MEMORANDUM

Scheldon Kress, M.D.
HFD-180

April 12, 2001

To: ODE III
C/O Florence Houn, M.D.
Victor Raczkowski, M.D.

I thought you would like to see this report of uterine rupture associated with cytotec. In addition, this woman [redacted] uterine rupture victims.

3688664-1-00-01

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

VOLUNTARY reporting by health professionals of adverse events and product problems

Internet Submission - Page 1

CDER

Form Approved: OMB No. 0910-0291 Expires: 12/31/00 See OMB statement on reverse

FDA Use Only

Triage unit sequence #: 139800

A. Patient information

1. Patient identifier	2. Age at time of event:	3. Sex	4. Weight
In confidence	31 Years or Date of birth:	☑ female ☐ male	160 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/yyyy)
- ☑ life-threatening
- ☐ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☑ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event (mm/dd/yyyy)

4. Date of this report (mm/dd/yyyy): 03/21/2001

5. Describe event or problem

I was given Cytotec, 25 mg, at _____ on July 21, 1998 by Dr. _____

I was not told that this off label drug was being used on my for induction of labor. I was not told of the risks of uterine rupture. _____ stuck this pill inside me and walked away. That was the last I saw of him until he came in at the end when they were doing my emergency C-section. My Dr. was not immediately available. I had a uterine rupture during a VBAC attempt. Cytotec, I believe was a big contributor to my uterine rupture. When they cut me open, they found that my daughter head and upper chest area were had pushed out through my old c-section scar into my abdomen. I had placenta abruptio. Due to this, she lost appoximately ten minutes of oxygen. She has been recently diagnosed with mild cerebral palsy. Because of this

6. Relevant tests/laboratory data, including dates

DSC

MAR 2 6 2001

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

I had a totally healthy pregnancy.

MAR 2 2 2001

CTV139800

C. Suspect medication(s)

1. Name (Procut Name)	(Labeled Strength)	(Mfr/Labeler)
#1 Cytotec	25mg	Searle
#2		

2. Dose/Frequency/Route used	3. Therapy dates (if unknown, give duration) From	To (or best estimate)
#1 25 mg	#1 07/21/1998	07/21/1998
#2	#2	

4. Diagnosis for use (separate indications with commas)
#1 Induction of labor
#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 Cytotec

2. Type of device Pill used to induce labor during VBAC attempt

3. Manufacturer name & address
Searle

RECEIVED
MAR 2 2 2001
MEDWATCH CTU

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

5. Expiration date (mm/dd/yyyy)

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

7. If implanted, give date (mm/dd/yyyy)

8. If explanted, give date (mm/dd/yyyy)

9. Device available for evaluation? (Do not send device to FDA)
☐ yes ☐ no ☐ returned to manufacturer on _____ (mm/dd/yyyy)

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

E. Reporter (see confidentiality section on back)

1. Name
phone

2. Health professional? ☐ yes ☑ no

3. Occupation

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

FDA Form 3500

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

B5. Describe event or problem continued

tragedy, ~~~~~ had it not been for my uterine rupture and finding out on the internet about other women's ruptures. We have close to 70 members who have had a uterine rupture. I know of six cases in our group where Cytotec was used. Two of the babies died, and some others are neurologically impaired for life! Our most recent member, ~~~~~ just joined our group. This was her first pregnancy. She had a uterine rupture, a hysterecthomy and lost her baby. She was in a medicated coma for 35 days. This drug causes spontaneous ruptures too. I beg of you, PLEASE STOP THIS TRAGEDY. You are aware there is a problem. You are aware that babies and mothers have died from the misuse of this drug. Our group would like to see Cytotec banned for use on all pregnant women. Yes, I understand that the Ru486 drug needs Misoprostol. But please understand, that for the woman that "WANT" their babies, we don't want them to die or be brain damaged. Is the government going to continue protecting the right of women to have an abortion over the right of other women who want to have their babies born healthy? Our group is starting to get media attention on this issue. Dateline, 60 minutes and others have contacted our group. Our stories will be airing soon. We would like to see Cytotec pulled from all hospital shelves IMMEDIATELY!!!!!!! This has to stop. We are no longer going to lie down and let these Doctors stick little pills into our cervix which could kill our unborn babies. WE WILL NOT TAKE THIS LYING DOWN! Do the right thing and stop this senseless tragedy.

D33

139800

SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINSTRATION	OPDRA POSTMARKETING SAFETY REVIEW	
: Victor Raczkowski, M.D., Deputy Office Director .ıice of Drug Evaluation III, HFD-103	**FROM:** **Toni Piazza-Hepp, Pharm.D., Associate Director, Division of Drug Risk Evaluation I I (DDREII) HFD-440**	**OPDRA PID # D000739** December 27, 2000 DEC 27 2000

DATE REQUESTED: 9/15/00	**REQUESTOR/Phone #:301-827-3144**	
DATE RECEIVED: 9/15/00		
DRUG (Est): misoprostol	**NDA # 19268**	**SPONSOR:** Searle
DRUG NAME (Trade): Cytotec		
EVENT: Uterine Rupture Update		

Executive Summary: Victor Raczkowski requested information on 9/15/00 regarding uterine rupture cases and misoprostol in ·ponse to an outside inquiry from a professional organization. The following information was provided to HFD-103 on 9/15/00:

1) A copy of a previous OPDRA document by Carol Pamer dated 6/16/98, which addressed uterine rupture and selected serious events associated with misoprostol use during pregnancy. Ten uterine rupture cases had been identified at that time. A hard copy is attached to this document.
2) A search in the Adverse Event Reporting System covering the time period 11/01/97 (cutoff of the previous search) to 09/15/00 for any cases of uterine rupture. This search identified 25 cases, however, 17 of them originated from ten literature articles; the years these were published were: 1995 (1), 1996 (1), 1998 (4), 1999 (1), 2000 (3). The year that the events occurred in the patients described in these articles is not known. Copies of all 25 cases were provided to Dr. Raczkowski.

A Dear Health Care Provider letter was issued by Searle on August 23, 2000 stating that the drug is contraindicated in pregnant women; the text is reproduced in this document.

Search Date: 09/15/00	**Search Type(s):** AERS

Search Criteria: Drug Names: **misoprostol (Cytotec)**

MEDDRA Preferred Terms (PT): Uterine injury NOS, Uterine perforation, Uterine Rupture

Re:Cytotec® (misoprostol)

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

Dear Health Care Provider:

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 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

Attachments: Monitored Adverse Reaction Report: Misoprostol (Cytotec), Uterine rupture and selected serious events associated with use during pregnancy dated 6/16/98.

Toni Piazza-Hepp 12/27/00
Reviewer's Signature / Date: 12/27/00

Toni Piazza-Hepp for Kathleen Uhl 12/27/00
Division Director Signature / Date: 12/27/00

Cc: NDA # 19268
HFD-180 Division File/Talarico / Kress (MO) / Kacuba(PM)
HFD-440 Uhl / Piazza-Hepp / Drug / Corken

HFD-103 F. Houn HFD-103 V Raizvolshi

MEMORANDUM

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

DATE:

FROM: Carol Pamer, R.Ph., Postmarketing Safety Evaluator
Reports Evaluation Branch, HFD-735

THROUGH: Ralph Lillie, R.Ph., Acting Director 6/16/99
Division of Pharmacovigilance and Epidemiology, HFD-730

TO: Lilia Talarico, M.D., Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

TO: Lisa Rarick, M.D., Director
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.

manufacturer has included extensive warnings and precautions concerning these uterine stimulatory effects in pregnancy ne current product labeling for Cytotec® . These extensive warnings are excerpted in Attachment #1. Note that *uterine rupture* per se is not specifically mentioned in the product labeling for Cytotec®.

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[5,6,7,8,9,10].

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 ...py 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. **Although uterine rupture does not appear in the product label, 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

---

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

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

[7] Nishioka FY. Prostaglandin E2 preparations for preinduction cervical ripening: pharmacy considerations. J Reprod Med 1993; 38(1 suppl):83-3.

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

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

[10] 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 are 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		

Drug Utilization Data (Note: Trade secret data. For FDA internal use only.)

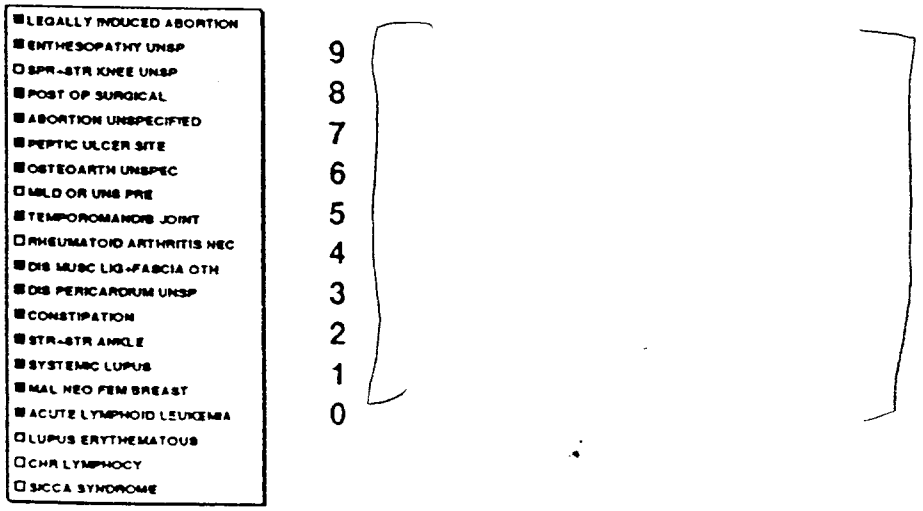
Data were obtained from the National Disease and Therapeutic Index (NDTI). A search of the database for ICD-9 codes in the age range 15 to 44 y.o. as of March 1998 resulted in the following data:

Cytotec (misoprostol)

Percentage of Drug Uses

Age group 15-44 y.o.

1995-1997 (IMS)



[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

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., has placed significant warnings regarding *potential* risks associated with the use of misoprostol during pregnancy, it would advisable for information concerning *actual* reports of adverse events to be added to the product labeling. These actual reports should be detailed in CONTRAINDICATIONS, WARNINGS, and/or PRECAUTIONS in conjunction with the current warnings of potential risks. Some suggested wording to assist in describing these events follows.

[ ]

Consideration should also be given to adding information concerning the 2 cases which were stated to be overdoses (950707-SK195, 971113-SK133) to the Overdosage section of the labeling.

Carol Pamer, R.Ph.

Toni Piazza-Hepp, PharmD
Group Leader

David Barash, R.Ph.
Branch Chief

cc: HFD-180 NDA 19268
HFD-180 Strongin/Robie-Suh
HFD-730 Acting Division Director (Lillie)
HFD-733 Acting Branch Chief (Rodriguez)/Wysowski
HFD-735 Barash/Piazza-Hepp/Farinas/Pamer/MAR/Chron

dfiles\mar\misogyn.fin

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. *

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:

****

* 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 uniess 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

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.

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.

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
061022-SK848	1996	US (FL)	**Uterine rupture.**	Unk	Unk	Unk	Vaginal	Induce abortion
061022-SK850	1996	US (FL)	**Uterine rupture.**	Unk	Unk	Unk	Vaginal	Induction of labor
070714-SK994	1996	US (FL)	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 (CA)	**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 (CA)	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 (VA)	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 (NY)	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 (CA)	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 (IA)	Hemorrhage, Hgb 4.5. Surgery required.	32 yrs.	Hosp, surgery required	Unk	Unk	Induce abortion
950707-SK495	1995	US (NC)	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 (MI)	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 (47151U/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)

MEMORANDUM

DATE: September 7, 2000

TO: Florence Houn, M.D., Office Director

FROM: Paul E. Levine, Jr., R.Ph., Regulatory Project Manager

SUBJECT: NDA 19-268, Cytotec®: DHCP Letter and Package Insert (PI)

CC: L.Talarico, K.Johnson

The final DHCP letter was submitted as a *General Correspondence* by the firm on August 21, 2000. The DHCP letter incorporates recommendations from the Advice (AD) letter issued by the Division on May 23, 2000. The AD letter was issued in response to the firm's March 9, 2000, correspondence requesting advice from the Agency on their draft DHCP letter. Both DDMAC and DRUDP were consulted prior to issuing the AD letter.

In response to your request, please find attached a copy of the following:

Attachment #1: The **final DHCP letter** submitted by the firm on August 21, 2000.
[Note: The firm simultaneously submitted this version to MedWatch]

Attachment #2: The May 23, 2000, **Advice letter**.

Attachment #3: Copies of the **DDMAC and DRUDP Consults** in response to the firm's March 09, 2000, request for comments on the draft DHCP letter

Attachment #4: The March 9, 2000, submission from the firm containing the draft **DHCP letter**.

Attachment #5: The **currently approved package insert** (approved 06/22/00).
[Note: the firm has a CBE supplement which is currently being reviewed. This could result in changes to the PI once completed]

Attachment #6: A copy of the **December 17, 1999, approvable letter**.

AP 6/22/00

A05450-3

SEARLE

Cytotec®
(misoprostol)

Revised: Mar. 6, 2000

CONTRAINDICATIONS AND WARNINGS

CYTOTEC (MISOPROSTOL) ADMINISTRATION BY ANY ROUTE IS CONTRAINDICATED, BECAUSE IT CAN CAUSE ABORTION, IN WOMEN WHO ARE PREGNANT (See **WARNINGS** and **PRECAUTIONS**).

- Anecdotal reports have been received, primarily from Brazil, of congenital anomalies and reports of fetal death in pregnancies in which misoprostol has been used as an abortifacient.

PATIENTS MUST BE ADVISED OF THE ABORTIFACIENT PROPERTY AND WARNED NOT TO GIVE THE DRUG TO OTHERS.

UTERINE RUPTURE HAS BEEN REPORTED WHEN CYTOTEC WAS ADMINISTERED INTRAVAGINALLY IN PREGNANT WOMEN TO INDUCE LABOR OR TO INDUCE ABORTION BEYOND THE FIRST TRIMESTER OF PREGNANCY.

UTERINE PERFORATION HAS BEEN REPORTED FOLLOWING ADMINISTRATION OF COMBINED VAGINAL-AND-ORAL CYTOTEC IN PREGNANT WOMEN TO INDUCE ABORTION. IN EACH OF THESE REPORTED CASES, THE GESTATIONAL AGE OF THE PREGNANCIES WAS UNKNOWN.

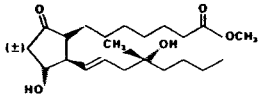
Cytotec should not be used in women of childbearing potential unless the patient requires nonsteroidal anti-inflammatory drug (NSAID) therapy and is at high risk of complications from gastric ulcers associated with use of the NSAID, or is at high risk of developing gastric ulceration. In such patients, 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.

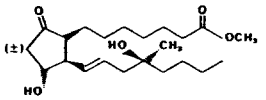
DESCRIPTION

Cytotec oral tablets contain either 100 mcg or 200 mcg of misoprostol, a synthetic prostaglandin E_1 analog.

Misoprostol contains approximately equal amounts of the two diastereomers presented below with their enantiomers indicated by (±):



and



$C_{22}H_{38}O_5$ M.W. = 382.5

(±) methyl 11α,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.

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 T_{max} 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	C_{max} (pg/ml)	AUC(0-4) (pg·hr/ml)	T_{max} (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 $T_{½}$, C_{max}, 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 1 week

administered 2 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 boxed **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 1 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 randomized to treatment 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	Therapy Duration			
	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 8 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 3 months' duration. It had no effect, compared to placebo, on gastrointestinal pain or discomfort associated with NSAID use.

CONTRAINDICATIONS

See boxed **CONTRAINDICATIONS AND WARNINGS.**

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

WARNINGS

See boxed **CONTRAINDICATIONS AND WARNINGS.**

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

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: Because of its abortifacient property, Cytotec is contraindicated for use by pregnant women. Cytotec may cause miscarriage if given to pregnant women at any time during pregnancy. Miscarriages caused by Cytotec may be incomplete, which could lead to 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 *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 1 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.** One case of amniotic fluid embolism, which resulted in maternal and fetal death, has been reported with use of misoprostol during pregnancy. Severe vaginal bleeding, retained placenta, shock, fetal bradycardia, and pelvic and/or orally over a range of doses.

Nonteratogenic effects: Cytotec may endanger pregnancy (may cause miscarriage) and thereby cause harm to the fetus when administered to a pregnant woman. 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 use of misoprostol as an abortifacient have been received (see boxed **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: 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 of Cytotec in pediatric patients have not been established.

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. There have been reports in which intravaginal administration of misoprostol in pregnant women resulted in rupture of the uterus and death of the infant. (See boxed **CONTRAINDICATIONS AND WARNINGS.**)

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

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 *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 *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

PATIENT INFORMATION

Read this leaflet before taking Cytotec® (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.

Do not take Cytotec if you are pregnant because it can cause miscarriage at any time during pregnancy. It is also important to avoid pregnancy while taking this medication and for at least one month or through one menstrual cycle after you stop taking it. Cytotec may cause the uterus to rupture (tear) in pregnant women if it is used to bring on (induce) labor or to cause an abortion after the first trimester of pregnancy. Miscarriages or rupture of the uterus may result in severe bleeding, hospitalization, surgery, infertility or death.

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.

