but dosage may need to be reduced if the usual dose is not tolerated.

Cytotec does not affect the hepatic mixed function oxidase (cytochrome P-450) enzyme systems in animals.

Drug interaction studies between misoprostol and several nonsteroidal anti-inflammatory drugs showed no effect on the kinetics of ibuprofen or diclofenac, and a 20% decrease in aspirin AUC, not thought to be clinically significant. Pharmacokinetic studies also showed a lack of drug interaction with antipyrine and propranolol when these drugs were given with misoprostol. Misoprostol given for one week had no effect on the steady state pharmacokinetics of diazepam when the two drugs were administered two hours apart.

The serum protein binding of misoprostol acid is less than 90% and is concentration-independent in the therapeutic range.

PHARMACODYNAMICS: Misoprostol has both antisecretory (inhibiting gastric acid secretion) and (in animals) mucosal protective properties. NSAIDs inhibit prostaglandin synthesis, and a deficiency of prostaglandins within the gastric mucosa may lead to diminishing bicarbonate and mucus secretion and may contribute to the mucosal damage caused by these agents. Misoprostol can increase bicarbonate and mucus production, but in man this has been shown at doses 200 mcg and above that are also antisecretory. It is therefore not

possible to tell whether the ability of misoprostol to prevent gastric ulcer is the result of its antisecretory effect, its mucosal protective effect, or both. In Vitro studies on canine parietal cells using tritiated misoprostol acid as the ligand have led to the identification and characterization of specific prostaglandin receptors. Receptor binding is saturable, reversible, and stereospecific. The sites have a high affinity for misoprostol, for its acid metabolite, and for other E type prostaglandins, but not for F or I prostaglandins and other unrelated compounds, such as histamine or cimetidine. Receptor-site affinity for misoprostol correlates well with an indirect index of antisecretory activity. It is likely that these specific receptors allow misoprostol taken with food to be effective topically, despite the lower serum concentrations attained.

Misoprostol produces a moderate decrease in pepsin concentration during basal conditions, but not during histamine stimulation. It has no significant effect on fasting or postprandial gastrin nor on intrinsic factor output.

EFFECTS ON GASTRIC ACID SECRETION: Misoprostol, over the range of 50-200 mcg, inhibits basal and nocturnal gastric acid secretion, and acid secretion in response to a variety of stimuli, including meals, histamine, pentagastrin, and coffee. Activity is apparent 30 minutes after oral administration and persists for at least 3 hours. In general, the effects of 50 mcg were modest and shorter lived, and only the 200-mcg dose had substantial effects on nocturnal secretion or on histamine and meal-stimulated secretion.

UTERINE EFFECTS: Cytotec has been shown to produce uterine contractions that may endanger pregnancy. (See Contraindications and Warnings.) In studies in women undergoing elective termination of pregnancy during the first trimester, Cytotec caused partial or complete expulsion of the uterine contents in 11% of the subjects and increased uterine bleeding in 41%.

OTHER PHARMACOLOGIC EFFECTS: Cytotec does not produce clinically significant effects on serum levels of prolactin, gonadotropins, thyroid- stimulating hormone, growth hormone, thyroxine, cortisol, gastrointestinal hormones (somatostatin, gastrin, vasoactive intestinal polypeptide, and motilin), creatinine, or uric acid. Gastric emptying, immunologic competence, platelet aggregation, pulmonary function, or the cardiovascular system are not modified by recommended doses of Cytotec.

CLINICAL STUDIES: In a series of small short-term (about one week) placebo-controlled studies in healthy human volunteers, doses of misoprostol were evaluated for their ability to prevent NSAID-induced mucosal injury. Studies of 200 mcg q.i.d. of misoprostol with tolmetin and naproxen, and of 100 and 200 mcg q.i.d. with ibuprofen, all showed reduction of the rate of significant endoscopic injury from about 70-75% on placebo to 10-30% on misoprostol. Doses of 25-200 mcg q.i.d. reduced aspirin-induced mucosal injury and bleeding.

PREVENTING GASTRIC ULCERS CAUSED BY NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS): Two 12-week, randomized, double-blind trials in osteoarthritic patients who had gastrointestinal symptoms but no ulcer on endoscopy while taking an NSAID compared the ability of 200 mcg of Cytotec, 100 mcg of Cytotec, and placebo to prevent gastric ulcer (GU) formation. Patients were approximately equally divided between ibuprofen, piroxicam, and naproxen, and continued this treatment throughout the 12 weeks. The 200-mcg dose caused a marked, statistically significant reduction in gastric ulcers in both studies. The lower dose was somewhat less effective, with a significant result in only one of the studies.