Revised: Mar. 6, 2000

G.D. Searle & Co.
Box 5110, Chicago IL 60680

Address medical inquiries to:
G.D. Searle & Co.
Healthcare Information Services
5200 Old Orchard Road
Skokie IL 60077

SEARLE

 Printed in USA

SEARLE

Cytotec®
(misoprostol)

A05450-3

SEARLE

SEARLE
5200 OLD ORCHARD ROAD
SKOKIE, ILLINOIS 60077
PHONE (847) 982-7000
FAX (847) 470-1480

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

CY20141A

SEARLE

08/31/00
N 6-T

August 21, 2000

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

Lilia Talarico, M.D. Director
Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research (HFD-180)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SUPPL NEW CORRESP

Re: NDA 19-268/S-031
Cytotec® (misoprostol)

Dear Dr. Talarico:

SLR-031-C

Please refer to our supplemental New Drug Application (S-031) dated October 13, 1998, to your letters relating to this supplement dated March 17, April 2, April 9, 1999 and to your approvable letter dated December 17, 1999 to which we responded on March 9, 2000.

We acknowledge receipt of your letter dated May 23, 2000, recommending changes to our draft "Dear Health Care Practitioner" ("HCP") letter. These recommendations have been incorporated into a final version with the exception of the suggested placement of the phrase "maternal and fetal death." We have left that phrase as it appears in our draft version since not all cases of maternal and fetal death, as reported to FDA, resulted from amniotic fluid embolism. A final version of our letter is enclosed for your records.

As the agency recommended, we have considered revising the HCP letter to include [redacted] We have also considered the agency's suggestion that we look at possible ways to expand the categories of health care professionals who are to receive this letter.

[redacted]

[redacted] these reasons, it appears extremely unlikely that [redacted] would be employed for the off-label use addressed in the HCP letter, and we have received no reports of such use.

Accordingly, we do not believe that referring to [redacted] along with Cytotec in the HCP letter would provide any new or useful information for practitioners who prescribe [redacted] for patients with arthritis.

Our defined audience for the HCP letter is a comprehensive list of practitioners most likely to be associated with misoprostol use for the off-label indications addressed in our HCP letter. Please note that, in response to the agency's suggestion, we have expanded our distribution to include both family and general practitioners who are likely prescribers of misoprostol and may assist in labor and delivery, and emergency room physicians, because they may assess patients who have been administered misoprostol for induction of labor or abortion.

If you have any questions or concerns, please address to the undersigned,

Sincerely,

Mary Jo Pritza, MPH, PharmD.
Regulatory Affairs Associate
Ph: 847-982-7831
Fax: 847-982-8090

cc: MEDWATCH-HF2

Levine

NDA 19-268/S-031

MAY 2 3 2000

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

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 ——————————, 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 ——————————— from the second sentence of the first paragraph.

3. Delete the term ———— ' 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 maternal and fetal 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 [redacted]; 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,

5-23-00

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

cc:
Archival NDA 19-268
HFD-180/Division file
HFD-180/P.Levine
/L.Talarico

— 15-23-00

Drafted by: PEL-05/12/00
Initialed by: BKS/May 22, 2000
LT/May 23, 2000
Final: BKS/May 23, 2000
Filename: DHCP letter 051100.doc

GC/ADVICE — 5/24/00

EPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

(26)

Division/Office): **Lana Pauls (HFD-580, DRUDP) PKLN Bldg. 17B45**	FROM: **Paul E. Levine, Jr. (HFD-180) PKLN Bldg. Rm 6B-17**

E	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
AR 31, 2000		**19-268/ SLR-031**	**BL**	**MAR 09, 2000**

AE OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Cytotec (misoprostol) Tablets		**Anti-ulcer**	**Apr 7, 2000**

AE OF FIRM: **G.D. Searle & Company**

REASON FOR REQUEST

I. General

- NEW PROTOCOL
- PROGRESS REPORT
- NEW CORRESPONDENCE
- DRUG ADVERTISING
- ADVERSE REACTION REPORT
- MANUFACTURING CHANGE/ADDITION
- MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

TISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
YPE A OR B NDA REVIEW OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
- BIOAVAILABILTY STUDIES
- PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
- COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

OMMENTS/SPECIAL INSTRUCTIONS: **On March 9, 2000, in response to our approvable letter on December 17, 1999, the firm (Searle) omitted a revised draft of a "Dear Healthcare Practitioner" (HCP) letter which they wish to implement immediately. A copy of the draft HCP ter, the approvable letter, the HCP letter submitted on June 3, 1999, and your comments in the September 13, 1999 meeting concerning the ne 3, 1999, letter are attached.**

e are requesting a review of the draft HCP letter to ensure that the wording is consistent with the Division's recommendations.

u may direct your questions to me at (301) 443-8347.

nks for your assistance. Paul E. Levine, Jr.

THOD OF DELIVERY (Check one)
☐ MAIL X HAND

IGNATURE OF DELIVERER

Memo to: Paul Levine, Jr. (HFD-180)

Memo from: Susan Allen, MD, MPH — 4/12/00
Acting Director, HFD-580

Date: April 12, 2000

Re: Request for Consultation regarding "Dear Healthcare Practitioner" Letter for NDA 19-268 (Cytotec Tablets)

Date received: April 7, 2000

The sponsor has submitted a Draft "Dear Healthcare Practitioner" letter dated March 9, 2000, addressing unapproved use of intravaginal or oral misoprostol in pregnant women for induction of labor or abortion.

This letter is compared to a previously submitted letter dated June 1, 1999. In light of comments made by this division at the September 13, 1999 internal meeting to discuss proposed revisions to the product label, the following modifications in the text of the letter are recommended:

1. The phrase [redacted] found in the second sentence of the first paragraph of the letter should be deleted. This text is redundant as can be seen from the first sentence in this paragraph.
2. The term [redacted] is alarmist in tone and should be deleted from the second sentence of the second paragraph of the letter.
3. In the first sentence of the third paragraph, the term [redacted] should be replaced with the term "off-label" or [redacted]. In addition, this paragraph should be reworded to follow the format of the related paragraph found in the June 1, 1999 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 salpingo-oophorectomy; amniotic fluid embolism resulting in maternal and fetal death; severe vaginal bleeding, retained placenta, shock, fetal bradycardia and pelvic pain."

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

(Division/Office):			FROM:	
it Staub, DDMAC			Kati Johnson, HFD-180, 827-7458	
TE 1 1/00	IND NO.	NDA NO. 19-268	TYPE OF DOCUMENT Dear Health Care Professional letter	DATE OF DOCUMENT 3/9/00
ME OF DRUG ytotec	PRIORITY CONSIDERATION HI	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE ASAP	

ME OF FIRM: Searle

CENTER FOR DRUG
REC'D
APR 17 2000
DDMAC
EVALUATION AND RESEARCH

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*: Mail #8912

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
TYPE A OR B NDA REVIEW END OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
- BIOAVAILABILTY STUDIES
- PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
- COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

Paul - FYI

OMMENTS/SPECIAL INSTRUCTIONS:

lease review the enclosed "Dear Health Care Professional" letter.
have also enclosed the currently approved labeling.

IGNATURE OF REQUESTER

-5-

METHOD OF DELIVERY (Check one)
☐ MAIL ☒ HAND

GNATURE OF DELIVERER

-5-

MEMO

To:	Kati Johnson	**From:**	Patricia Staub, DDMA
		Date:	04/25/00
Re:	DDMAC Consult on Dear Doctor Letter for Cytotec	**CC:**	Leah Palmer

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** X **Per Your Request**

- **Comments:**

Cytotec Dear Health Care Practitioner Letter Comments (DDMAC)

1. The clarity of the first sentence of the letter could be improved by moving the phrase "*in women who are pregnant*" before the phrase "*because it can cause abortion.*" Highlighting, bolding, or bulleting this information would also add emphasis and increase clarity.

2. Inconsistent references to Cytotec by brand or generic name in the body of the letter is confusing. Clarity would be enhanced by consistently referring to the product as either Cytotec or misoprostol.

3. The purpose of this letter is unclear.

4.

5. Requirements as to the envelope size and IMPORTANT DRUG WARNING caption that must appear on the envelope is found in 21 C.F.R. 200.5.

-END-

DRAFT

SEARLE

NDA 19-268/S-031

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

March 9, 2000

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research (HFD 180)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Talarico:

Please refer to the Supplement (S-031) submitted October 13, 1998 to our approved New Drug Application (NDA 19-268), to your letters relating to this supplement dated March 17, April 2 and April 9, 1999 and to your Approvable letter for this supplement dated December 17, 1999, providing revised draft labeling text for Cytotec® (misoprostol).

To avoid further delay in implementation of this important labeling change, Searle accepts, as written, the revised labeling text provided with the December 17, 1999 approvable letter. We note for the record, [redacted]

We are currently in the process of revising the labeling for printing. The final printed labeling (FPL) will be submitted for review and approval prior to use. Since it will incorporate the exact wording found approvable in your letter of December 17, 1999, we would appreciate an expedited review of the FPL when it is submitted. Your prompt approval will allow implementation of the revised labeling at the earliest possible opportunity.

In the meantime, to minimize further delay as we proceed to final approval of this supplement, I enclose the revised draft of a "Dear Healthcare Practitioner" letter which we wish to implement immediately. As indicated previously, this letter would be targeted to the following professional groups (audience size is estimated in parentheses):

- Obstetrics and Gyencological Physicians (31,000)
- Hospital Pharmacists (21,000)
- Nurse Practtioners in Female Care (3,810)
- Nurse Practioners in Womens Health (1,911)
- Nurse Practitioners in Reproductive Health (55)
- Family Planning Centers (2,118)
- Midwives (7,027)

(Total: 66,921)

Please direct further correspondence on this NDA to the attention of my associate, Mary Jo Pritza, MPH, PharmD., Regulatory Associate. Thank you.

Sincerely,

Peter F. East

Peter F. East
Associate Director,
Regulatory Affairs
Tel: 847 982-8606
Fax: 847 982-8152

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY
APPLICATION NUMBER

PLICANT INFORMATION

ME OF APPLICANT	DATE OF SUBMISSION
. D. Searle & Co.	March 9, 2000
LEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
47) 982-8606	(847) 982-8152

PLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or ail Code, and U.S. License number if previously issued)*:	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
001 Searle Parkway kokie, IL 60077	

ODUCT DESCRIPTION

EW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) **NDA 19-268**

STABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY	
isoprostol	Cytotec®	
HEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)		CODE NAME (*If any*)
)methyl 11a, 16-dihydroxy-16-methyl-9-oxyprost-13^{E}-en-1-oate		
OSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
ablet	100 mcg/200 mcg	Oral

ROPOSED) INDICATION(S) FOR USE:
or the prevention of NSAID induced gastric ulcers in patient at high risk of complications from gastric ulcers

. ICATION INFORMATION

PPLICATION TYPE
heck one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
ame of Drug — Holder of Approved Application

YPE OF SUBMISSION
heck one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY, MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

EASON FOR SUBMISSION
Reference to S-031

ROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

UMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

STABLISHMENT INFORMATION

rovide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, ddress, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) onducted at this site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

ross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current pplication)

make another copy

NDA 19-268/S-031

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

DEC 17 1999

Dear Mr. East:

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

We acknowledge receipt of your submissions dated November 24, 1998 and June 3 and October 4, 1999.

We further acknowledge our letters dated:

A. March 17, 1999, in which we provided revised draft labeling text for the package inserts;

B. April 2, 1999, in which we stated that the labeling text for the package inserts provided in the March 17, 1999 letter was misleading and not fully reflective of the underlying scientific data;

C. and April 9, 1999, that provided further revised draft labeling text for the package insert.

These supplements propose the following change: the addition of statements regarding uterine perforation and uterine rupture to the boxed CONTRAINDICATIONS AND WARNINGS and the WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of the package inserts and the patient information leaflet.

We note the concerns expressed in your letters dated June 3 and October 4, 1999. However, after completing our review of these applications, we have concluded that the attached revised draft labeling text for the package inserts most effectively conveys the risks associated with misoprostol use in pregnant women. Based on our completed review of these applications, as amended, we find them approvable. Before these applications may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert).

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 copies of the final printed labeling (to each application) ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. 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.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with this change prior to approval of these supplemental applications.

If you have any questions, contact Brian Strongin RPh, MBA, Project Manager, at (301) 827-7310.

Sincerely,

12-17-99

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

Enclosure

SEARLE

Cytotec®

(misoprostol)

CONTRAINDICATIONS AND WARNINGS

CYTOTEC (MISOPROSTOL) ADMINISTRATION BY ANY ROUTE IS CONTRAINDICATED, BECAUSE IT CAN CAUSE ABORTION, IN WOMEN WHO ARE PREGNANT (See WARNINGS and PRECAUTIONS).

- Anecdotal reports have been received, primarily from Brazil, of congenital anomalies and reports of fetal death in pregnancies in which misoprostol has been used as an abortifacient.

PATIENTS MUST BE ADVISED OF THE ABORTIFACIENT PROPERTY AND WARNED NOT TO GIVE THE DRUG TO OTHERS.

UTERINE RUPTURE HAS BEEN REPORTED WHEN CYTOTEC WAS ADMINISTERED INTRAVAGINALLY IN PREGNANT WOMEN TO INDUCE LABOR OR TO INDUCE ABORTION BEYOND THE FIRST TRIMESTER OF PREGNANCY.

UTERINE PERFORATION HAS BEEN REPORTED FOLLOWING ADMINISTRATION OF COMBINED VAGINAL-AND-ORAL CYTOTEC IN PREGNANT WOMEN TO INDUCE ABORTION. IN EACH OF THESE REPORTED CASES, THE GESTATIONAL AGE OF THE PREGNANCIES WAS UNKNOWN.

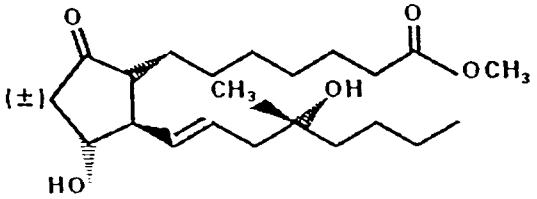
Cytotec should not be used in women of childbearing potential unless the patient requires nonsteroidal anti-inflammatory drug (NSAID) therapy and is at high risk of complications from gastric ulcers associated with use of the NSAID, or is at high risk of developing gastric ulceration. In such patients, 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 contraception 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.**

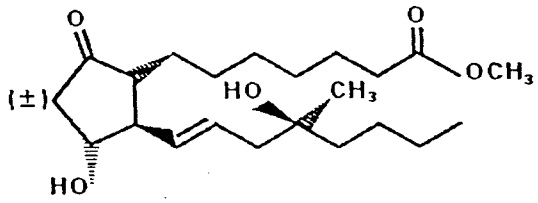
DESCRIPTION

Cytotec oral tablets contain either 100 mcg or 200 mcg of misoprostol, a synthetic prostaglandin E_1 analog.

Misoprostol contains approximately equal amounts of the two diastereomers presented below with their enantiomers indicated by (±):



and



$C_{22}H_{38}O_5$ M.W. = 382.5

(±) methyl 11α,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.

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 T_{max} 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	C_{max}(pg/ml)	AUC(0-4) (pg·hr/ml)	T_{max}(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 $T_{1/2}$, C_{max}, 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 1 week had no effect on the steady state pharmacokinetics of diazepam when the two drugs were administered 2 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 boxed *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 1 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	Therapy Duration			
	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 8 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 3 months' duration. It had no effect, compared to placebo, on gastrointestinal pain or discomfort associated with NSAID use.

CONTRAINDICATIONS

See boxed *CONTRAINDICATIONS AND WARNINGS.*

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

WARNINGS

See boxed *CONTRAINDICATIONS AND WARNINGS.*

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: Because of its abortifacient property, Cytotec is contraindicated for use by pregnant women. Cytotec may cause miscarriage if given to pregnant women at any time during pregnancy. Miscarriages caused by Cytotec may be incomplete, which could lead to 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 *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 1 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.*

One case of amniotic fluid embolism, which resulted in maternal and fetal death, has been reported with use of misoprostol during pregnancy. Severe vaginal bleeding, retained placenta, shock, fetal bradycardia, and pelvic pain have also been reported. These women were administered misoprostol vaginally and/or orally over a range of doses.

Nonteratogenic effects: Cytotec may endanger pregnancy (may cause miscarriage) and thereby cause harm to the fetus when administered to a pregnant woman. 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 use of misoprostol as an abortifacient have been received (see boxed *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: 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.

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. There have been reports in which intravaginal administration of misoprostol in pregnant women resulted in rupture of the uterus and death of the infant. (See boxed *Contraindications and Warnings.*)

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 *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 *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°C (77°F), in a dry area.

Caution: Federal law prohibits dispensing without prescription.

PATIENT INFORMATION

Read this leaflet before taking Cytotec® (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.

Do not take Cytotec if you are pregnant because it can cause miscarriage at any time during pregnancy. It is also important to avoid pregnancy while taking this medication and for at least one month or through one menstrual cycle after you stop taking it. Cytotec may cause the uterus to rupture (tear) in pregnant women if it is used to bring on (induce) labor or to cause an abortion after the first trimester of pregnancy. Miscarriages or rupture of the uterus may result in severe bleeding, hospitalization, surgery, infertility or death.

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.

8/8/95

G.D. Searle & Co.
Box 5110, Chicago IL 60680

Address medical inquiries to:
G.D. Searle & Co.
Healthcare Information Services
5200 Old Orchard Road
Skokie IL 60077

SEARLE

non responsive
draft labeling

24 pages
withheld

cc:
Archival NDAs 19-268, 20-607
HFD-180/Div. Files
HFD-180/B.Strongin
HFD-180/H.Gallo-Torres
HFD-180/L.Goldkind
DISTRICT OFFICE

E 12-9-99

Drafted by: BKS/November 8, 1999
Initialed by: KJ/November 22, 1999
FH/November 24, 1999
LR/November 29, 1999
LT/December 8, 1999
final: BKS/December 9, 1999
filename: 19268911.0

APPROVABLE (AE)

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: 19-268/SLR-031

Name of Drug: Cytotec® (misoprostol) Tablets

Sponsor: G. D. Searle & Company

Material Reviewed

Submission Date: April 12, 2000 (Final Printed Labeling)

Receipt Date: April 13, 2000

Background and Summary Description: NDA 19-268 for Cytotec (mistoprostol) Tablets was approved December 17, 1988 for the prevention of NSAID-induced ulcers in patients at high risk of complications from such ulcers.