PREVENTION OF GASTRIC ULCERS INDUCED BY IBUPROFEN, PIROXICAM, OR NAPROXEN
(No. of patients with ulcer(s) (%))

	Therapy Duration

Therapy	4 weeks	8 weeks	12 weeks	
Study No. 1				
Cytotec 200 mcg q.i.d. (n=74)	1 (1.4)	0	0	1 (1.4)
Cytotec 100 mcg q.i.d. (n=77)	3 (3.9)	1 (1.3)	1 (1.3)	5 (6.5)
Placebo (n=76)	11 (14.5)	4 (5.3)	4 (5.3)	19 (25.0)
Study No. 2				
Cytotec 200 mcg q.i.d. (n=65)	1 (1.5)	1 (1.5)	0	2 (3.1)
Cytotec 100 mcg q.i.d. (n=66)	2 (3.0)	2 (3.0)	1 (1.5)	5 (7.6)
Placebo (n=62)	6 (9.7)	2 (3.2)	3 (4.8)	11 (17.7)
Studies No. 1 & No. 2**				
Cytotec 200 mcg q.i.d. (n=139)	2 (1.4)	1 (0.7)	0	3 (2.2)
Cytotec 100 mcg q.i.d. (n=143)	5 (3.5)	3 (2.1)	2 (1.4)	10 (7.0)
Placebo (n=138)	17 (12.3)	6 (4.3)	7 (5.1)	30 (21.7)

* Statistically significantly different from placebo at the 5% level.
** Combined data from Study No. 1 and Study No. 2.

In these trials there were no significant differences between Cytotec and placebo in relief of day or night abdominal pain. No effect of Cytotec in preventing duodenal ulcers was demonstrated, but relatively few duodenal lesions were seen.

In another clinical trial, 239 patients receiving aspirin 650-1300 mg q.i.d. for rheumatoid arthritis who had endoscopic evidence of duodenal and/or gastric inflammation were randomized to misoprostol 200 mcg q.i.d. or placebo for eight weeks while continuing to receive aspirin. The study evaluated the possible interference of Cytotec on the efficacy of aspirin in these patients with rheumatoid arthritis by analyzing joint tenderness, joint swelling, physician's clinical assessment, patient's assessment, change in ARA classification, change in handgrip strength, change in duration of morning stiffness, patient's assessment of pain at rest, movement, interference with daily activity, and ESR. Cytotec did not interfere with the efficacy of aspirin in these patients with rheumatoid arthritis.

INDICATIONS AND USAGE:

Cytotec (misoprostol) is indicated for the prevention of NSAID (nonsteroidal anti- inflammatory drugs, including aspirin)-induced gastric ulcers in patients at high risk of complications from gastric ulcer, eg, the elderly and patients with concomitant debilitating disease, as well as patients at high risk of developing gastric ulceration, such as patients with a history of ulcer. Cytotec has not been shown to prevent duodenal ulcers in patients taking NSAIDs. Cytotec should be taken for the duration of NSAID therapy. Cytotec has been shown to prevent gastric ulcers in controlled studies of three months' duration. It had no effect, compared to placebo, on gastrointestinal pain or discomfort associated with NSAID use.

CONTRAINDICATIONS:

****
* *

****
* CONTRAINDICATIONS AND WARNINGS *
* Cytotec (misoprostol) is contraindicated, *
* because of its abortifacient property, in *
* women who are pregnant. (See Precautions.) *
* Patients must be advised of the *
* abortifacient property and warned not to *
* give the drug to others. Cytotec should not *
* be used in women of childbearing potential *
* unless the patient requires nonsteroidal *
* anti-inflammatory drug (NSAID) therapy and *
* is at high risk of complications from *
* gastric ulcers associated with use of the *
* NSAID, or is at high risk of developing *
* gastric ulceration. In such patients, *
* Cytotec may be prescribed if the patient *
* --has had a negative Serum pregnancy test *
* within two weeks prior to beginning *
* therapy. *
* --is capable of complying with effective *
* contraceptive measures. *
* --has received both oral and written *
* warnings of the hazards of misoprostol, the *
* risk of possible contraception failure, and *
* the danger to other women of childbearing *
* potential should the drug be taken by *
* mistake. *
* --will begin Cytotec only on the second or *
* third day of the next normal menstrual *
* period. *
* *
****

Cytotec should not be taken by anyone with a history of allergy to prostaglandins.