NDA 19-268/SLR-031, submitted October 13, 1998, provides for warnings regarding uterine perforation and rupture to be added to the CONTRAINDICATIONS AND WARNINGS box, the WARNINGS section, and ADVERSE REACTION section of the package insert. This supplement was approved on March 17, 1999 on draft labeling. Upon further review of the scientific data by The Division of Reproductive and Urologic Drug Products (HFD-580), the Agency informed Searle in an April 2, 1999 letter that the labeling attached to the March 17, 1999 letter was misleading and issued in error. The Agency sent "FDA revised labeling" to the firm April 9, 1999. The firm responded on June 3, 1999, and the supplement was Approvable, pending FPL, on December 17, 1999. The firm responded April 12, 2000 with FPL.

Review

The submitted package insert, identified as " A05450-3, Revised: Mar. 6, 2000", was compared to the FDA revised labeling in the December 17, 1999 Approvable letter. The following revisions were noted. Deletions are shown as ~~strikeouts~~ and additions are shown as double underlines.

1. Throughout the package insert the parenthetical phase has been revised

   from:

   ---

   to:

"(See boxed **CONTRAINDICATIONS AND WARNINGS.**)"

Comment: This is an appropriate editorial revision.

2. The PRECAUTIONS section, "Pediatric" subsection, has been revised as follows:

"Pediatric Use: Safety and effectiveness of Cytotec ——— pediatric patients have not been established."

Comment: This is an acceptable editorial revision.

3. The caution statement has been revised as follows:

——— **RX only**."

Comment: This revision was made to comply with FDAMA legislation and is acceptable.

4. The following phrases have been added to read:

"©2000, G.D. Searle & Co.
Printed in USA"

5. A revision date and an identifier have been added to read:

"Revised: Mar. 6, 2000
A05450-3"

Comment: These are appropriate editorial revisions.

Conclusions

The submitted package insert is acceptable and the supplement should be approved.

Regulatory Health Project Manager

Supervisory Comment/Concurrence:

cc:
Original NDA 19-268/SLR-031
HFD-180/Div. Files
HFD-180/A.Kacuba

Draft: A.Kacuba/June 16, 2000
R/d Initials: K.Johnson/June 19, 2000
Final: AK/June 19, 2000
Filename: c:\mydocuments\Paul\19268\S-031-labeling review.doc

CSO REVIEW

9/22/06

Foreign labeling

SEARLE

Worldwide Regulatory Affairs

Facsimile Transmission

Searle
Worldwide Regulatory Affairs
4901 Searle Parkway
Skokie, Illinois 60077
U.S.A.

Fax Number: (847) 982-8090
(847) 982-8152

	Name:	Location:
TO:	ALICE KOCUBA	Proj. Mgr - FDA
		301-443-9285
CC:		
FROM:	MARY JO PRITZA	# 847-982-7831

No. of Pages (including cover page) 28

MESSAGE: ALICE → following: UK SPC German SPC + French SPC - I will fax the French version as soon as possible need most current version from affiliate. Please call w/ questions -

SUMMARY OF PRODUCT CHARACTERISTICS

CYTOTEC

1. NAME OF THE MEDICINAL PRODUCT

Cytotec.

2. QUALITATIVE & QUANTITATIVE COMPOSITION

Each tablet contains 200 micrograms misoprostol.

3. PHARMACEUTICAL FORM

White to off-white hexagonal tablets scored both sides, engraved SEARLE 1461 on one side for oral administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cytotec is indicated for the healing of duodenal ulcer and gastric ulcer including those induced by nonsteroidal anti-inflammatory drugs (NSAID) in arthritic patients at risk, whilst continuing their NSAID therapy. In addition, Cytotec can be used for the prophylaxis of NSAID-induced ulcers.

4.2 Posology and Method of Administration

Adults

Healing of duodenal ulcer, gastric ulcer and NSAID-induced peptic ulcer: 800 micrograms daily in two or four divided doses taken with breakfast and / or each main meal and at bedtime.

Treatment should be given initially for at least 4 weeks even if symptomatic relief has been achieved sooner. In most patients ulcers will be healed in 4 weeks but treatment may be continued for up to 8 weeks if required. If the ulcer relapses further treatment courses may be given.

Prophylaxis of NSAID-induced peptic ulcer: 200 micrograms twice daily, three times daily or four times daily. Treatment can be continued as required. Dosage should be individualised according to the clinical condition of each patient.

Elderly

The usual dosage may be used.

Renal impairment: Available evidence indicates that no adjustment of dosage is necessary in patients with renal impairment.

Hepatic impairment: Cytotec is metabolised by fatty acid oxidising systems present in organs throughout the body. Its metabolism and plasma levels are therefore unlikely to be affected markedly in patients with hepatic impairment.

Children

Use of Cytotec in children has not yet been evaluated in the treatment of peptic ulceration or NSAID-induced peptic ulcer disease.

4.3 **Contraindications**

Use in pregnancy and lactation:

Cytotec is contraindicated in pregnant women and in women planning a pregnancy as it increases uterine tone and contractions in pregnancy which may cause partial or complete expulsion of the products of conception.

It is also contraindicated in patients with a known allergy to prostaglandins.

4.4 **Special Warnings and Special Precautions for Use**

Warnings

Use in pre-menopausal women (see also Contraindications): Cytotec should not be used in pre-menopausal women unless the patient requires nonsteroidal anti-inflammatory (NSAID) therapy and is at high risk of complications from NSAID-induced ulceration.

In such patients it is advised that Cytotec should only be used if the patient:

- takes effective contraceptive measures
- has been advised of the risks of taking Cytotec if pregnant (see Contraindications)

Precautions

The results of clinical studies indicate that Cytotec does not produce hypotension at dosages effective in promoting the healing of gastric and duodenal ulcers. Nevertheless, Cytotec should be used with caution in the presence of disease states where hypotension might precipitate severe complications, e.g., cerebrovascular disease, coronary artery disease or severe peripheral vascular disease including hypertension.

There is no evidence that Cytotec has adverse effects on glucose metabolism in human volunteers or patients with diabetes mellitus.

4.5 Interactions with other medicaments and other forms of interaction

Cytotec is predominantly metabolised via fatty acid oxidising systems and has shown no adverse effect on the hepatic microsomal mixed function oxidase (P450) enzyme system. In specific studies no clinically significant pharmacokinetic interaction has been demonstrated with antipyrine, diazepam and propranolol. In extensive clinical studies no drug interactions have been attributed to Cytotec. Additional evidence shows no clinically important pharmacokinetic or pharmacodynamic interaction with nonsteroidal anti-inflammatory drugs including aspirin, diclofenac and ibuprofen.

4.6 Pregnancy and Lactation

Pregnancy

See Contraindications.

Lactation

It is not known if the active metabolite of Cytotec is excreted in breast milk; therefore Cytotec should not be administered during breast feeding.

4.7 Effects on ability to drive and to use machines

Not applicable.

4.8 Undesirable effects

Gastrointestinal system: Diarrhoea has been reported and is occasionally severe and prolonged and may require withdrawal of the drug. It can be minimised by using single doses not exceeding 200 micrograms with food and by avoiding the use of predominantly magnesium containing antacids when an antacid is required.

Abdominal pain with or without associated dyspepsia or diarrhoea can follow misoprostol therapy.

Other gastrointestinal adverse effects reported include dyspepsia, flatulence, nausea and vomiting.

Female reproductive system: Menorrhagia, vaginal bleeding and intermenstrual bleeding have been reported in pre-and post-menopausal women.

Other adverse events: Skin rashes have been reported. Dizziness has been infrequently reported.

The pattern of adverse events associated with Cytotec is similar when an NSAID is given concomitantly.

4.9 Overdose

Intensification of pharmacological effects may occur with overdose. In the event of overdosage symptomatic and supportive therapy should be given as appropriate. In clinical trials patients have tolerated 1200 micrograms daily for three months without significant adverse effects.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Cytotec is an analogue of naturally occurring prostaglandin E_1 which promotes peptic ulcer healing and symptomatic relief. As a PGE, analogue it shares some at least, of that hormone's effects on smooth muscle.

Cytotec protects the gastroduodenal mucosa by inhibiting basal, stimulated and nocturnal acid secretion and by reducing the volume of gastric secretions, the proteolytic activity of the gastric fluid, and increasing bicarbonate and mucus secretion.

5.2 Pharmacokinetic properties

Cytotec is rapidly absorbed following oral administration, with peak plasma levels of the active metabolite (misoprostol acid) occurring after about 30 minutes. The plasma elimination half-life of misoprostol acid is 20-40 minutes. No accumulation of misoprostol acid in plasma occurs after repeated dosing of 400 micrograms twice daily.

5.3 Preclinical Safety Data

In single and repeat-dose studies in dogs, rats and mice at multiples of the human dose, toxicological findings were consistent with the known pharmacological effects of the E-type prostaglandins, the main symptoms being diarrhoea, vomiting, mydriasis, tremors and hyperpyrexia. Gastric mucosal hyperplasia was also observed in the mouse, rat and the dog. In the rat and the dog the hyperplasia was reversible on discontinuation of misoprostol following one year of dosing. Histological examination of gastric biopsies in humans has shown no adverse tissue response after up to one year's treatment. In studies of fertility, teratogenicity and peri/post-natal toxicity in rats and rabbits there were no major findings. A decrease in implantations and some pup growth retardation was observed at doses greater than 100 times the human dose. It was concluded that misoprostol does not significantly affect fertility, is not teratogenic or embryotoxic and does not affect rat pups in the peri/post-natal period.

Misoprostol was negative in a battery of 6 in vitro assays and one in vivo test to assess mutagenic potential. In carcinogenicity studies in the rat and mouse it was concluded that there was no risk of carcinogenic hazard.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cytotec tablets contain : microcrystalline cellulose, sodium starch glycolate, hydrogenated castor oil, hydroxypropyl methyl cellulose (H.P.M.C.)

6.2 Incompatibilities

None known.

6.3 Shelf-life

Cytotec tablets have a shelf-life of 3 years when stored in cold-formed aluminium blisters.

6.4 Special Precautions for Storage

Store below 30°C (86°F).

6.5 Nature and Contents of a Container

Cold-formed aluminium blister packs of 56, 60.,112, 120 or 140 tablets.

6.6 Special Instructions for Use/Handling

None.

7. MARKETING AUTHORISATION HOLDER

Monsanto plc
Trading as Searle
P O Box 53
Lane End Road
High Wycombe
Buckinghamshire
HP12 4HL

8. MARKETING AUTHORISATION NUMBER

PL 8821/0019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

First authorised 27/7/88 (PL 0020/0115)
Last renewed 13/1/99.

10. DATE OF (PARTIAL) REVISION OF THE TEXT)

January 1999

SEARLE

(27)

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077
PHONE (847) 982-7000
FAX (847) 982-4701

Current German SPC

TECHNICAL INFORMATION

1. Name of the drug

Cytotec® 200

Active ingredient: misoprostol

2. Prescription status/pharmacy required

Requires prescription.

3. Composition of the drug

3.1 Material or indication group

Gastrointestinal agent

3.2 Pharmaceutically active components according to nature and amount

1 Tablet contains

misoprostol 200 µg

3.3 Other components

Microcrystalline cellulose, methylhydroxypropylcellulose; poly(O-carboxymethyl)starch; sodium salt; hydrogenated castor oil.

4. Area of application

For the prevention and treatment of drug-induced (for example, anti-inflammatories, acetylsalicylic acid) gastromucosal damage.

The prevention of drug-induced gastric mucosal damage should extend mainly to patients with a corresponding disposition. Data available so far do not allow a well-founded more extensive definition of the treatment groups.

In each case, it should be examined if the dose of the gastric-mucosa-damaging medication could be reduced or if the drug could be discontinued.

For the treatment of acute duodenal and gastric ulcers.

5. Contraindications

Cytotec® 200 should not be used in case of hypersensitivity to misoprostol, other prostaglandins or to one of the other components and in the case of inflammatory intestinal diseases.

The preparation must not be taken during pregnancy, since misoprostol, the active ingredient of Cytotec® 200, can have an effect on the uterine musculature. Women in the childbearing age who do not use or take any contraceptive means must not become pregnant while taking Cytotec® 200. If pregnancy occurs while taking Cytotec® 200, the preparation must be discontinued.

Since it is not known if Cytotec® 200 is transferred into mother's milk, lactating mothers must not be treated with Cytotec® 200.

An especially careful medical monitoring is required for patients who tend to have diarrhea or for whom dehydration could be dangerous.

Prostaglandins of the E-type, to which misoprostol, the active ingredient of Cytotec® 200 belongs, can cause a drop in blood pressure because of the dilatation of the peripheral vessels. Therefore, Cytotec® 200 should be used with caution in patients with cerebral vessel disease or coronary heart disease in whom a drop in blood pressure could lead to complications.

Since sufficient clinical experience with the use of misoprostol in children and adolescents is not available, Cytotec® 200 should not be used by patients under the age of 18 years.

6. Side effects

Frequent: stomach aches, temporary soft stools to diarrhea.

Occasional: digestive disturbances, nausea, vomiting, burping, bloating, constipation, dizziness, feeling dazed, tinnitus, headache, infections of the upper respiratory passages and joint pain.

Rare: pain or cramps in the area of the uterus, changes of menstruation and increase of menstrual bleeding, breakthrough bleeding or bleeding after menopause; in these cases, as well as in the case of severe diarrhea, the use of Cytotec® 200 should be discontinued and a physician consulted.

7. Interactions with other drugs

High-dose antacids can lead to a limitation of the bioavailability of misoprostol. Magnesium-containing antacids may enhance misoprostol-related diarrhea. The effect of laxatives can be enhanced.

Interactions with other drugs, especially with anti-inflammatories, for example, diclofenac, naproxen, ibuprofen, indomethacin, piroxicam and acetylsalicylic acid have not been observed so far.

8. Warnings

None

9. Important incompatibilities

None known.

10. Dosage with individual and daily doses

Unless otherwise prescribed:

- for the prevention and treatment of drug-induced mucosal damage: 2-4 times daily, 1 tablet of Cytotec® 200 (corresponding to 400-800 μg of misoprostol),

- for the treatment of acute gastric and duodenal ulcers, drug-induced gastric ulcers: 4 times daily, 1 tablet of Cytotec® 200 (corresponding to 800 µg of misoprostol).

Elderly patients, patients with kidney function impairment:
In elderly patients and in those with slight to moderate kidney function disturbances, adjustment of the dosage is not absolutely necessary. In the case of patient with severe kidney function disturbances, the treatment should begin with low doses and these patients must be monitored.

11. Nature and duration of application

When there are 2 applications, the tablets should be taken in the morning and in the evening, otherwise after the 3 main meals and additionally optionally before bedtime. The drug should be taken after meals with sufficient fluids (approximately 1 glass of water).

In the preventive treatment, the duration of application should be identical to that of the therapy duration of the drug that damages the gastric mucosa (for example, anti-inflammatory, acetylsalicylic acid), where the extent of the preventive action for periods beyond 12 months cannot be evaluated sufficiently based on data available so far.

For the treatment of existing ulcers, mucosal hemorrhage and mucosal defects, the duration of application is 4 weeks, and can be extended to 8 weeks if necessary.

12. Emergency measures, symptoms and antidotes

a) Symptoms of intoxication

The toxic dose of misoprostol in humans has not yet been established. Daily doses up to 1600 µg were tolerated and led only to gastrointestinal symptoms. In animals, the toxic effects are similar to those that have been reported for other prostaglandins: slackening of the smooth musculature, damping of the central nervous system, shortness of breath.

Clinical signs which can indicate an overdose are: sedation, tremor, cramps, dyspnea, stomach ache, contractions of the uterus, diarrhea, fever, palpitations, hypotonia or bradycardia.

b) Therapy of intoxications

A special antidote is not available yet and, therefore, the treatment in case of an overdose is aimed at elimination of the symptoms and support of important vital functions.

13. Pharmacological and toxicological properties, pharmacokinetics and bio-availability, as long as these data are necessary for therapeutic application

13.1 Pharmacological properties

a) Inhibition of acid secretion

The antisecretory action of misoprostol is manifested both in the inhibition of the basal acid secretion as well as in the inhibition of acid secretion, stimulated by histamine, pentagastrin, tetragastrin, betazole, food intake and caffeine. In addition, misoprostol reduces nocturnal acid secretion.

In-vitro investigations showed that the mechanism of inhibition of acid secretion occurs by direct attack at the parietal cells rather than by indirect mechanisms. In comparison to intravenous and intragastral administration, the injection of misoprostol into the innervated Pavlov pocket of dogs leads to inhibition of acid secretion, even at low dosages. This leads to the assumption that the local action of misoprostol predominates. In animal experiments, only a slight or no effect on the serum-gastrin level was present.

b) Mucosa protective action

In animals and in humans, misoprostol exhibits mucosa-protecting properties, which enhance the integrity of the gastric mucosal barrier to harmful substances.

Dosages of 25 µg and 50 µg of misoprostol, which show only slight antisecretory effects, lead with the simultaneous administration of acetylsalicylic acid to protection of the mucosa in humans by reducing the gastric bleeding caused by acetylsalicylic acid and reducing fecal blood loss.

The pretreatment with acid-inhibitory doses of 200 µg of misoprostol leads to a significant protection of the gastric mucosa against acetylsalicylic-acid-related damage. In the model of

a gastritis produced by ethanol in healthy subjects, 200 μg of misoprostol was found to be about 80% more effective than placebo.

Although the mechanism of cytoprotection has not been clarified unequivocally so far, it seems that misoprostol stimulates the physiological processes in the gastroduodenal mucosa. Thus, misoprostol increases the bicarbonate secretion in the duodenum in a dose-dependent manner, it increases the thickness or the adherent mucus layer in the stomach and the quantity of the soluble mucus in a stomach aspirate. In addition, 200 μg of misoprostol increases the mucosa blood volume in humans by more than 15% in comparison to the normal value. In the case of rats, the mucosal bleeding remains unchanged, while it increases in dogs.

b)[should be c)] Inhibition of pepsin secretion

Misoprostol reduces the secretion of pepsin and the volume of gastric acid both under normal conditions and also under stimulation.

13.2 Toxicological properties

a) Chronic/acute toxicity

The testing of the chronic toxicity of misoprostol was carried out on dogs and rats with up to 480 μg/kg/day and 9000 μg/kg/day per os, respectively.

The noteworthy clinical symptoms in these studies were diarrhea, vomiting, soft and/or slimy stools, increased rectal temperature in the case of dogs, as well as diarrhea, salivation, reduced body weight and increased food intake in rats. All these symptoms abate after a recovery phase.

In both animal species, after long administration, hyperplasia of the gastric mucosa occurred, which, however, proved to be reversible after the discontinuation of the drug. Autonomous growth or atypical cells were not observed.

b) Mutagenic and tumor-producing potential

Results of carcinogenicity experiments on mice and rats showed no indication of a carcinogenic action.

The results of the mutagenicity tests showed no indication of a mutagenic action.

c) Reproduction toxicity

Embryotoxicity studies on rats and rabbits at doses up to 1600 µg/kg/day and 1000 µg/kg/day, respectively, showed no indication of a teratogenic potential. The progeny of rats showed a lower weight gain when misoprostol was administered during fetal development and the lactation period at a dose of 10 mg/kg. Within the framework of fertility studies on male and female rats, a reduction of the implantation rate and an increase of the progeny death rate were found.

13.3 Pharmacokinetics

After oral administration, misoprostol is resorbed rapidly. The maximum plasma level of the active metabolite, misoprostol acid, is reached approximately after 12 minutes. The plasma elimination half-life of misoprostol acid is 20-30 minutes. The plasma elimination half-life of other misoprostol metabolites is 1.5 hours.

The mean maximum plasma level, the C_{max} values, after the administration of individual doses in the range from 200-400 µg, show a linear relationship to the applied dose. After daily administration of 2-4 times 200 µg of misoprostol, the steady-state plasma levels are reached on the second day of treatment. After multiple administration of misoprostol, no cumulation of misoprostol acid in the plasma was detected.

Seventy-three % of the radioactivity of an oral dose of radioactive-labeled misoprostol is excreted with the urine, 15% with the feces. Approximately 56% of the total radioactivity is excreted with the urine within 8 hours.

Misoprostol is metabolized through the fatty acid oxidizing systems (beta- and omega-oxidation), which are present in all organs. In animal studies, misoprostol shows no action on microsomal oxidases (Cytochrome P450) of the liver.

In patients with low or moderate kidney function disturbances, there is an increase of $t_{½}$, of the maximum plasma level, C_{max}, and the areas under the plasma level-time curves, the AUC values. A correlation between the degree of kidney damage and the increase of the AUC

values could not be detected. In anuric patients, there is a doubling of the C_{max}, AUC and $t_{½}$ values for misoprostol acid in comparison to patients with healthy kidneys.

Additional intake of low-dosage antacids showed no interactions. High-dose antacids could lead to a limitation of the bioavailability of misoprostol.

The serum protein binding of misoprostol is less than 90% and is concentration-independent in the therapeutic range. The serum-protein bonding of the free acid of misoprostol is approximately 81-89%. Cumulation of misoprostol in the erythrocytes does not occur.

14. Other information

a) Pregnancy:

Pregnancy can be endangered by the intake of Cytotec® 200 and may cause miscarriage. The active ingredient misoprostol may cause contractions of the uterus and bleeding and may lead to the loss of the fetus. The abortion can be incomplete.

When a woman is pregnant or becomes pregnant during treatment with Cytotec® 200, the preparation must be discontinued because there is a potential risk to the fetus (see point 5 "Contraindications").

After misuse of Cytotec® 200, in individual cases, malformed newborn or death of the fetus may occur.

b) Lactation

Although so far it is not known if misoprostol or its metabolites are transferred into mother's milk, Cytotec® 200 should not be used by lactating mothers.

c) Other information

Combined intake of nonsteroidal anti-inflammatories with misoprostol, gastric and duodenal ulcers, bleeding and perforation may occur, especially in patients who tend to gastrointestinal complaints.

Therefore, even if symptoms are absent, one must always consider the possibility of gastric and duodenal ulcers.

Especially patients with corresponding anamnesis require special monitoring by the physician.

Symptomatic response to therapy with misoprostol does not exclude the malignant nature of a disease.

15. Shelf life

The shelf life is 3 years.

The drug should not be used after the expiration date!

16. Special storage information

Protect against moisture!

16a. Special precautionary measures for the disposal of unused drugs

None

17. Forms of dispensation and package sizes

Packages with 50 (N2) and 100 (N3) tablets
Institutional packaging with 500 (10 x 50) tablets

18. Status of information

February 1997

19. Name of the company and address of the pharmaceutical company

HEUMANN PHARMA GMBH
Heideloffstr. 18-28
90478 Nürnberg
Telephone No. 0911/43 02-0
Telefax No. 0911/43 02-438
A COMPANY OF THE SEARLE GROUP

REMARKS

Dr. Bohn/Dr. Lang:

Dr. Lützenkirchen:

Dr. Bühl:

Dr. Hoffmann:

Marketing Services:

Dr. Vergin:

SEARLE

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077
PHONE (847) 982-7000
FAX (847) 982-4701

Current French SPC

APPENDIX I

SUMMARY OF THE CHARACTERISTICS OF THE PRODUCT

NAME

CYTOTEC 200 micrograms, scored tablet

QUALITATIVE AND QUANTITATIVE COMPOSITION

Misoprostol	200.0 µg
in the form of misoprostol dispersion/HPMC at 1 percent*	20.2 mg
Microcrystalline cellulose	175.8 mg
Sodium carboxymethylstarch	3.0 mg
Hydrogenated castor oil	1.0 mg

for one tablet of 200 mg

* Composition of the dispersion:
spray: misoprostol 1%
hypromellose 99%
intermediate solvent: ethanol

PHARMACEUTICAL FORM

Scored tablet

CLINICAL DATA

Therapeutic indications:

- treatment of ongoing gastric or duodenal ulcer;
- treatment of gastroduodenal lesions induced by NSAIDs, limited to subjects for whom the continuation of anti-inflammatories is indispensable;
- preventive treatment of gastric and duodenal lesions and of severe gastroduodenal complications induced by NSAIDs in subjects at risk (notably, age > 65 years, previous history of gastroduodenal ulcer or intolerance to NSAIDs) for whom anti-inflammatory treatment is indispensable.

Dosage and mode of administration:

Mode of administration

Oral route

The tablets are to be swallowed as such with a large glass of water.

Dosage:

- Treatment of developing ulcer and gastroduodenal lesions: 1 200 mg tablet 4 times per day, that is, 800 μg per day.

- The duration of the treatment is limited to 4 to 8 weeks.

- Preventive treatment against lesions and gastroduodenal complications:
  ½ 200 μg tablet 4 times per day or 1 200 μg tablet twice per day, that is, 400 μg per day for 10 days.
  If this dose is well-tolerated, then 1 200 μg tablet 4 times per day, that is, 800 μg per day.
  In case of intolerance (diarrhea) at the high dose, the dose of 400 μg per day should be pursued.

Frequency of administration:

As a function of indication, the dosage is to be distributed into 2 to 4 intakes per day, after meals and, if necessary, at bedtime.

Contraindications:

Hypersensitivity to one of the constituents of the product.

Since this drug has a powerful activity on the contractility of uterine muscle, it may cause interruption of pregnancy.

Utilization in pregnant women is therefore contraindicated (except in the case of prescription in a hospital environment with reference to Articles L 162.2 and L 176 of the Public Health Code).

Use in women of child-bearing age in the absence of effective contraception is contraindicated.

Special warnings and precautions during use:

Warning

When taking NSAIDs, it is appropriate to monitor specifically the appearance of digestive symptomatology because of the possible gravity of gastrointestinal manifestations. Misoprostol cannot protect against them completely.

In case of gastroduodenal effects, the rule should be to interrupt the anti-inflammatory treatment, if that is possible.

In a controlled study versus placebo, carried out on more than 8800 patients followed for 6 months, misoprostol at 800 μg caused a significant decrease of severe gastroduodenal complications related to NSAIDs (25 complications in 4404 patients treated with misoprostol and 42 complications in 4439 patients on placebo).

Precautions during use

Contrary to other E-type prostaglandins, misoprostol does not cause hypotension at therapeutic doses. However, misoprostol should be prescribed with precaution in diseases where the appearance of hypotension may cause complications.

In case of gastric ulcer, it is recommended to verify the benign nature of the lesion before treatment.

Interactions with other drugs and other types of interactions

Pregnancy and lactation:

Pregnancy

Study in animals did not show any evidence of a teratogenic effect, but fetotoxicity occurred at elevated doses.

In clinical experience, at the present time, there are no pertinent data available for evaluating a possible effect of malformation of misoprostol when it is administered during pregnancy within the framework of an *oral prescription*. However, some cases of pregnancies exposed to self-medication *aimed at abortion (oral and/or vaginal)* evoke a deleterious effect of misoprostol used under these conditions (anomalies of the members of the frontotemporal bone and cranial pairs with hypomimy [phonetic] and anomalies of suction and swallowing). At the present time, the possibility of risk of malformation is not to be excluded.

Consequently, the utilization of misoprostol is contraindicated during pregnancy. This element does not constitute a systematic argument for recommending interruption of pregnancy, but leads to an attitude of prudence and to oriented prenatal monitoring (echography of the target organs).

Lactation

Considering the absence of data concerning the passage of misoprostol into mother's milk, the utilization of the drug is to be avoided during lactation.

Effects on the ability to drive and operate machinery

Warn patients of the possible appearance of vertigo.

Adverse effects

The most frequently reported adverse effect during clinical trials was moderate diarrhea, which ceased even when the treatment was continued.

The incidence of diarrhea increases during the administration of two daily intakes and therefore one should reduce the dosage temporarily or give the doses in fractions administered in 4 intakes.

Other adverse effects: nausea (transient and moderate), headaches, vertigo, abdominal discomfort.

Overdosage

- Transfer immediately to a hospital environment.

- Rapid evacuation of the ingested product.
- Symptomatic treatment.

PHARMACOLOGICAL PROPERTIES

ANTIULCER. PROSTAGLANDIN
(A: metabolism)

Pharmacodynamic properties
Misoprostol is a synthetic prostaglandin E_1 analog.

The antisecretory and cytoprotective activity of misoprostol was evidenced on animal models and in pharmacological clinical studies in humans.

In the latter case, there is antisecretory action on the spontaneous diurnal or nocturnal secretion and on the secretion stimulated by histamine, pentagastrin, protein meals or coffee.

The cytoprotective action was evaluated in animals and in humans showing a protection against aspirin, alcohol and a nonsteroidal anti-inflammatory.

Pharmacokinetic properties
Labeled misoprostol is absorbed rapidly after oral administration (t_{max}: 30 minutes).

The half-life is 1 hour, 30 minutes.

Seventy-three percent of the radioactive product is excreted in the urine and 15 percent in the feces.

Approximately 56 percent is eliminated in the urine during the 8 hours following administration.

PHARMACEUTICAL DATA

Shelf life

3 years

Nature and content of the container

60 tablets in a bottle (amber glass)

60 tablets in a thermoformed sheet (PE/PVC/PVDC/Alu)

PRESENTATION AND ADMINISTRATIVE IDENTIFICATION NUMBER

328 785-5: 60 tablets in a bottle (amber glass)

328 786-4: 60 tablets in a thermoformed sheet (PE/PVC/PVDC/Alu)

CLASSIFICATION REGARDING DISPENSATION

List I

OWNER OF THE AUTHORIZATION OF MARKETING

MONSANTO FRANCE SA

Division Searle

Immeuble Elysées La Défense

7, Place du Dôme

92056 PARIS LA DEFENSE CEDEX

Date of last revision of the AMM: 9/23/97

APPENDIX II

PACKAGE INSERT

IDENTIFICATION OF THE DRUG

NAME

CYTOTEC 200 micrograms, scored tablet

QUALITATIVE AND QUANTITATIVE COMPOSITIONS

Misoprostol	200 µg
in the form of a 1% dispersion in HPMC*	20.2 mg

Excipients: microcrystalline cellulose, sodium carboxymethylstarch, hydrogenated castor oil

for one 200 mg tablet

PHARMACEUTICAL FORM

Scored tablet, box of 60

PHARMACOTHERAPEUTIC CLASS

ANTIULCER. PROSTAGLANDIN

(A: metabolism)

NAME AND ADDRESS OF THE OWNER

MONSANTO FRANCE S.A.
Division SEARLE
Immeuble Elysées La Défense
7, Place du Dôme
92056 Paris La Défense Cedex

Manufactured by: SEARLE
Division of Monsanto plc
High Wycombe
ENGLAND

WHEN SHOULD THIS DRUG BE USED? (THERAPEUTIC INDICATIONS)

This drug is indicated in:

- treatment:
  - ongoing or duodenal ulcer;
  - diseases of the stomach and the duodenum due to the intake of nonsteroidal anti-inflammatory drugs, when the continuation of the latter is indispensable;

- prevention of diseases of the stomach and duodenum due to the intake of nonsteroidal anti-inflammatory drugs, in certain subjects.

ATTENTION!

WHEN SHOULD THIS DRUG NOT BE USED? (CONTRAINDICATIONS)

This drug SHOULD NOT BE USED during pregnancy or in women who can become pregnant in the absence of EFFECTIVE contraception (estroprogestative pill or IUD).

Allergy to misoprostol (prostaglandin)

PRECAUTIONS FOR USE

In women of child-bearing age, absence of pregnancy in progress must be ensured and effective contraception should be practiced.

DRUG INTERACTIONS AND OTHER INTERACTIONS

IN ORDER TO AVOID ANY INTERACTIONS AMONG SEVERAL DRUGS, ANY OTHER TREATMENT IN COURSE SHOULD BE REPORTED TO YOUR PHYSICIAN OR TO YOUR PHARMACIST.

PREGNANCY - LACTATION

The utilization of the drug is contraindicated during pregnancy. If you discover during the treatment that you are pregnant, stop the intake of this drug and consult your physician immediately.

In women who can become pregnant, EFFECTIVE contraception (that is, with an IUD or estroprogestative pill) must be ensured before beginning the treatment with this drug.

In case of lactation, this drug should be avoided.

DRIVERS AND MACHINE OPERATORS

In rare cases, the intake of this drug may cause vertigo.

EXCIPIENTS, THE KNOWLEDGE OF WHICH IS NECESSARY FOR RISK-FREE UTILIZATION IN SOME PATIENTS

Hydrogenated castor oil

HOW TO USE THIS DRUG

DOSAGE

- The dosage is a function of the indication. It varies from ½ of a 200 µg tablet 4 times per day or 1 200 µg tablet twice per day to 1 200 µg tablet 4 times per day, that is from 400 to 800 µg.

IN ALL CASES, YOU MUST CONFORM STRICTLY TO THE PRESCRIPTION OF YOUR PHYSICIAN.

MODE AND ROUTE OF ADMINISTRATION

Oral route

The tablets are to be swallowed as such with a large glass of water.

FREQUENCY AND TIME AT WHICH THE DRUG SHOULD BE ADMINISTERED

Depending on the indication, the dose should be divided into 2 or 4 intakes per day, after a meal and, if necessary, at bedtime.

IN ALL CASES, YOU MUST CONFORM STRICTLY TO THE PRESCRIPTION OF YOUR PHYSICIAN

DURATION OF THE TREATMENT

IN ALL CASES, YOU MUST CONFORM STRICTLY TO THE PRESCRIPTION OF YOUR PHYSICIAN

ACTION TO BE TAKEN IN CASE OF OVERDOSAGE

In case of overdosage or accidental poisoning, inform your physician immediately.

ADVERSE AND UNPLEASANT EFFECTS (UNDESIRABLE EFFECTS)

AS ALL ACTIVE PRODUCT, THIS PRODUCT MAY CAUSE UNPLEASANT EFFECTS OF VARYING DEGREE IN CERTAIN PERSONS.

Digestive problems of the type of especially diarrhea may occur, as well as nausea, headache, vertigo and abdominal discomfort.

You must inform your physician.

DO NOT HESITATE TO ASK THE OPINION OF YOUR PHYSICIAN OR OF YOUR PHARMACIST AND TO REPORT ANY ADVERSE AND UNPLEASANT EFFECT THAT WAS NOT MENTIONED IN THIS NOTE.

STORAGE

DO NOT USE AFTER THE EXPIRATION DATE, WHICH APPEARS ON THE OUTSIDE PACKAGING.