WARNINGS:

****
* *
* CONTRAINDICATIONS AND WARNINGS *
* Cytotec (misoprostol) is contraindicated, *
* because of its abortifacient property, in *
* women who are pregnant. (See Precautions.) *
* Patients must be advised of the *
* abortifacient property and warned not to *
* give the drug to others. Anecdotal reports, *
* primarily from Brazil, of congenital *
* anomalies and reports of fetal death *
* subsequent to misuse of misoprostol as an *
* abortifacient have been received. Cytotec *
* should not be used in women of childbearing *
* potential unless the patient requires *
* nonsteroidal anti-inflammatory drug (NSAID) *
* therapy and is at high risk of *
* complications from gastric ulcers *
* associated with use of the NSAID, or is at *
* high risk of developing gastric ulceration. *

* In such patients, Cytotec may be prescribed *
* if the patient *
* --has had a negative serum pregnancy test *
* within 2 weeks prior to beginning therapy. *
* --is capable of complying with effective *
* contraceptive measures. *
* --has received both oral and written *
* warnings of the hazards of misoprostol, the *
* risk of possible contraception failure, and *
* the danger to other women of childbearing *
* potential should the drug be taken by *
* mistake. *
* --will begin Cytotec only on the second or *
* third day of the next normal menstrual *
* period. *
* *
****

PRECAUTIONS:

INFORMATION FOR PATIENTS: Cytotec is contraindicated in women who are pregnant, and should not be used in women of childbearing potential unless the patient requires nonsteroidal anti-inflammatory drug (NSAID) therapy and is at high risk of complications from gastric ulcers associated with the use of the NSAID, or is at high risk of developing gastric ulceration. Women of childbearing potential should be told that they must not be pregnant when Cytotec therapy is initiated, and that they must use an effective contraception method while taking Cytotec. See boxed CONTRAINDICATIONS AND WARNINGS.

Patients should be advised of the following:

Cytotec is intended for administration along with nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, to decrease the chance of developing an NSAID-induced gastric ulcer.

Cytotec should be taken only according to the directions given by a physician. If the patient has questions about or problems with Cytotec, the physician should be contacted promptly.

THE PATIENT SHOULD NOT GIVE CYTOTEC TO ANYONE ELSE. Cytotec has been prescribed for the patient's specific condition, may not be the correct treatment for another person, and may be dangerous to the other person if she were to become pregnant.

The Cytotec package the patient receives from the pharmacist will include a leaflet containing patient information. The patient should read the leaflet before taking Cytotec and each time the prescription is renewed because the leaflet may have been revised.

Keep Cytotec out of the reach of children.

SPECIAL NOTE FOR WOMEN: CYTOTEC MUST NOT BE USED BY PREGNANT WOMEN. CYTOTEC MAY CAUSE MISCARRIAGE. MISCARRIAGES CAUSED BY CYTOTEC MAY BE INCOMPLETE, WHICH COULD LEAD TO POTENTIALLY DANGEROUS BLEEDING, HOSPITALIZATION, SURGERY, INFERTILITY, OR MATERNAL OR FETAL DEATH.

Cytotec is available only as a unit-of-use package that includes a leaflet containing patient information. See Patient Information at the end of this labeling.

DRUG INTERACTIONS: See Actions/Clinical Pharmacology. Cytotec has not been shown to interfere with the beneficial effects of aspirin on signs and symptoms of rheumatoid arthritis. Cytotec does not exert clinically significant effects on the absorption, blood levels, and antiplatelet effects of therapeutic doses of aspirin. Cytotec has no clinically significant effect on the kinetics of diclofenac or ibuprofen.