DATE OF REVISION OF THE PACKAGE INSERT

January 7, 1999

SEARLE

Worldwide Regulatory Affairs

Facsimile Transmission

Searle
Worldwide Regulatory Affairs
4901 Searle Parkway
Skokie, Illinois 60077
U.S.A.

Fax Number: (847) 982-8090
(847) 982-8152

	Name:	Location:
TO:	ALICE KOCUBA	Proj. Mgr. FDA
		301-743-9285
CC:		
FROM:	MARY-JO PRITZA	# 847-982-7831

No. of Pages (including cover page) 28

MESSAGE: ALICE → following: UK SPC German SPC + French SPC — I will fax the French version as soon as possible need most current version from affiliate. Please call w/ questions —

SUMMARY OF PRODUCT CHARACTERISTICS

CYTOTEC

1. NAME OF THE MEDICINAL PRODUCT

Cytotec.

2. QUALITATIVE & QUANTITATIVE COMPOSITION

Each tablet contains 200 micrograms misoprostol.

3. PHARMACEUTICAL FORM

White to off-white hexagonal tablets scored both sides, engraved SEARLE 1461 on one side for oral administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cytotec is indicated for the healing of duodenal ulcer and gastric ulcer including those induced by nonsteroidal anti-inflammatory drugs (NSAID) in arthritic patients at risk, whilst continuing their NSAID therapy. In addition, Cytotec can be used for the prophylaxis of NSAID-induced ulcers.

4.2 Posology and Method of Administration

Adults

Healing of duodenal ulcer, gastric ulcer and NSAID-induced peptic ulcer: 800 micrograms daily in two or four divided doses taken with breakfast and / or each main meal and at bedtime.

Treatment should be given initially for at least 4 weeks even if symptomatic relief has been achieved sooner. In most patients ulcers will be healed in 4 weeks but treatment may be continued for up to 8 weeks if required. If the ulcer relapses further treatment courses may be given.

Prophylaxis of NSAID-induced peptic ulcer: 200 micrograms twice daily, three times daily or four times daily. Treatment can be continued as required. Dosage should be individualised according to the clinical condition of each patient.

Elderly

The usual dosage may be used.

Renal impairment: Available evidence indicates that no adjustment of dosage is necessary in patients with renal impairment.

Hepatic impairment: Cytotec is metabolised by fatty acid oxidising systems present in organs throughout the body. Its metabolism and plasma levels are therefore unlikely to be affected markedly in patients with hepatic impairment.

Children

Use of Cytotec in children has not yet been evaluated in the treatment of peptic ulceration or NSAID-induced peptic ulcer disease.

4.3 **Contraindications**

Use in pregnancy and lactation:

Cytotec is contraindicated in pregnant women and in women planning a pregnancy as it increases uterine tone and contractions in pregnancy which may cause partial or complete expulsion of the products of conception.

It is also contraindicated in patients with a known allergy to prostaglandins.

4.4 **Special Warnings and Special Precautions for Use**

Warnings

Use in pre-menopausal women (see also Contraindications): Cytotec should not be used in pre-menopausal women unless the patient requires nonsteroidal anti-inflammatory (NSAID) therapy and is at high risk of complications from NSAID-induced ulceration.

In such patients it is advised that Cytotec should only be used if the patient:

- takes effective contraceptive measures
- has been advised of the risks of taking Cytotec if pregnant (see Contraindications)

Precautions

The results of clinical studies indicate that Cytotec does not produce hypotension at dosages effective in promoting the healing of gastric and duodenal ulcers. Nevertheless, Cytotec should be used with caution in the presence of disease states where hypotension might precipitate severe complications, e.g., cerebrovascular disease, coronary artery disease or severe peripheral vascular disease including hypertension.

There is no evidence that Cytotec has adverse effects on glucose metabolism in human volunteers or patients with diabetes mellitus.

4.9 Overdose

Intensification of pharmacological effects may occur with overdose. In the event of overdosage symptomatic and supportive therapy should be given as appropriate. In clinical trials patients have tolerated 1200 micrograms daily for three months without significant adverse effects.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Cytotec is an analogue of naturally occurring prostaglandin E_1 which promotes peptic ulcer healing and symptomatic relief. As a PGE, analogue it shares some at least, of that hormone's effects on smooth muscle.

Cytotec protects the gastroduodenal mucosa by inhibiting basal, stimulated and nocturnal acid secretion and by reducing the volume of gastric secretions, the proteolytic activity of the gastric fluid, and increasing bicarbonate and mucus secretion.

5.2 Pharmacokinetic properties

Cytotec is rapidly absorbed following oral administration, with peak plasma levels of the active metabolite (misoprostol acid) occurring after about 30 minutes. The plasma elimination half-life of misoprostol acid is 20-40 minutes. No accumulation of misoprostol acid in plasma occurs after repeated dosing of 400 micrograms twice daily.

5.3 Preclinical Safety Data

In single and repeat-dose studies in dogs, rats and mice at multiples of the human dose, toxicological findings were consistent with the known pharmacological effects of the E-type prostaglandins, the main symptoms being diarrhoea, vomiting, mydriasis, tremors and hyperpyrexia. Gastric mucosal hyperplasia was also observed in the mouse, rat and the dog. In the rat and the dog the hyperplasia was reversible on discontinuation of misoprostol following one year of dosing. Histological examination of gastric biopsies in humans has shown no adverse tissue response after up to one year's treatment. In studies of fertility, teratogenicity and peri/post-natal toxicity in rats and rabbits there were no major findings. A decrease in implantations and some pup growth retardation was observed at doses greater than 100 times the human dose. It was concluded that misoprostol does not significantly affect fertility, is not teratogenic or embryotoxic and does not affect rat pups in the peri/post-natal period.

Misoprostol was negative in a battery of 6 in vitro assays and one in vivo test to assess mutagenic potential. In carcinogenicity studies in the rat and mouse it was concluded that there was no risk of carcinogenic hazard.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cytotec tablets contain : microcrystalline cellulose, sodium starch glycolate, hydrogenated castor oil; hydroxypropyl methyl cellulose (H.P.M.C.)

6.2 Incompatibilities

None known.

6.3 Shelf-life

Cytotec tablets have a shelf-life of 3 years when stored in cold-formed aluminium blisters.

6.4 Special Precautions for Storage

Store below 30°C (86°F).

6.5 Nature and Contents of a Container

Cold-formed aluminium blister packs of 56, 60.,112, 120 or 140 tablets.

6.6 Special Instructions for Use/Handling

None.

7. MARKETING AUTHORISATION HOLDER

Monsanto plc
Trading as Searle
P O Box 53
Lane End Road
High Wycombe
Buckinghamshire
HP12 4HL

8. MARKETING AUTHORISATION NUMBER

PL 8821/0019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

First authorised 27/7/88 (PL 0020/0115)
Last renewed 13/1/99.

10. DATE OF (PARTIAL) REVISION OF THE TEXT)

January 1999

SEARLE

(27)

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077
PHONE (847) 982-7000
FAX (847) 982-4701

Current German SPC

TECHNICAL INFORMATION

1. Name of the drug

Cytotec® 200

Active ingredient: misoprostol

2. Prescription status/pharmacy required

Requires prescription.

3. Composition of the drug

3.1 Material or indication group

Gastrointestinal agent

3.2 Pharmaceutically active components according to nature and amount

1 Tablet contains

misoprostol 200 µg

3.3 Other components

Microcrystalline cellulose, methylhydroxypropylcellulose; poly(O-carboxymethyl)starch; sodium salt; hydrogenated castor oil.

4. Area of application

For the prevention and treatment of drug-induced (for example, anti-inflammatories, acetylsalicylic acid) gastromucosal damage.

The prevention of drug-induced gastric mucosal damage should extend mainly to patients with a corresponding disposition. Data available so far do not allow a well-founded more extensive definition of the treatment groups.

In each case, it should be examined if the dose of the gastric-mucosa-damaging medication could be reduced or if the drug could be discontinued.

For the treatment of acute duodenal and gastric ulcers.

5. Contraindications

Cytotec® 200 should not be used in case of hypersensitivity to misoprostol, other prostaglandins or to one of the other components and in the case of inflammatory intestinal diseases.

The preparation must not be taken during pregnancy, since misoprostol, the active ingredient of Cytotec® 200, can have an effect on the uterine musculature. Women in the childbearing age who do not use or take any contraceptive means must not become pregnant while taking Cytotec® 200. If pregnancy occurs while taking Cytotec® 200, the preparation must be discontinued.

Since it is not known if Cytotec® 200 is transferred into mother's milk, lactating mothers must not be treated with Cytotec® 200.

An especially careful medical monitoring is required for patients who tend to have diarrhea or for whom dehydration could be dangerous.

Prostaglandins of the E-type, to which misoprostol, the active ingredient of Cytotec® 200 belongs, can cause a drop in blood pressure because of the dilatation of the peripheral vessels. Therefore, Cytotec® 200 should be used with caution in patients with cerebral vessel disease or coronary heart disease in whom a drop in blood pressure could lead to complications.

Since sufficient clinical experience with the use of misoprostol in children and adolescents is not available, Cytotec® 200 should not be used by patients under the age of 18 years.

6. Side effects

Frequent: stomach aches, temporary soft stools to diarrhea.

Occasional: digestive disturbances, nausea, vomiting, burping, bloating, constipation, dizziness, feeling dazed, tinnitus, headache, infections of the upper respiratory passages and joint pain.

Rare: pain or cramps in the area of the uterus, changes of menstruation and increase of menstrual bleeding, breakthrough bleeding or bleeding after menopause; in these cases, as well as in the case of severe diarrhea, the use of Cytotec® 200 should be discontinued and a physician consulted.

7. Interactions with other drugs

High-dose antacids can lead to a limitation of the bioavailability of misoprostol. Magnesium-containing antacids may enhance misoprostol-related diarrhea. The effect of laxatives can be enhanced.

Interactions with other drugs, especially with anti-inflammatories, for example, diclofenac, naproxen, ibuprofen, indomethacin, piroxicam and acetylsalicylic acid have not been observed so far.

8. Warnings

None

9. Important incompatibilities

None known.

10. Dosage with individual and daily doses

Unless otherwise prescribed:

- for the prevention and treatment of drug-induced mucosal damage: 2-4 times daily, 1 tablet of Cytotec® 200 (corresponding to 400-800 µg of misoprostol),

- for the treatment of acute gastric and duodenal ulcers, drug-induced gastric ulcers: 4 times daily, 1 tablet of Cytotec® 200 (corresponding to 800 µg of misoprostol).

Elderly patients, patients with kidney function impairment:
In elderly patients and in those with slight to moderate kidney function disturbances, adjustment of the dosage is not absolutely necessary. In the case of patient with severe kidney function disturbances, the treatment should begin with low doses and these patients must be monitored.

11. Nature and duration of application

When there are 2 applications, the tablets should be taken in the morning and in the evening, otherwise after the 3 main meals and additionally optionally before bedtime. The drug should be taken after meals with sufficient fluids (approximately 1 glass of water).

In the preventive treatment, the duration of application should be identical to that of the therapy duration of the drug that damages the gastric mucosa (for example, anti-inflammatory, acetylsalicylic acid), where the extent of the preventive action for periods beyond 12 months cannot be evaluated sufficiently based on data available so far.

For the treatment of existing ulcers, mucosal hemorrhage and mucosal defects, the duration of application is 4 weeks, and can be extended to 8 weeks if necessary.

12. Emergency measures, symptoms and antidotes

a) Symptoms of intoxication

The toxic dose of misoprostol in humans has not yet been established. Daily doses up to 1600 µg were tolerated and led only to gastrointestinal symptoms. In animals, the toxic effects are similar to those that have been reported for other prostaglandins: slackening of the smooth musculature, damping of the central nervous system, shortness of breath.

Clinical signs which can indicate an overdose are: sedation, tremor, cramps, dyspnea, stomach ache, contractions of the uterus, diarrhea, fever, palpitations, hypotonia or bradycardia.

b) Therapy of intoxications

A special antidote is not available yet and, therefore, the treatment in case of an overdose is aimed at elimination of the symptoms and support of important vital functions.

13. Pharmacological and toxicological properties, pharmacokinetics and bio-availability, as long as these data are necessary for therapeutic application

13.1 Pharmacological properties

a) Inhibition of acid secretion

The antisecretory action of misoprostol is manifested both in the inhibition of the basal acid secretion as well as in the inhibition of acid secretion, stimulated by histamine, pentagastrin, tetragastrin, betazole, food intake and caffeine. In addition, misoprostol reduces nocturnal acid secretion.

In-vitro investigations showed that the mechanism of inhibition of acid secretion occurs by direct attack at the parietal cells rather than by indirect mechanisms. In comparison to intravenous and intragastral administration, the injection of misoprostol into the innervated Pavlov pocket of dogs leads to inhibition of acid secretion, even at low dosages. This leads to the assumption that the local action of misoprostol predominates. In animal experiments, only a slight or no effect on the serum-gastrin level was present.

b) Mucosa protective action

In animals and in humans, misoprostol exhibits mucosa-protecting properties, which enhance the integrity of the gastric mucosal barrier to harmful substances.

Dosages of 25 µg and 50 µg of misoprostol, which show only slight antisecretory effects, lead with the simultaneous administration of acetylsalicylic acid to protection of the mucosa in humans by reducing the gastric bleeding caused by acetylsalicylic acid and reducing fecal blood loss.

The pretreatment with acid-inhibitory doses of 200 µg of misoprostol leads to a significant protection of the gastric mucosa against acetylsalicylic-acid-related damage. In the model of

a gastritis produced by ethanol in healthy subjects, 200 µg of misoprostol was found to be about 80% more effective than placebo.

Although the mechanism of cytoprotection has not been clarified unequivocally so far, it seems that misoprostol stimulates the physiological processes in the gastroduodenal mucosa. Thus, misoprostol increases the bicarbonate secretion in the duodenum in a dose-dependent manner, it increases the thickness or the adherent mucus layer in the stomach and the quantity of the soluble mucus in a stomach aspirate. In addition, 200 µg of misoprostol increases the mucosa blood volume in humans by more than 15% in comparison to the normal value. In the case of rats, the mucosal bleeding remains unchanged, while it increases in dogs.

b)[should be c)] Inhibition of pepsin secretion

Misoprostol reduces the secretion of pepsin and the volume of gastric acid both under normal conditions and also under stimulation.

13.2 Toxicological properties

a) Chronic/acute toxicity

The testing of the chronic toxicity of misoprostol was carried out on dogs and rats with up to 480 µg/kg/day and 9000 µg/kg/day per os, respectively.

The noteworthy clinical symptoms in these studies were diarrhea, vomiting, soft and/or slimy stools, increased rectal temperature in the case of dogs, as well as diarrhea, salivation, reduced body weight and increased food intake in rats. All these symptoms abate after a recovery phase.

In both animal species, after long administration, hyperplasia of the gastric mucosa occurred, which, however, proved to be reversible after the discontinuation of the drug. Autonomous growth or atypical cells were not observed.

b) Mutagenic and tumor-producing potential

Results of carcinogenicity experiments on mice and rats showed no indication of a carcinogenic action.

The results of the mutagenicity tests showed no indication of a mutagenic action.

c) Reproduction toxicity

Embryotoxicity studies on rats and rabbits at doses up to 1600 µg/kg/day and 1000 µg/kg/day, respectively, showed no indication of a teratogenic potential. The progeny of rats showed a lower weight gain when misoprostol was administered during fetal development and the lactation period at a dose of 10 mg/kg. Within the framework of fertility studies on male and female rats, a reduction of the implantation rate and an increase of the progeny death rate were found.

13.3 Pharmacokinetics

After oral administration, misoprostol is resorbed rapidly. The maximum plasma level of the active metabolite, misoprostol acid, is reached approximately after 12 minutes. The plasma elimination half-life of misoprostol acid is 20-30 minutes. The plasma elimination half-life of other misoprostol metabolites is 1.5 hours.

The mean maximum plasma level, the C_{max} values, after the administration of individual doses in the range from 200-400 µg, show a linear relationship to the applied dose. After daily administration of 2-4 times 200 µg of misoprostol, the steady-state plasma levels are reached on the second day of treatment. After multiple administration of misoprostol, no cumulation of misoprostol acid in the plasma was detected.

Seventy-three % of the radioactivity of an oral dose of radioactive-labeled misoprostol is excreted with the urine, 15% with the feces. Approximately 56% of the total radioactivity is excreted with the urine within 8 hours.

Misoprostol is metabolized through the fatty acid oxidizing systems (beta- and omega-oxidation), which are present in all organs. In animal studies, misoprostol shows no action on microsomal oxidases (Cytochrome P450) of the liver.

In patients with low or moderate kidney function disturbances, there is an increase of $t_{½}$, of the maximum plasma level, C_{max}, and the areas under the plasma level-time curves, the AUC values. A correlation between the degree of kidney damage and the increase of the AUC

values could not be detected. In anuric patients, there is a doubling of the C_{max}, AUC and $t_{½}$ values for misoprostol acid in comparison to patients with healthy kidneys.

Additional intake of low-dosage antacids showed no interactions. High-dose antacids could lead to a limitation of the bioavailability of misoprostol.

The serum protein binding of misoprostol is less than 90% and is concentration-independent in the therapeutic range. The serum-protein bonding of the free acid of misoprostol is approximately 81-89%. Cumulation of misoprostol in the erythrocytes does not occur.

14. Other information

a) Pregnancy:

Pregnancy can be endangered by the intake of Cytotec® 200 and may cause miscarriage. The active ingredient misoprostol may cause contractions of the uterus and bleeding and may lead to the loss of the fetus. The abortion can be incomplete.

When a woman is pregnant or becomes pregnant during treatment with Cytotec® 200, the preparation must be discontinued because there is a potential risk to the fetus (see point 5 "Contraindications").