ANIMAL TOXICOLOGY: A reversible increase in the number of normal surface gastric

epithelial cells occurred in the dog, rat, and mouse. No such increase has been observed in humans administered Cytotec for up to one year.
An apparent response of the female mouse to Cytotec in long-term studies at 100 to 1000 times the human dose was hyperostosis, mainly of the medulla of sternebrae. Hyperostosis did not occur in long-term studies in the dog and rat and has not been seen in humans treated with Cytotec.
CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: There was no evidence of an effect of Cytotec on tumor occurrence or incidence in rats receiving daily doses up to 150 times the human dose for 24 months. Similarly, there was no effect of Cytotec on tumor occurrence or incidence in mice receiving daily doses up to 1000 times the human dose for 21 months. The mutagenic potential of Cytotec was tested in several In Vitro assays, all of which were negative. Misoprostol, when administered to breeding male and female rats at doses 6.25 times to 625 times the maximum recommended human therapeutic dose, produced dose-related pre- and post-implantation losses and a significant decrease in the number of live pups born at the highest dose. These findings suggest the possibility of a general adverse effect on fertility in males and females.
PREGNANCY: PREGNANCY CATEGORY X. See boxed CONTRAINDICATIONS AND WARNINGS.
NONTERATOGENIC EFFECTS: Cytotec may endanger pregnancy (may cause miscarriage) and thereby cause harm to the fetus when administered to a pregnant women. Cytotec produces uterine contractions, uterine bleeding, and expulsion of the products of conception. Miscarriages caused by Cytotec may be incomplete. In studies in women undergoing elective termination of pregnancy during the first trimester, Cytotec caused partial or complete expulsion of the products of conception in 11% of the subjects and increased uterine bleeding in 41%. Anecdotal reports, primarily from Brazil, of congenital anomalies and reports of fetal death subsequent to misuse of misoprostol as an abortifacient have been received (see Contraindications and Warnings.) If a woman is or becomes pregnant while taking this drug, the drug should be discontinued and the patient apprised of the potential hazard to the fetus.
TERATOGENIC EFFECTS: Cytotec is not fetotoxic or teratogenic in rats and rabbits at doses 625 and 63 times the human dose, respectively.
NURSING MOTHERS: See Contraindications. It is unlikely that Cytotec is excreted in human milk since it is rapidly metabolized throughout the body. However, it is not known if the active metabolite (misoprostol acid) is excreted in human milk. Therefore, Cytotec should not be administered to nursing mothers because the potential excretion of misoprostol acid could cause significant diarrhea in nursing infants.
PEDIATRIC USE: Safety and effectiveness in children below the age of 18 years have not been established.

DRUG INTERACTIONS:

See Actions/Clinical Pharmacology. Cytotec has not been shown to interfere with the beneficial effects of aspirin on signs and symptoms of rheumatoid arthritis. Cytotec does not exert clinically significant effects on the absorption, blood levels, and antiplatelet effects of therapeutic doses of aspirin. Cytotec has no clinically significant effect on the kinetics of diclofenac or ibuprofen. (See Also PRECAUTIONS)

ADVERSE REACTIONS:

The following have been reported as adverse events in subjects receiving Cytotec:
GASTROINTESTINAL: In subjects receiving Cytotec 400 or 800 mcg daily in clinical trials, the most frequent gastrointestinal adverse events were diarrhea and abdominal pain. The incidence of diarrhea at 800 mcg in controlled trials in patients on NSAIDs ranged from 14-40% and in all studies (over 5,000 patients) averaged 13%. Abdominal pain occurred in 13-20% of patients in NSAID trials and

about 7% in all studies, but there was no consistent difference from placebo. Diarrhea was dose related and usually developed early in the course of therapy (after 13 days), usually was self-limiting (often resolving after 8 days), but sometimes required discontinuation of Cytotec (2% of the patients). Rare instances of profound diarrhea leading to severe dehydration have been reported. Patients with an underlying condition such as inflammatory bowel disease, or those in whom dehydration, were it to occur, would be dangerous, should be monitored carefully if Cytotec is prescribed. The incidence of diarrhea can be minimized by administering after meals and at bedtime, and by avoiding coadministration of Cytotec with magnesium- containing antacids.
GYNECOLOGICAL: Women who received Cytotec during clinical trials reported the following gynecological disorders: spotting (0.7%), cramps (0.6%), hypermenorrhea (0.5%), menstrual disorder (0.3%) and dysmenorrhea (0.1%). Postmenopausal vaginal bleeding may be related to Cytotec administration. If it occurs, diagnostic workup should be undertaken to rule out gynecological pathology.
ELDERLY: There were no significant differences in the safety profile of Cytotec in approximately 500 ulcer patients who were 65 years of age or older compared with younger patients.
Additional adverse events which were reported are categorized as follows:
INCIDENCE GREATER THAN 1%: In clinical trials, the following adverse reactions were reported by more than 1% of the subjects receiving Cytotec and may be causally related to the drug: nausea (3.2%), flatulence (2.9%), headache (2.4%), dyspepsia (2.0%), vomiting (1.3%), and constipation (1.1%). However, there were no significant differences between the incidences of these events for Cytotec and placebo.
CAUSAL RELATIONSHIP UNKNOWN: The following adverse events were infrequently reported. Causal relationships between Cytotec and these events have not been established but cannot be excluded:
Body As A Whole: aches/pains, asthenia, fatigue, fever, rigors, weight changes.
Skin: rash, dermatitis, alopecia, pallor, breast pain.
Special Senses: abnormal taste, abnormal vision, conjunctivitis, deafness, tinnitus, earache.
Respiratory: upper respiratory tract infection, bronchitis, bronchospasm, dyspnea, pneumonia, epistaxis.
Cardiovascular: chest pain, edema, diaphoresis, hypotension, hypertension, arrhythmia, phlebitis, increased cardiac enzymes, syncope.
Gastrointestinal: GI bleeding, GI inflammation/infection, rectal disorder, abnormal hepatobiliary function, gingivitis, reflux, dysphagia, amylase increase.
Hypersensitivity: Anaphylaxis.
Metabolic: glycosuria, gout, increased nitrogen, increased alkaline phosphatase.
Genitourinary: polyuria, dysuria, hematuria, urinary tract infection.
Nervous System/Psychiatric: anxiety, change in appetite, depression, drowsiness, dizziness, thirst, impotence, loss of libido, sweating increase, neuropathy, neurosis, confusion.
Musculoskeletal: arthralgia, myalgia, muscle cramps, stiffness, back pain.
Blood/Coagulation: anemia, abnormal differential, thrombocytopenia, purpura, ESR increased.