After misuse of Cytotec® 200, in individual cases, malformed newborn or death of the fetus may occur.

b) Lactation

Although so far it is not known if misoprostol or its metabolites are transferred into mother's milk, Cytotec® 200 should not be used by lactating mothers.

c) Other information

Combined intake of nonsteroidal anti-inflammatories with misoprostol, gastric and duodenal ulcers, bleeding and perforation may occur, especially in patients who tend to gastrointestinal complaints.

Therefore, even if symptoms are absent, one must always consider the possibility of gastric and duodenal ulcers.

Especially patients with corresponding anamnesis require special monitoring by the physician.

Symptomatic response to therapy with misoprostol does not exclude the malignant nature of a disease.

15. Shelf life

The shelf life is 3 years.

The drug should not be used after the expiration date!

16. Special storage information

Protect against moisture!

16a. Special precautionary measures for the disposal of unused drugs

None

17. Forms of dispensation and package sizes

Packages with 50 (N2) and 100 (N3) tablets
Institutional packaging with 500 (10 x 50) tablets

18. Status of information

February 1997

19. Name of the company and address of the pharmaceutical company

HEUMANN PHARMA GMBH
Heideloffstr. 18-28
90478 Nürnberg
Telephone No. 0911/43 02-0
Telefax No. 0911/43 02-438
A COMPANY OF THE SEARLE GROUP

REMARKS

Dr. Bohn/Dr. Lang:

Dr. Lützenkirchen:

Dr. Bühl:

Dr. Hoffmann:

Marketing Services:

Dr. Vergin:

SEARLE

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077
PHONE (847) 982 7000
FAX (847) 982-4701

Current French SPC

APPENDIX I

SUMMARY OF THE CHARACTERISTICS OF THE PRODUCT

NAME

CYTOTEC 200 micrograms, scored tablet

QUALITATIVE AND QUANTITATIVE COMPOSITION

Misoprostol	200.0 µg
in the form of misoprostol dispersion/HPMC at 1 percent*	20.2 mg
Microcrystalline cellulose	175.8 mg
Sodium carboxymethylstarch	3.0 mg
Hydrogenated castor oil	1.0 mg

for one tablet of 200 mg

* Composition of the dispersion:
spray: misoprostol 1%
hypromellose 99%
intermediate solvent: ethanol

PHARMACEUTICAL FORM

Scored tablet

CLINICAL DATA

Therapeutic indications:

- treatment of ongoing gastric or duodenal ulcer;
- treatment of gastroduodenal lesions induced by NSAIDs, limited to subjects for whom the continuation of anti-inflammatories is indispensable;
- preventive treatment of gastric and duodenal lesions and of severe gastroduodenal complications induced by NSAIDs in subjects at risk (notably, age > 65 years, previous history of gastroduodenal ulcer or intolerance to NSAIDs) for whom anti-inflammatory treatment is indispensable.

Dosage and mode of administration:

Mode of administration

Oral route

The tablets are to be swallowed as such with a large glass of water.

Dosage:

- Treatment of developing ulcer and gastroduodenal lesions: 1 200 mg tablet 4 times per day, that is, 800 µg per day.

- The duration of the treatment is limited to 4 to 8 weeks.

- Preventive treatment against lesions and gastroduodenal complications:
  ½ 200 µg tablet 4 times per day or 1 200 µg tablet twice per day, that is, 400 µg per day for 10 days.
  If this dose is well-tolerated, then 1 200 µg tablet 4 times per day, that is, 800 µg per day.
  In case of intolerance (diarrhea) at the high dose, the dose of 400 µg per day should be pursued.

Frequency of administration:

As a function of indication, the dosage is to be distributed into 2 to 4 intakes per day, after meals and, if necessary, at bedtime.

Contraindications:

Hypersensitivity to one of the constituents of the product.

Since this drug has a powerful activity on the contractility of uterine muscle, it may cause interruption of pregnancy.

Utilization in pregnant women is therefore contraindicated (except in the case of prescription in a hospital environment with reference to Articles L 162.2 and L 176 of the Public Health Code).

Use in women of child-bearing age in the absence of effective contraception is contraindicated.

Special warnings and precautions during use:

Warning

When taking NSAIDs, it is appropriate to monitor specifically the appearance of digestive symptomatology because of the possible gravity of gastrointestinal manifestations. Misoprostol cannot protect against them completely.

In case of gastroduodenal effects, the rule should be to interrupt the anti-inflammatory treatment, if that is possible.

In a controlled study versus placebo, carried out on more than 8800 patients followed for 6 months, misoprostol at 800 μg caused a significant decrease of severe gastroduodenal complications related to NSAIDs (25 complications in 4404 patients treated with misoprostol and 42 complications in 4439 patients on placebo).

Precautions during use

Contrary to other E-type prostaglandins, misoprostol does not cause hypotension at therapeutic doses. However, misoprostol should be prescribed with precaution in diseases where the appearance of hypotension may cause complications.

In case of gastric ulcer, it is recommended to verify the benign nature of the lesion before treatment.

Interactions with other drugs and other types of interactions

Pregnancy and lactation:

Pregnancy

Study in animals did not show any evidence of a teratogenic effect, but fetotoxicity occurred at elevated doses.

In clinical experience, at the present time, there are no pertinent data available for evaluating a possible effect of malformation of misoprostol when it is administered during pregnancy within the framework of an *oral prescription*. However, some cases of pregnancies exposed to self-medication *aimed at abortion (oral and/or vaginal)* evoke a deleterious effect of misoprostol used under these conditions (anomalies of the members of the frontotemporal bone and cranial pairs with hypomimy [phonetic] and anomalies of suction and swallowing). At the present time, the possibility of risk of malformation is not to be excluded.

Consequently, the utilization of misoprostol is contraindicated during pregnancy. This element does not constitute a systematic argument for recommending interruption of pregnancy, but leads to an attitude of prudence and to oriented prenatal monitoring (echography of the target organs).

Lactation

Considering the absence of data concerning the passage of misoprostol into mother's milk, the utilization of the drug is to be avoided during lactation.

Effects on the ability to drive and operate machinery

Warn patients of the possible appearance of vertigo.

Adverse effects

The most frequently reported adverse effect during clinical trials was moderate diarrhea, which ceased even when the treatment was continued.

The incidence of diarrhea increases during the administration of two daily intakes and therefore one should reduce the dosage temporarily or give the doses in fractions administered in 4 intakes.

Other adverse effects: nausea (transient and moderate), headaches, vertigo, abdominal discomfort.

Overdosage

- Transfer immediately to a hospital environment.

- Rapid evacuation of the ingested product.
- Symptomatic treatment.

PHARMACOLOGICAL PROPERTIES

ANTIULCER. PROSTAGLANDIN
(A: metabolism)

Pharmacodynamic properties
Misoprostol is a synthetic prostaglandin E_1 analog.

The antisecretory and cytoprotective activity of misoprostol was evidenced on animal models and in pharmacological clinical studies in humans.

In the latter case, there is antisecretory action on the spontaneous diurnal or nocturnal secretion and on the secretion stimulated by histamine, pentagastrin, protein meals or coffee.

The cytoprotective action was evaluated in animals and in humans showing a protection against aspirin, alcohol and a nonsteroidal anti-inflammatory.

Pharmacokinetic properties
Labeled misoprostol is absorbed rapidly after oral administration (t_{max}: 30 minutes).

The half-life is 1 hour, 30 minutes.

Seventy-three percent of the radioactive product is excreted in the urine and 15 percent in the feces.

Approximately 56 percent is eliminated in the urine during the 8 hours following administration.

PHARMACEUTICAL DATA

Shelf life

3 years

Nature and content of the container

60 tablets in a bottle (amber glass)

60 tablets in a thermoformed sheet (PE/PVC/PVDC/Alu)

PRESENTATION AND ADMINISTRATIVE IDENTIFICATION NUMBER

328 785-5: 60 tablets in a bottle (amber glass)

328 786-4: 60 tablets in a thermoformed sheet (PE/PVC/PVDC/Alu)

CLASSIFICATION REGARDING DISPENSATION

List I

OWNER OF THE AUTHORIZATION OF MARKETING

MONSANTO FRANCE SA

Division Searle

Immeuble Elysées La Défense

7, Place du Dôme

92056 PARIS LA DEFENSE CEDEX

Date of last revision of the AMM: 9/23/97

APPENDIX II

PACKAGE INSERT

IDENTIFICATION OF THE DRUG

NAME

CYTOTEC 200 micrograms, scored tablet

QUALITATIVE AND QUANTITATIVE COMPOSITIONS

Misoprostol	200 µg
in the form of a 1% dispersion in HPMC*	20.2 mg

Excipients: microcrystalline cellulose, sodium carboxymethylstarch, hydrogenated castor oil

for one 200 mg tablet

PHARMACEUTICAL FORM

Scored tablet, box of 60

PHARMACOTHERAPEUTIC CLASS

ANTIULCER. PROSTAGLANDIN

(A: metabolism)

NAME AND ADDRESS OF THE OWNER

MONSANTO FRANCE S.A.
Division SEARLE
Immeuble Elysées La Défense
7, Place du Dôme
92056 Paris La Défense Cedex

Manufactured by: SEARLE
Division of Monsanto plc
High Wycombe
ENGLAND

WHEN SHOULD THIS DRUG BE USED? (THERAPEUTIC INDICATIONS)

This drug is indicated in:

- treatment:
  - ongoing or duodenal ulcer;
  - diseases of the stomach and the duodenum due to the intake of nonsteroidal anti-inflammatory drugs, when the continuation of the latter is indispensable;

- prevention of diseases of the stomach and duodenum due to the intake of nonsteroidal anti-inflammatory drugs, in certain subjects.

ATTENTION!

WHEN SHOULD THIS DRUG NOT BE USED? (CONTRAINDICATIONS)

This drug SHOULD NOT BE USED during pregnancy or in women who can become pregnant in the absence of EFFECTIVE contraception (estroprogestative pill or IUD).

Allergy to misoprostol (prostaglandin)

PRECAUTIONS FOR USE

In women of child-bearing age, absence of pregnancy in progress must be ensured and effective contraception should be practiced.

DRUG INTERACTIONS AND OTHER INTERACTIONS

IN ORDER TO AVOID ANY INTERACTIONS AMONG SEVERAL DRUGS, ANY OTHER TREATMENT IN COURSE SHOULD BE REPORTED TO YOUR PHYSICIAN OR TO YOUR PHARMACIST.

PREGNANCY - LACTATION

The utilization of the drug is contraindicated during pregnancy. If you discover during the treatment that you are pregnant, stop the intake of this drug and consult your physician immediately.

In women who can become pregnant, EFFECTIVE contraception (that is, with an IUD or estroprogestative pill) must be ensured before beginning the treatment with this drug.

In case of lactation, this drug should be avoided.

DRIVERS AND MACHINE OPERATORS

In rare cases, the intake of this drug may cause vertigo.

EXCIPIENTS, THE KNOWLEDGE OF WHICH IS NECESSARY FOR RISK-FREE UTILIZATION IN SOME PATIENTS

Hydrogenated castor oil

HOW TO USE THIS DRUG

DOSAGE

- The dosage is a function of the indication. It varies from ½ of a 200 µg tablet 4 times per day or 1 200 µg tablet twice per day to 1 200 µg tablet 4 times per day, that is from 400 to 800 µg.

IN ALL CASES, YOU MUST CONFORM STRICTLY TO THE PRESCRIPTION OF YOUR PHYSICIAN.

MODE AND ROUTE OF ADMINISTRATION

Oral route

The tablets are to be swallowed as such with a large glass of water.

FREQUENCY AND TIME AT WHICH THE DRUG SHOULD BE ADMINISTERED

Depending on the indication, the dose should be divided into 2 or 4 intakes per day, after a meal and, if necessary, at bedtime.

IN ALL CASES, YOU MUST CONFORM STRICTLY TO THE PRESCRIPTION OF YOUR PHYSICIAN

DURATION OF THE TREATMENT

IN ALL CASES, YOU MUST CONFORM STRICTLY TO THE PRESCRIPTION OF YOUR PHYSICIAN

ACTION TO BE TAKEN IN CASE OF OVERDOSAGE

In case of overdosage or accidental poisoning, inform your physician immediately.

ADVERSE AND UNPLEASANT EFFECTS (UNDESIRABLE EFFECTS)

AS ALL ACTIVE PRODUCT, THIS PRODUCT MAY CAUSE UNPLEASANT EFFECTS OF VARYING DEGREE IN CERTAIN PERSONS.

Digestive problems of the type of especially diarrhea may occur, as well as nausea, headache, vertigo and abdominal discomfort.

You must inform your physician.

DO NOT HESITATE TO ASK THE OPINION OF YOUR PHYSICIAN OR OF YOUR PHARMACIST AND TO REPORT ANY ADVERSE AND UNPLEASANT EFFECT THAT WAS NOT MENTIONED IN THIS NOTE.

STORAGE

DO NOT USE AFTER THE EXPIRATION DATE, WHICH APPEARS ON THE OUTSIDE PACKAGING.

DATE OF REVISION OF THE PACKAGE INSERT

January 7, 1999

Success by age for women with gestational age ≤63 days

Age	Success		Total
	No	Yes	
<25	99 (12.5%)	691 (87.5%)	790 (100.0%)
25-29	105 (17.5%)	495 (82.5%)	600 (100.0%)
30-34	60 (15.2%)	336 (84.8%)	396 (100.0%)
≥35	31 (13.5%)	198 (86.5%)	229 (100.0%)
Total	295 (14.6%)	1720 (85.4%)	2015 (100.0%)

Note: Pearson Chi-Square = 0.071, which is not significant at the 0.05 level.

Success by age for women with gestational age ≤49 days

Age	Success		Total
	No	Yes	
<25	18 (6.2%)	272 (93.8%)	290 (100.0%)
25-29	17 (6.8%)	234 (93.2%)	251 (100.0%)
30-34	18 (10.0%)	162 (90.0%)	180 (100.0%)
≥35	12 (11.3%)	94 (88.7%)	106 (1000%)
Total	65 (7.9%)	762 (92.1%)	827 (100.0%)

Note: Pearson Chi-Square = 0.222, which is not significant at the 0.05 level.

Flo,
Ridgely sent this down. This is what the Pop Council submitted re drug efficacy/age. They have not submitted any raw data.
=
SC

A05450-3

SEARLE

Cytotec®
(misoprostol)

Revised: Mar. 6, 2000

CONTRAINDICATIONS AND WARNINGS

CYTOTEC (MISOPROSTOL) ADMINISTRATION BY ANY ROUTE IS CONTRAINDICATED, BECAUSE IT CAN CAUSE ABORTION, IN WOMEN WHO ARE PREGNANT (See **WARNINGS** and **PRECAUTIONS**).

- Anecdotal reports have been received, primarily from Brazil, of congenital anomalies and reports of fetal death in pregnancies in which misoprostol has been used as an abortifacient.

PATIENTS MUST BE ADVISED OF THE ABORTIFACIENT PROPERTY AND WARNED NOT TO GIVE THE DRUG TO OTHERS.

UTERINE RUPTURE HAS BEEN REPORTED WHEN CYTOTEC WAS ADMINISTERED INTRAVAGINALLY IN PREGNANT WOMEN TO INDUCE LABOR OR TO INDUCE ABORTION BEYOND THE FIRST TRIMESTER OF PREGNANCY.

UTERINE PERFORATION HAS BEEN REPORTED FOLLOWING ADMINISTRATION OF COMBINED VAGINAL-AND-ORAL CYTOTEC IN PREGNANT WOMEN TO INDUCE ABORTION. IN EACH OF THESE REPORTED CASES, THE GESTATIONAL AGE OF THE PREGNANCIES WAS UNKNOWN.

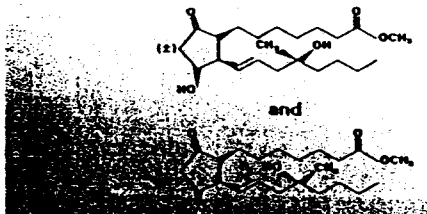
Cytotec should not be used in women of childbearing potential unless the patient requires nonsteroidal anti-inflammatory drug (NSAID) therapy and is at high risk of complications from gastric ulcers associated with use of the NSAID, or is at high risk of developing gastric ulceration. In such patients, 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.

DESCRIPTION

Cytotec oral tablets contain either 100 mcg or 200 mcg of misoprostol, a synthetic prostaglandin E_1 analog.

Misoprostol contains approximately equal amounts of the two diastereomers presented below with their enantiomers indicated by (±):



Misoprostol is a water-soluble, viscous liquid.

Inactive ingredients of tablets are hydrogenated castor oil, hydroxypropyl methylcellulose, microcrystalline cellulose, and sodium starch glycolate.

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 T_{max} 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	C_{max} (pg/ml)	AUC(0-4) (pg·hr/ml)	T_{max} (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 $T_{½}$, C_{max}, 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 1 week

nad no effect on the steady state pharmacokinetics of diazepam when the two drugs were administered 2 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 boxed **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 1 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 equa divided between ibuprofen, piroxicam, a naproxen, and continued this treatme throughout the 12 weeks. The 200-mcg do caused a marked, statistically significant red tion in gastric ulcers in both studies. T lower dose was somewhat less effective, w a significant result in only one of the studi

Prevention of Gastric Ulcers Induced by Ibuprofen, Piroxicam, or Naproxen
[No. of patients with ulcer(s) (%)]

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

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

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

In another clinical trial, 239 patients rec ing aspirin 650–1300 mg q.i.d. for rheumat arthritis who had endoscopic evidence of d denal and/or gastric inflammation were r domized to misoprostol 200 mcg q.i.d. placebo for 8 weeks while continuing receive aspirin. The study evaluated the p sible interference of Cytotec on the efficac aspirin in these patients with rheumat arthritis by analyzing joint tenderness, j swelling, physician's clinical assessme patient's assessment, change in ARA clas cation, change in handgrip strength, chang duration of morning stiffness, patient's ass ment of pain at rest, movement, interfere with daily activity, and ESR. Cytotec did interfere with the efficacy of aspirin in th patients with rheumatoid arthritis.

INDICATIONS AND USAGE

Cytotec (misoprostol) is indicated for the p vention of NSAID (nonsteroidal anti-infl matory drugs, including aspirin)-indu gastric ulcers in patients at high risk of c plications from gastric ulcer, eg, the eld and patients with concomitant debilita disease, as well as patients at high risk developing gastric ulceration, such as tients with a history of ulcer. Cytotec has been shown to prevent duodenal ulcer patients taking NSAIDs. Cytotec should taken for the duration of NSAID ther Cytotec has been shown to prevent ga ulcers in controlled studies of 3 mon duration. It had no effect, compared placebo, on gastrointestinal pain or disc fort associated with NSAID use.

CONTRAINDICATIONS

See boxed **CONTRAINDICATIONS A WARNINGS.**

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

WARNINGS

See boxed **CONTRAINDICATIONS A WARNINGS.**

PRECAUTIONS

Information for patients: Cytotec is cor indicated in women who are pregnant, should not be used in women of childbea potential unless the patient requires non roidal anti-inflammatory drug (NSAID) the and is at high risk of complications f gastric ulcers associated with the use of

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: Because of its abortifacient property, Cytotec is contraindicated for use by pregnant women. Cytotec may cause miscarriage if given to pregnant women at any time during pregnancy. Miscarriages caused by Cytotec may be incomplete, which could lead to 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 *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 1 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.** One case of amniotic fluid embolism, which resulted in maternal and fetal death, has been reported with use of misoprostol during pregnancy. Severe vaginal bleeding, retained placenta, shock, fetal bradycardia, and pelvic pain have also been reported. These women were administered misoprostol vaginally and/or orally over a range of doses.

Nonteratogenic effects: Cytotec may endanger pregnancy (may cause miscarriage) and thereby cause harm to the fetus when administered to a pregnant woman. 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 use of misoprostol as an abortifacient have been received (see boxed **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: 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 of Cytotec in pediatric patients have not been established.

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. There have been reports in which intravaginal administration of misoprostol in pregnant women resulted in rupture of the uterus and death of the infant. (See boxed **CONTRAINDICATIONS AND WARNINGS.**)

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 *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 *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°C (77°F), in a dry area.

Rx only

PATIENT INFORMATION

Read this leaflet before taking Cytotec® (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.

Do not take Cytotec if you are pregnant because it can cause miscarriage at any time during pregnancy. It is also important to avoid pregnancy while taking this medication and for at least one month or through one menstrual cycle after you stop taking it. Cytotec may cause the uterus to rupture (tear) in pregnant women if it is used to bring on (induce) labor or to cause an abortion after the first trimester of pregnancy. Miscarriages or rupture of the uterus may result in severe bleeding, hospitalization, surgery, infertility or death.

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.

Revised: Mar. 6, 2000

G.D. Searle & Co.
Box 5110, Chicago IL 60680

Address medical inquiries to:
G.D. Searle & Co.
Healthcare Information Services
5200 Old Orchard Road
Skokie IL 60077

SEARLE

 Printed in USA

SEARLE

Cytotec®
(misoprostol)

A05450-3

A05450-1

SEARLE

Cytotec® (misoprostol)

Revised: Aug. 8, 1995

CONTRAINDICATIONS AND WARNINGS

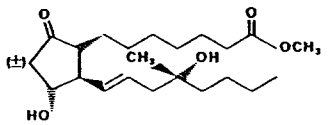
Cytotec (misoprostol) is contraindicated, because of its abortifacient property, in women who are pregnant. (See *Precautions*.) Patients must be advised of the abortifacient property and warned not to give the drug to others. Anecdotal reports, primarily from Brazil, of congenital anomalies and reports 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.

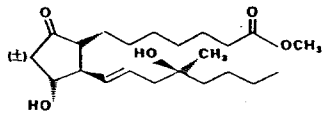
DESCRIPTION

Cytotec oral tablets contain either 100 mcg or 200 mcg of misoprostol, a synthetic prostaglandin E_1 analog.

Misoprostol contains approximately equal amounts of the two diastereomers presented below with their enantiomers indicated by (±):



and



$C_{22}H_{38}O_5$ M.W. = 382.5

(±) methyl 11α,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.

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 T_{max} 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	C_{max} (pg/ml)	AUC(0-4) (pg·hr/ml)	T_{max} (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 $T_{½}$, C_{max}, 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 1 week had no effect on the steady state pharmaco-

kinetics of diazepam when the two drugs were administered 2 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 1 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	Therapy Duration 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 8 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 3 months' duration. It had no effect, compared to placebo, on gastrointestinal pain or discomfort associated with NSAID use.

CONTRAINDICATIONS

See boxed *CONTRAINDICATIONS AND WARNINGS.*

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

WARNINGS

See boxed *CONTRAINDICATIONS AND WARNINGS.*

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 non-

steroidal 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 *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 1 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 woman. 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.

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 *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 *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°C (77°F), in a dry area.

Caution: Federal law prohibits dispensing without prescription.

PATIENT INFORMATION

Read this leaflet before taking Cytotec® (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.

G.D. Searle & Co.
Box 5110, Chicago IL 60680

Address medical inquiries to:
G.D. Searle & Co.
Healthcare Information Services
5200 Old Orchard Road
Skokie IL 60077

SEARLE

SEARLE

Cytotec®
(misoprostol)

Revised: Aug. 8, 1995

A05450-1

Previously Approved

SEARLE

Cytotec®
(misoprostol)

Revised: Aug. 8, 1995

CONTRAINDICATIONS AND WARNINGS

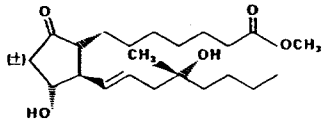
Cytotec (misoprostol) is contraindicated, because of its abortifacient property, in women who are pregnant. (See *Precautions.*) Patients must be advised of the abortifacient property and warned not to give the drug to others. Anecdotal reports, primarily from Brazil, of congenital anomalies and reports 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.

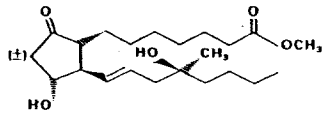
DESCRIPTION

Cytotec oral tablets contain either 100 mcg or 200 mcg of misoprostol, a synthetic prostaglandin E_1 analog.

Misoprostol contains approximately equal amounts of the two diastereomers presented below with their enantiomers indicated by (±):



and



$C_{22}H_{38}O_5$ M.W. = 382.5

(±) methyl 11α,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.

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 T_{max} 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	C_{max} (pg/ml)	AUC(0-4) (pg·hr/ml)	T_{max} (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 $T_{½}$, C_{max}, 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 1 week had no effect on the steady state pharmaco-

kinetics of diazepam when the two drugs were administered 2 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 1 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	Therapy Duration 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 8 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 3 months' duration. It had no effect, compared to placebo, on gastrointestinal pain or discomfort associated with NSAID use.

CONTRAINDICATIONS

See boxed *CONTRAINDICATIONS AND WARNINGS.*

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

WARNINGS

See boxed *CONTRAINDICATIONS AND WARNINGS.*

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 non-

steroidal 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 *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 1 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 woman. 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.

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 *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 *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°C (77°F), in a dry area.

Caution: Federal law prohibits dispensing without prescription.

PATIENT INFORMATION

Read this leaflet before taking Cytotec® (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.

G.D. Searle & Co.
Box 5110, Chicago IL 60680

Address medical inquiries to:
G.D. Searle & Co.
Healthcare Information Services
5200 Old Orchard Road
Skokie IL 60077

SEARLE

SEARLE
Cytotec®
(misoprostol)

Revised: Aug. 8, 1995

5-031

A05450-3

SEARLE

Cytotec®
(misoprostol)

Revised: Mar. 6, 2000

CONTRAINDICATIONS AND WARNINGS

CYTOTEC (MISOPROSTOL) ADMINISTRATION BY ANY ROUTE IS CONTRAINDICATED, BECAUSE IT CAN CAUSE ABORTION, IN WOMEN WHO ARE PREGNANT (See **WARNINGS** and **PRECAUTIONS**).

- Anecdotal reports have been received, primarily from Brazil, of congenital anomalies and reports of fetal death in pregnancies in which misoprostol has been used as an abortifacient.

PATIENTS MUST BE ADVISED OF THE ABORTIFACIENT PROPERTY AND WARNED NOT TO GIVE THE DRUG TO OTHERS.

UTERINE RUPTURE HAS BEEN REPORTED WHEN CYTOTEC WAS ADMINISTERED INTRAVAGINALLY IN PREGNANT WOMEN TO INDUCE LABOR OR TO INDUCE ABORTION BEYOND THE FIRST TRIMESTER OF PREGNANCY.

UTERINE PERFORATION HAS BEEN REPORTED FOLLOWING ADMINISTRATION OF COMBINED VAGINAL-AND-ORAL CYTOTEC IN PREGNANT WOMEN TO INDUCE ABORTION. IN EACH OF THESE REPORTED CASES, THE GESTATIONAL AGE OF THE PREGNANCIES WAS UNKNOWN.

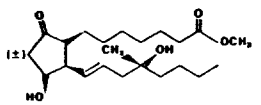
Cytotec should not be used in women of childbearing potential unless the patient requires nonsteroidal anti-inflammatory drug (NSAID) therapy and is at high risk of complications from gastric ulcers associated with use of the NSAID, or is at high risk of developing gastric ulceration. In such patients, 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.

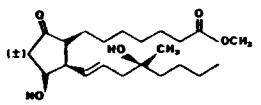
DESCRIPTION

Cytotec oral tablets contain either 100 mcg or 200 mcg of misoprostol, a synthetic prostaglandin E_1 analog.

Misoprostol contains approximately equal amounts of the two diastereomers presented below with their enantiomers indicated by (±):



and



$C_{22}H_{38}O_5$ M.W. = 382.5

(±) methyl 11α,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.

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 T_{max} 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	C_{max} (pg/ml)	AUC(0-4) (pg·hr/ml)	T_{max} (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 $T_{½}$, C_{max}, 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 1 week

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 boxed **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 1 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 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	Therapy Duration 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 8 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 3 months' duration. It had no effect, compared to placebo, on gastrointestinal pain or discomfort associated with NSAID use.

CONTRAINDICATIONS

See boxed **CONTRAINDICATIONS AND WARNINGS.**

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

WARNINGS

See boxed **CONTRAINDICATIONS AND WARNINGS.**

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

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: Because of its abortifacient property, Cytotec is contraindicated for use by pregnant women. Cytotec may cause miscarriage if given to pregnant women at any time during pregnancy. Miscarriages caused by Cytotec may be incomplete, which could lead to 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 *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 1 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.** One case of amniotic fluid embolism, which resulted in maternal and fetal death, has been reported with use of misoprostol during pregnancy. Severe vaginal bleeding, retained placenta, shock, fetal bradycardia, and pelvic

Nonteratogenic effects: Cytotec may endanger pregnancy (may cause miscarriage) and thereby cause harm to the fetus when administered to a pregnant woman. 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 use of misoprostol as an abortifacient have been received (see boxed **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: 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 of Cytotec in pediatric patients have not been established.

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. There have been reports in which intravaginal administration of misoprostol in pregnant women resulted in rupture of the uterus and death of the infant. (See boxed **CONTRAINDICATIONS AND WARNINGS.**)

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

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 *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 *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

PATIENT INFORMATION

Read this leaflet before taking Cytotec® (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.

Do not take Cytotec if you are pregnant because it can cause miscarriage at any time during pregnancy. It is also important to avoid pregnancy while taking this medication and for at least one month or through one menstrual cycle after you stop taking it. Cytotec may cause the uterus to rupture (tear) in pregnant women if it is used to bring on (induce) labor or to cause an abortion after the first trimester of pregnancy. Miscarriages or rupture of the uterus may result in severe bleeding, hospitalization, surgery, infertility or death.

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.

Revised: Mar. 6, 2000

G.D. Searle & Co.
Box 5110, Chicago IL 60680

Address medical inquiries to:
G.D. Searle & Co.
Healthcare Information Services
5200 Old Orchard Road
Skokie IL 60077

SEARLE

 Printed in USA

SEARLE

Cytotec®
(misoprostol)

A05450-3

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,

— 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

SEARLE

08/31/00
NC-T

August 21, 2000

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

Lilia Talarico, M.D. Director
Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research (HFD-180)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SUPPL NEW CORRESP

Re: NDA 19-268/S-031
Cytotec® (misoprostol)

SLR-031-C

Dear Dr. Talarico:

Please refer to our supplemental New Drug Application (S-031) dated October 13, 1998, to your letters relating to this supplement dated March 17, April 2, April 9, 1999 and to your approvable letter dated December 17, 1999 to which we responded on March 9, 2000.

We acknowledge receipt of your letter dated May 23, 2000, recommending changes to our draft "Dear Health Care Practitioner" ("HCP") letter. These recommendations have been incorporated into a final version with the exception of the suggested placement of the phrase "maternal and fetal death." We have left that phrase as it appears in our draft version since not all cases of maternal and fetal death, as reported to FDA, resulted from amniotic fluid embolism. A final version of our letter is enclosed for your records.

As the agency recommended, we have considered revising the HCP letter to include _____ We have also considered the agency's suggestion that we look at possible ways to expand the categories of health care professionals who are to receive this letter.

Accordingly, we do not believe that referring ——— along with Cytotec in the HCP letter would provide any new or useful information for practitioners who prescribe ——— for patients with arthritis.

Our defined audience for the HCP letter is a comprehensive list of practitioners most likely to be associated with misoprostol use for the off-label indications addressed in our HCP letter. Please note that, in response to the agency's suggestion, we have expanded our distribution to include both family and general practitioners who are likely prescribers of misoprostol and may assist in labor and delivery, and emergency room physicians, because they may assess patients who have been administered misoprostol for induction of labor or abortion.

If you have any questions or concerns, please address to the undersigned,

Sincerely,

Mary Jo Pritza, MPH, PharmD.
Regulatory Affairs Associate
Ph: 847-982-7831
Fax: 847-982-8090

cc: MEDWATCH-HF2

SEARLE

SEARLE
5200 OLD ORCHARD ROAD
SKOKIE, ILLINOIS 60077
PHONE (847) 982-7000
FAX (847) 470-1480

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

CY20141A

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

WOCII · 6th Floor HFD-001
Phone: 301-594-5400
Fax: 301-594-6197

DATE: 11/3/00

TO: ~~LR to Hoon~~ Lilia Talarico, Alice Kaul
Dan Shames, Terri Rumble

FROM: Jane Axelrad

Number of Pages (Excluding Cover Sheet)

AMERICAN COLLEGE OF OBSTETRICIANS
& GYNECOLOGISTS
WOMENS HEALTH CARE PHYSICIANS

DEPARTMENT OF GOVERNMENT RELATIONS AND OUTREACH
409 12th Street, SW
Washington, DC 20024-2188
(202) 863-2509
FAX (202) 488-3985

DATE: 11/3/00

TO: Linda Suydam

FROM: Dawn McGinnes

RE: Attachments

NUMBER OF PAGES (including this page): 5

RECIPIENT'S FAX NUMBER: 301/443-3100

COMMENTS:

IF THERE IS A TRANSMISSION PROBLEM, OR IF YOU WOULD LIKE TO SPEAK WITH SOMEONE AT ACOG, PLEASE CALL (202) 863-2509

References

1. Hofmeyr GJ, Gulmezoglu AM. Vaginal misoprostol for cervical ripening and labour induction in late pregnancy (Cochrane Review). In: The Cochrane Library, Issue 3, 2000. Oxford: Update Software
2. Wing DA. Labor induction with misoprostol. Am J Obstet Gynecol 1999;181:339–345
3. Nunes F, Rodrigues R, Meirinho M. Randomized comparison between intravaginal misoprostol and dinoprostone for cervical ripening and induction of labor. Am J Obstet Gynecol 1999;181:626–629
4. Blanchette HA, Nayak S, Erasmus S. Comparison of the safety and efficacy of intravaginal misoprostol (prostaglandin E1) with those of dinoprostone (prostaglandin E2) for cervical ripening and induction of labor in a community hospital. Am J Obstet Gynecol 1999;180:1551–1559
5. American College of Obstetricians and Gynecologists. Induction of labor with misoprostol. ACOG Committee Opinion 228. Washington, DC: ACOG, 1999
6. American College of Obstetricians and Gynecologists. Induction of labor. ACOG Practice Bulletin 10. Washington, DC: ACOG, 1999
7. El-Refaey H, O'Brien P, Morafa W, Walder J, Rodeck C. Use of oral misoprostol in the prevention of postpartum haemorrhage. Br J Obstet Gynaecol 1997;104:336–339
8. O'Brien P, El-Refaey H, Gordon A, Geary M, Rodeck CH. Rectally administered misoprostol for the treatment of postpartum hemorrhage unresponsive to oxytocin and ergometrine: a descriptive study. Obstet Gynecol 1998;92:212–214
9. Bamigboye AA, Hofmeyr GJ, Merrell DA. Rectal misoprostol in the prevention of postpartum hemorrhage: a placebo-controlled trial. Am J Obstet Gynecol 1998;179:1043–1046
10. Surbek DV, Fehr PM, Hosli I, Holzgreve W. Oral misoprostol for third stage of labor: a randomized placebo-controlled trial. Obstet Gynecol 1999;94:255–258
11. Hofmeyr GJ, Nikodem VC, de Jager M, Gelbart BR. A randomised placebo controlled trial of oral misoprostol in the third stage of labour. Br J Obstet Gynaecol 1998;105:971–975
12. Bamigboye AA, Merrell DA, Hofmeyr GJ, Mitchell R. Randomized comparison of rectal misoprostol with Syntometrine for management of third stage of labor. Acta Obstet Gynecol Scand 1998;77:178–181

SEARLE

Searle
5200 Old Orchard Road
Skokie, Illinois 60077
Phone (847) 982-7000
Fax (847) 470-2460

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

Re: Cytotec® (misoprostol)

August 23, 2000

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

CY201-11A

TOM A. COBURN, M.D.
2d District, Oklahoma

COMMITTEE ON COMMERCE
SUBCOMMITTEES:
HEALTH AND ENVIRONMENT
ENERGY AND POWER

Congress of the United States
House of Representatives
Washington, DC 20515–3602

215 State Street, Suite 815
Muskogee, OK 74401
(918) 687-2533
(918) 682-8503 (Fax)

120 S. Missouri, Room 105
Claremore, OK 74017
(918) 341-9336
(918) 341-9437 (Fax)

24 "A" Street N.E., Room 202
Miami, OK 74354
(918) 542-5337
(918) 542-5367 (Fax)

October 16, 2000

Ralph W. Hale, MD, FACOG
Executive Vice President
American College of Obstetricians and Gynecologists
409 12th St. SW
Washington DC 20024-2188

Dear Dr. Hale,

Thank you for your letter stating ACOG's opposition to H.R. 5385 and S. 3157, the RU-486 Patient Health and Safety Act. Of course, I am not surprised by ACOG's opposition to this legislation because I am familiar with July 27, 2000 communication from ACOG to the FDA regarding the patient protection guidelines the FDA was reportedly considering. As you can see, my bill is nothing other than an attempt to codify most of those very same guidelines.