OVERDOSAGE:

The toxic dose of Cytotec in humans has not been determined. Cumulative total daily doses of 1600 mcg have been tolerated, with only symptoms of gastrointestinal discomfort being reported. In animals, the acute toxic effects are diarrhea, gastrointestinal lesions, focal cardiac necrosis, hepatic necrosis, renal tubular necrosis, testicular atrophy, respiratory difficulties, and depression of the central nervous system. Clinical signs that may indicate

an overdose are sedation, tremor, convulsions, dyspnea, abdominal pain, diarrhea, fever, palpitations, hypotension, or bradycardia. Symptoms should be treated with supportive therapy.
It is not known if misoprostol acid is dialyzable. However, because misoprostol is metabolized like a fatty acid, it is unlikely that dialysis would be appropriate treatment for overdosage.

DOSAGE AND ADMINISTRATION:

The recommended adult oral dose of Cytotec for the prevention of NSAID-induced gastric ulcers is 200 mcg four times daily with food. If this dose cannot be tolerated, a dose of 100 mcg can be used. (See Actions/Clinical Pharmacology: Clinical Studies.) Cytotec should be taken for the duration of NSAID therapy as prescribed by the physician. Cytotec should be taken with a meal, and the last dose of the day should be at bedtime.
RENAL IMPAIRMENT: Adjustment of the dosing schedule in renally impaired patients is not routinely needed, but dosage can be reduced if the 200-mcg dose is not tolerated. (See Actions/Clinical Pharmacology.)

HOW SUPPLIED:

Cytotec 100-mcg tablets are white, round, with SEARLE debossed on one side and 1451 on the other side; supplied as:

NDC NUMBER	SIZE
0025-1451-60	unit-of-use bottle of 60
0025-1451-20	unit-of-use bottle of 120
0025-1451-34	carton of 100 unit dose

Cytotec 200-mcg tablets are white, hexagonal, with SEARLE debossed above and 1461 debossed below the line on one side and a double stomach debossed on the other side; supplied as:

NDC NUMBER	SIZE
0025-1461-60	unit-of-use bottle of 60
0025-1461-31	unit-of-use bottle of 100
0025-1461-34	carton of 100 unit dose

Store at or below 25 deg C (77 deg F) in a dry area.
Caution: Federal law prohibits dispensing without prescription.
8/08/95--A05450-1
For photo(s) of this product, click here, or use the button on the toolbar.

PATIENT PACKAGE INSERT:

PATIENT INFORMATION
Read this leaflet before taking Cytotec(R) (misoprostol) and each time your prescription is renewed, because the leaflet may be changed.
Cytotec (misoprostol) is being prescribed by your doctor to decrease the chance of getting stomach ulcers related to the arthritis/pain medication that you take.
Cytotec can cause miscarriage, often associated with potentially dangerous bleeding. This may result in hospitalization, surgery, infertility, or death. DO NOT TAKE IT IF YOU ARE PREGNANT AND DO NOT BECOME PREGNANT WHILE TAKING THIS MEDICINE.
If you become pregnant during Cytotec therapy, stop taking Cytotec and contact your physician immediately. Remember that even if you are on a means of birth control it is still possible to become pregnant. Should this occur, stop taking Cytotec and contact your physician immediately.
Cytotec may cause diarrhea, abdominal cramping, and/or nausea in some people. In

most cases these problems develop during the first few weeks of therapy and stop after about a week. You can minimize possible diarrhea by making sure you take Cytotec with food.
Because these side effects are usually mild to moderate and usually go away in a matter of days, most patients can continue to take Cytotec. If you have prolonged difficulty (more than 8 days), or if you have severe diarrhea, cramping and/or nausea, call your doctor.
Take Cytotec only according to the directions given by your physician.
Do not give Cytotec to anyone else. It has been prescribed for your specific condition, may not be the correct treatment for another person, and would be dangerous if the other person were pregnant.
This information sheet does not cover all possible side effects of Cytotec. This patient information leaflet does not address the side effects of your arthritis/pain medication. See your doctor if you have questions.
Keep out of reach of children.

****

[redacted]

****

[redacted]

Cytotec has not been in my drug group for over a year now. I remember Searle had proposed a "Dear Healthcare Practitioner" letter some time ago, but I don't know what happen to it. [redacted] is now the Project Manager in our Division for Cytotec. [redacted] do you know anything about the "Dear Doctor" letter?

[redacted]

[redacted] -I received a copy of Health News Daily for 8/28. It contains an
>article about a letter Searle recently sent to doctors concerning the
>unapproved use of cytotec for abortion. It appears to have been timed
to
>coincide with the 9/30 PDUFA date for RU-486. According to the
article,
>"The letter was drafted in collaboration with FDA, the agency
indicated."
>Do you know anything about this? Thanks.
>
[redacted]
>
[redacted]
>FDA.OCC
> [redacted]
[redacted]
>
>This email message is intended for the exclusive use of the
recipient(s)
>named above. It may contain information that is protected, privileged,
or
>confidential, and it should not be disseminated, distributed, or copied
to
>persons not authorized to receive such information. If you are not the
>intended recipient, any dissemination, distribution or copying is
strictly
>prohibited. If you think you have received this e-mail in error,
please
>e-mail the sender immediately at [redacted]
>

To: [redacted]
Cc:
Cc:

SEARLE

SEARLE
5200 Old Orchard Road
Skokie, Illinois 60077
PHONE (847) 982-7000
FAX (847) 470-1460

IMPORTANT DRUG WARNING CONCERNING UNAPPROVED USE OF INTRAVAGINAL OR ORAL MISOPROSTOL IN PREGNANT WOMEN FOR INDUCTION OF LABOR OR ABORTION

August 23, 2000

Re: Cytotec® (misoprostol)

Dear Health Care Practitioner:

The purpose of this letter is to remind you that Cytotec administration by any route is contraindicated in women who are pregnant because it can cause abortion. Cytotec is not approved for the induction of labor or abortion.

Cytotec is indicated for the prevention of NSAID (nonsteroidal anti-inflammatory drugs, including aspirin)-induced gastric ulcers in patients at high risk of complications from gastric ulcer, e.g., the elderly and patients with concomitant debilitating disease, as well as patients at high risk of developing gastric ulceration, such as patients with a history of ulcer.

The uterotonic effect of Cytotec is an inherent property of prostaglandin E_1 (PGE_1), of which Cytotec is a stable, orally active, synthetic analog. Searle has become aware of some instances where Cytotec, outside of its approved indication, was used as a cervical ripening agent prior to termination of pregnancy, or for induction of labor, in spite of the specific contraindications to its use during pregnancy.

Serious adverse events reported following off-label use of Cytotec in pregnant women include maternal or fetal death; uterine hyperstimulation, rupture or perforation requiring uterine surgical repair, hysterectomy or salpingo-oophorectomy; amniotic fluid embolism; severe vaginal bleeding, retained placenta, shock, fetal bradycardia and pelvic pain.

Searle has not conducted research concerning the use of Cytotec for cervical ripening prior to termination of pregnancy or for induction of labor, nor does Searle intend to study or support these uses. Therefore, Searle is unable to provide complete risk information for Cytotec when it is used for such purposes. In addition to the known and unknown acute risks to the mother and fetus, the effect of Cytotec on the later growth, development and functional maturation of the child when Cytotec is used for induction of labor or cervical ripening has not been established.

Searle promotes the use of Cytotec only for its approved indication. Please read the enclosed updated complete Prescribing Information for Cytotec.

Further information may be obtained by calling 1-800-323-4204.

Michael Cullen, MD
Medical Director, U.S.
Searle

CYT0141A

MIF 008892

APPENDIX C
THE POPULATION COUNCIL PROTOCOL 166B
STUDY PROTOCOL AND AMENDMENTS AND GENERAL INFORMATION

A. Date Protocol Filed to IND — and Dates Amended:

Date Filed: August 3, 1994
Dates Amended: November 2, 1994
May 5, 1995

B. Protocol Cover Sheet

C. Protocol, Protocol Amendments, Sample Informed Consent Form, and Case Report Forms

D. Mifepristone and Misoprostol Drug Lot Numbers

Mifepristone: JMP25524-109 (all centers)
Misoprostol:
Center 21: 4P456, 4P457
Center 22: 04H437, 4H438, 4H438A, 4N451
Center 23: 4F434, 4N454, 5B468
Center 24: 4F434, 4S459, 4S462, 5B468
Center 25: 4N453
Center 26: 4F434, 4F435, 4K446, 4S462
Center 27: 3P411, 4P456, 4S459, 5C476, 5D479
Center 28: 4P455, 4P456, 4S459, 5D479
Center 29: 4H438A

E. Publications Based on the Study

Spitz IM, Bardin CW, Benton L, Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United States. New Engl J Med 1998;338:1241-7.

Winikoff B, Ellertson C, Elul B, Sivin I for the mifepristone clinical trials group. Acceptability and feasibility of early pregnancy termination by mifepristone - misoprostol: results of a large multicenter trial in the United States. Arch Fam Med 1998;7:360-6.

Continuation of Protocol 166B

Appendix C

Part B. Protocol Cover Sheet

APPENDIX C
THE POPULATION COUNCIL PROTOCOL 166B

B. PROTOCOL COVER SHEET

Study Phase: III

Name of Drug:
Active Ingredient: Mifepristone
Dosage: 600 mg
Route of Administration: oral
Duration of Treatment: single dose

Objective: the study was conducted to evaluate the effectiveness, safety, acceptability, feasibility of using mifepristone and misoprostol in a setting within the United States health care system for the induction of abortion in women whose duration of amenorrhea was no more than 63 days.

Patient Population: women at least 18 years of age who were ≤ 63 days from onset of their last menstrual period and who requested a voluntary termination of pregnancy.

Structure: open-label, single treatment group with patients stratified by gestational age (≤ 49, 50 - 56, 57 - 63 days).
Multicenter: yes
Number of Centers: 9
Common Training: yes
Blinding: none
Method of Patient Assignment: all patients were assigned to treatment with 600 mg mifepristone and 400 μg misoprostol.

Concurrent Control: none

Estimated Total Sample Size: 1050

Statistical Rationale Provided: no

Primary Efficacy Variable: proportion of patients with complete expulsion of the products of conception.

Adverse Reactions: observed/volunteered

Plan for Data Analysis: yes

Continuation of Protocol 166B

Appendix C

Part C. Protocol and Informed Consent, Protocol Amendments, Case Record Forms

Amendment 3
May 5, 1995

CONFIDENTIAL

EVALUATION OF THE EFFICACY, SAFETY AND ACCEPTABILITY OF MIFEPRISTONE AND MISOPROSTOL IN INDUCING ABORTION IN PREGNANT WOMEN WITH AMENORRHEA OF UP TO 63 DAYS

PROTOCOL NUMBER: 166A,B

SPONSOR: The Population Council, Inc.
1230 York Avenue
New York, New York 10021

_____

Signature, Principal Investigator

Protocol approved by The Population Council's IRB on September 14, 1994
Amendment No. 1 approved by The Population Council's IRB on November 2, 1994
Amendment No. 2 and 3 approved by The Population Council's IRB on May 5, 1995

TABLE OF CONTENTS

PAGE

1. INTRODUCTION

Mifepristone is a synthetic steroid currently used for medical abortion in France, Sweden, United Kingdom and China. It acts as a competitive blocker of progesterone and cortisol through binding to their receptors. Because of its antiprogesterone activity, mifepristone has been developed primarily as a medical abortifacient. When used alone in different regimens with total doses ranging from 140 to 1600 mg administered over one to ten days, the success rate of abortion in women with amenorrhea of less than 50 days duration usually varied between 64-85%[1].

Subsequent studies demonstrated that when mifepristone (600 mg) was followed two days later by a prostaglandin analog administered either by the intramuscular route (sulprostone, a prostaglandin E_2 analog), or as a vaginal pessary (gemeprost, a prostaglandin E_1 analog), the efficacy rate for complete abortion increased to 95% and above. Based on these observations, mifepristone has been marketed in France since September 1989 as a medical alternative to surgical abortion for the termination of pregnancies in women with amenorrhea of 49 days or less. Recently, this mifepristone - prostaglandin regimen was approved in the United Kingdom, and in Sweden. In the latter two countries, this combination is used in women with amenorrhea of up to 63 days.

In Europe there is now an accumulated experience with over 150,000 subjects who have received mifepristone together with various prostaglandins. Clinical trials have been conducted in several countries and have confirmed the initial experience. Unlike treatment with mifepristone alone where the success rate decreased with advancing duration of amenorrhea, the combination was effective up to 63 days of amenorrhea and in various published studies, the incidence of abortion induction ranged from 92.7% to 99%[1].

The most comprehensive study published to date comprises 16,369 subjects from over 450 clinics[2]. In this study 0.8% of the cases experienced uterine bleeding significant enough to necessitate vacuum aspiration or dilatation and curettage and in 0.07% (11 women), a blood transfusion was required. Significant cardiovascular side effects were reported in four cases following sulprostone administration. In three of these subjects, there was severe hypotension necessitating infusion of macromolecular solutes and in the final subject, a 38 year-old smoker, there was an acute myocardial infarction. In these four subjects, symptoms commenced within one hour of sulprostone administration and all recovered uneventfully. However, in general use, there was a fatal myocardial infarction in one woman, who was a 31-year-old heavy smoker, following sulprostone[3]. No cardiovascular complications have been reported following gemeprost, but this may be related to the fact that this analog has been used less often than sulprostone. Sulprostone is rapidly absorbed into the circulation following intramuscular injection.

therefore, it is not unreasonable to assume that this prostaglandin carries a higher risk of cardiovascular problems than preparations that are administered orally or vaginally and are absorbed more gradually. Moreover, gemeprost, unlike sulprostone, is an E_1 analog.

As a consequence, parenteral prostaglandins should be used cautiously in women with heart disease, those over 35 years of age or in heavy smokers. The French health authorities have in fact withdrawn sulprostone as one of the prostaglandin preparations which can be given with mifepristone.

Because of the cardiovascular side effects reported with sulprostone as well as the inconvenience of both sulprostone and gemeprost which both require refrigeration, alternate prostaglandin preparations are now being used. Misoprostol, (methyl 11α, 16-dihydroxy-16-methyl-9-oxoprost-13 E-en-1-oate) is a prostaglandin E_1 analog that has been safely used for the prevention of nonsteroidal anti-inflammatory drug-induced gastric ulcers in patients at high risk for complications from gastric ulcers for many years; for this indication, it is given in an oral dose of 200 μg four times daily. Its effects on uterine tone are similar to those of other prostaglandins. Misoprostol is inexpensive, orally active and stable. In a recently published French study in women with amenorrhea of 49 days or less, one group comprising 505 women received 400 μg misoprostol 48 hours after mifepristone; the success rate for termination of pregnancy was 96.9%[4]. A second group of 390 women initially followed the same protocol, —

— In this second group, the overall success rate was 98.7%. These results indicate that the combination of mifepristone and misoprostol is of equal or greater effectiveness than the combination of mifepristone and either parenteral or vaginal prostaglandin for the termination of early pregnancy.[4] No serious cardiovascular side effects have been observed. Other side effects were neither more frequent nor more severe than after either parenteral or vaginal prostaglandin preparations[4].

A study from Britain reported complete abortion in 92 out of 99 women with amenorrhea of less than 57 days who were given 200 mg mifepristone followed 48 hours later by 600 μg misoprostol. There were three on-going pregnancies and four incomplete abortions. Vomiting was exhibited in 24% and diarrhea in 7% of the women. No analgesia was needed in 62% of the women[5].

In the two studies reported above, approximately 60-80% of women aborted during the four hours following prostaglandin administration. A number of side effects have been observed during this four hour period. These include: uterine pain, nausea, vomiting and diarrhea. In one of these studies the incidence of nausea, vomiting and diarrhea were 43%, 17% and 14% respectively[4].