Each one of those guidelines has but one purpose: the protection of patient health and safety. It was a sad day when the FDA approved RU-486 — the first drug ever approved for the specific purpose of ending a human life. But that was made even worse by the fact that the FDA succumbed to the political pressure brought by ACOG and other elements of the abortion lobby by dropping most of the proposed patient protections, and thereby recklessly exposing women to avoidable risk.

Let us review the patient protection standards to which you objected and which the FDA dropped under that pressure, evidently in response to those objections.

1) Limit distribution of the drug only to licenced physicians. The point of this, obviously, is to ensure that mifepristone is administered only under a doctor's direct supervision. The FDA actually retained this standard, but your objection to it raises very troubling concerns about ACOG's commitment to patient protection.

2) Require the physician to be "trained and authorized by law" to provide surgical abortions. I am surprised that ACOG would object either to training or legal authorization for a physician. The legal authorization is a matter of state law. As for training in abortion procedures, the real issue in connection with a mifepristone/misoprostol abortion is the ability to handle complications, and especially the ability to perform a dilatation and curettage in the event of an incomplete abortion — a rather common complication, according to the clinical trials. I have dealt with this in my bill by adding to the original FDA proposal a distinct requirement that the prescribing physician be qualified to handle the complications of an incomplete abortion or an ectopic pregnancy.

429 Cannon House Office Building
Washington, DC 20515
(202) 225-2701 Fax: (202) 225-3038

E-mail: rep.coburn@m...
Web site: www.house...

My bill does not address the paradox that the FDA has approved a drug which, used by itself, is not efficacious in achieving the intended purpose of a completed abortion, and which becomes effective only when used in combination with another drug whose manufacturer has warned is unsafe in that application. The FDA cannot escape the logical dilemma of having approved a drug that is either ineffective (when used without misoprostol) or unsafe (when used with misoprostol).

Your justification for authorizing the use of misoprostol for chemically inducing abortion is that without misoprostol, mifepristone is ineffective. That is what is known as circular reasoning.

The evidence that we have from the clinical trials about the safety of the mifepristone/misoprostol combination for abortion is not entirely encouraging. There were no deaths among the sample population, but the rate of incomplete abortions was nearly 8 percent and the incidence of hemorrhaging was 5 percent. These are both potentially serious complications with rates of occurrence that are too high to be dismissed as "rare." In France, where far more stringent safety precautions are in effect, one death and two near-fatal cardiac arrests were recorded within the first two years of availability. In 1991, in response to concerns about such complications, France banned the use of mifepristone by women over 35 and by smokers. The U.S. clinical trials reportedly did not include smokers or women over 35 among the subjects, but neither of these conditions is listed in the label, the prescriber's agreement, the patient agreement, or the medication guide as a contraindication. Undoubtedly, some women from both of those risk categories will be likely to receive the drug combination because neither they nor their doctors have any way of knowing these factors pose an additional risk.

You will note that my legislation does not at all address the question of the use of misoprostol to induce labor. As a practitioner, I am grateful to Searle for calling attention to the risks and contraindications of induction with misoprostol. But I am also cognizant of the benefits of using misoprostol for induction in some cases. The freedom of doctors to weigh the risks and benefits and then to act in the best interest of their patients is not at all affected by my legislation and is irrelevant to the conditions under which mifepristone was approved.

I have no doubt that if women were asked whether their doctor should have to be able to read a sonogram, handle complications, and get them admitted to a hospital in case of emergency, they would not hesitate to demand those levels of competence. Nor do I have any doubt that women would expect their doctors to be trained in the use of a potentially risky drug. In light of the very real and very serious risks to maternal health associated with this method of abortion, I remain amazed and dismayed that ACOG opposes the elementary patient protection standards that I have proposed. I encourage you to reconsider your position.

Sincerely,

Tom A. Coburn, M.D.
Member of Congress

APPROVED

JUN 2 2 2000

A05450-3

SEARLE

Cytotec®
(misoprostol)

Revised: Mar. 6, 2000

CONTRAINDICATIONS AND WARNINGS

CYTOTEC (MISOPROSTOL) ADMINISTRATION BY ANY ROUTE IS CONTRAINDICATED, BECAUSE IT CAN CAUSE ABORTION, IN WOMEN WHO ARE PREGNANT (See **WARNINGS** and **PRECAUTIONS**).

- Anecdotal reports have been received, primarily from Brazil, of congenital anomalies and reports of fetal death in pregnancies in which misoprostol has been used as an abortifacient.

PATIENTS MUST BE ADVISED OF THE ABORTIFACIENT PROPERTY AND WARNED NOT TO GIVE THE DRUG TO OTHERS.

UTERINE RUPTURE HAS BEEN REPORTED WHEN CYTOTEC WAS ADMINISTERED INTRAVAGINALLY IN PREGNANT WOMEN TO INDUCE LABOR OR TO INDUCE ABORTION BEYOND THE FIRST TRIMESTER OF PREGNANCY.

UTERINE PERFORATION HAS BEEN REPORTED FOLLOWING ADMINISTRATION OF COMBINED VAGINAL-AND-ORAL CYTOTEC IN PREGNANT WOMEN TO INDUCE ABORTION. IN EACH OF THESE REPORTED CASES, THE GESTATIONAL AGE OF THE PREGNANCIES WAS UNKNOWN.

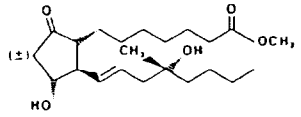
Cytotec should not be used in women of childbearing potential unless the patient requires nonsteroidal anti-inflammatory drug (NSAID) therapy and is at high risk of complications from gastric ulcers associated with use of the NSAID, or is at high risk of developing gastric ulceration. In such patients, 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.

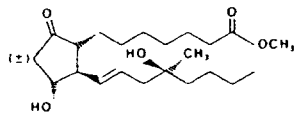
DESCRIPTION

Cytotec oral tablets contain either 100 mcg or 200 mcg of misoprostol, a synthetic prostaglandin E_1 analog.

Misoprostol contains approximately equal amounts of the two diastereomers presented below with their enantiomers indicated by (±):



and



$C_{22}H_{38}O_5$ M.W. = 382.5

(±) methyl 11α,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.

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 T_{max} 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	C_{max} (pg/ml)	AUC(0-4) (pg·hr/ml)	T_{max} (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 $T_{½}$, C_{max}, 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 1 week had no effect on the steady state pharmacokinetics of diazepam when the two drugs were administered 2 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 boxed **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 1 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	Therapy Duration			
	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 8 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 3 months' duration. It had no effect, compared to placebo, on gastrointestinal pain or discomfort associated with NSAID use.

CONTRAINDICATIONS

See boxed **CONTRAINDICATIONS AND WARNINGS.**

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

WARNINGS

See boxed **CONTRAINDICATIONS AND WARNINGS.**

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: Because of its abortifacient property, Cytotec is contraindicated for use by pregnant women. Cytotec may cause miscarriage if given to pregnant women at any time during pregnancy. Miscarriages caused by Cytotec may be incomplete, which could lead to 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 *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 1 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.** One case of amniotic fluid embolism, which resulted in maternal and fetal death, has been reported with use of misoprostol during pregnancy. Severe vaginal bleeding, retained placenta, shock, fetal bradycardia, and pelvic

pain have also been reported. These women were administered misoprostol vaginally and/or orally over a range of doses.

Nonteratogenic effects: Cytotec may endanger pregnancy (may cause miscarriage) and thereby cause harm to the fetus when administered to a pregnant woman. 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 use of misoprostol as an abortifacient have been received (see boxed **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: 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 of Cytotec in pediatric patients have not been established.

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. There have been reports in which intravaginal administration of misoprostol in pregnant women resulted in rupture of the uterus and death of the infant. (See boxed **CONTRAINDICATIONS AND WARNINGS.**)

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 *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 *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°C (77°F), in a dry area.

Rx only

PATIENT INFORMATION

Read this leaflet before taking Cytotec® (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.

Do not take Cytotec if you are pregnant because it can cause miscarriage at any time during pregnancy. It is also important to avoid pregnancy while taking this medication and for at least one month or through one menstrual cycle after you stop taking it. Cytotec may cause the uterus to rupture (tear) in pregnant women if it is used to bring on (induce) labor or to cause an abortion after the first trimester of pregnancy. Miscarriages or rupture of the uterus may result in severe bleeding, hospitalization, surgery, infertility or death.

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.

Revised: Mar. 6, 2000

G.D. Searle & Co.
Box 5110, Chicago IL 60680

Address medical inquiries to:
G.D. Searle & Co.
Healthcare Information Services
5200 Old Orchard Road
Skokie IL 60077

SEARLE

 Printed in USA

SEARLE

Cytotec®
(misoprostol)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

The American College of Obstetricians and Gynecologists
Attention: Ralph W. Hale, M.D., FACOG
Executive Vice President
PO Box 96920
Washington DC, 20090-6920

Dear Dr. Hale:

Please refer to the meeting between representatives of your organization and FDA on June 6, 2001.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-1602.

Sincerely,

—S—

Alice Kacuba, RN, MSN, RAC
Regulatory Health Project Manager
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Date: June 6, 2001
Time: 1-3 PM
Location: Parklawn Building, Conference Room "K"

Application: N/A

Type of Meeting: Meeting with ACOG

Meeting Chair: Dr. Florence Houn

Meeting Recorder: Ms. Alice Kacuba

FDA Attendees, Titles, and Office/Division:

Center for Drug Evaluation and Research (HFD-001)

Dr. Janet Woodcock, Director

Office of Review Management (HFD-1004)

Dr. Sandra Kweder, Acting Director

Office of Review Management (HFD-002)

Dr. Sol Sobel, Deputy Director

Office of Drug Evaluation III (HFD-103)

Dr. Florence Houn, Office Director

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Ms. Alice Kacuba, Regulatory Health Project Manager

Division of Reproductive and Urologic Drug Products (HFD-580)

Dr. Dan Shames, Deputy Director
Dr. Dena Hixon, Medical Team Leader

Discussion Points (bullet format):

Misoprostol:
Dr. Lockwood of ACOG provided a historical prespective from the ACOG point of view. ACOG conducted a review of the literature and developed a Committee Opinion Number 228, November 1999, "Induction of Labor With Misoprostol" on the use of misoprostol for cervical ripening. ACOG considered the August 23, 2000 Dear Healthcare Provider letter to be alarming and ill timed. The August 23, 2000 Dear Healthcare Provider letter contradicted the ACOG Practice Bulletin Number 10 entitled "Induction of Labor", November 1999.

Following Searle's Dear Healthcare Practitioner letter, ACOG reviewed the literature again and found no data that was different from the prior review which lead to the publication of the November 1999 Practice Bulletin. Therefore, ACOG published a response to Searle's Dear Healthcare Practitioner letter in a ACOG Committee Opinion entitled, "Response to Searle's Drug Warning on Misoprostol", December 2000.

The Agency stated that the Agency is sensitive to the position that the August 23, 2000 Dear Healthcare Practitioner letter put ACOG in and acknowledged that ACOG wants therapeutic products available. While the Agency can not speak of the specifics, we disagree with the Searle's August 23, 2000 Dear Healthcare Practitioner letter and the labeling that was attached. We have been actively working with Searle to correct the labeling and believe that the outcome of this endeavor will address the concerns of ACOG. Labeling changes require back and forth negotiations with the firm and take time.

In 1997 and 1998 we did see adverse events of uterine rupture. Whenever numerous adverse events are seen with a drug, we request the firm to revise the labeling to include the adverse events. While the Agency did ask Searle to consider distributing a Dear Healthcare Practitioner letter, the timing of the distribution of this letter was unknown. FDA will comment, when requested by a sponsor, on letters to health care professionals. The August 23, 2000, letter to health care professionals was developed in relation to the use of misoprostol for reducing the risk of NSAID-induced ulcers. With the approval of the mifepristone/misoprostol medical abortion regimen, statements in the Cytotec labeling contraindicating the use of misoprostol to induce abortion are misleading.

[redacted]

In response from a question from ACOG on what types of studies would be required for such an application, the Agency stated that possibly a 505(b)(2) application containing existing data on misoprostol.. Also required would be clinical studies to ascertain the lowest effective dose of the [redacted] Currently, no information exists on the lowest effective dose as it is difficult to split a tablet in more than quarters.

In the discussion regarding the need to develop a registry to document uterine rupture, both FDA and ACOG agreed that documenting such events through MedWatch was adequate. While a registry would collect safety information, a registry would not collect efficacy information.

In response to a question from ACOG regarding the pending Citizen's petition from ACOG, the Agency stated that they will respond once the misoprostol labeling issue is resolved. ACOG stated that it appreciated the Agency meeting with them and working to resolve this issue.

Betamethasone:

In response to a question from ACOG regarding the status of the betamethasone drug shortage, the Agency responded that it was currently resolved although it is still in limited supply and is being designated for OB use only. Drug shortages are often due to manufacturing problems.

Pre-term labor:

Having completed the discussion on misoprostol, the Agency stated that we would like to use ACOG's expertise and asked if ACOG would entertain questions from the Agency regarding clinical trial design of products for pre-term labor.

ACOG explained that 24 to 32 weeks was the critical period to prevent pre-term labor. It would be important to show that a drug significantly prolonged the pregnancy by approximately 10 days versus prolonging pregnancy for 48 hours. A potential active comparator could be magnesium sulfate. A rescue arm would probably be needed.

Minutes Preparer: _____

Chair Concurrence: _____ 9/3/01

SEARLE

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

GENERAL CORRESPONDENCE

February 23, 2001

Lilia Talarico, M.D., Director
Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research (HFD-180)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 19-268
Cytotec® (misoprostol) Tablets

Dear Dr. Talarico:

Please refer to FDA's letter dated December 15, 2000 and to Searle's Cytotec® (misoprostol) labeling counterproposal submitted February 20, 2001. In response to FDA's request of February 21, 2001, Searle has provided the following questions in support of our submission and requested meeting date.

1. Searle maintains that Cytotec® (misoprostol) remain contraindicated during pregnancy in those patients for whom the product is intended. Can FDA explain why this product is no longer considered "contraindicated" for Cytotec's labeled use?
2. Searle supports inclusion of new text within the Black Box CIW section that describes adverse events associated with Cytotec if administered to women who are pregnant. Does FDA agree to the addition of this new text, and if not what are your reasons?
3. Cytotec is not indicated for use in women who are pregnant when used for its approved indication. Why does FDA suggest the addition of new text [redacted]
4. [redacted]
5. [redacted]
6. [redacted]

7. [redacted]

8. Searle believes the adverse events associated with an incomplete abortion describe important safety information and should be included in the label. Could FDA provide reasons to not include this information?

If you have any questions or concerns, please contact the undersigned.

Sincerely,

Mary Jo Pritza, MPH, PharmD.
Regulatory Associate
Worldwide Regulatory Affairs
Phone: (847) 982-7831
Fax: (847) 982-8090/8152

Cc: Alice Kacuba

MJP/jr

SEARLE

GENERAL CORRESPONDENCE

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077
PHONE (847) 982-7000
FAX (847) 982-4701

February 16, 2001

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research (HFD-180)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Meeting Request
Re: NDA 19-268
Cytotec® (misoprostol) Tablet

Dear Dr. Talarico:

We would like to reschedule the meeting from December 18, 2000 with the Office of Drug Evaluation III and the Division of Gastrointestinal and Coagulation Drug Products to discuss FDA's proposed Cytotec labeling changes provided in your fax of December 15, 2000.

Approved indication:
Cytotec is indicated for the prevention of NSAID (non-steroidal 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.

Meeting type: Type A

Purpose of the meeting:
To discuss FDA's proposed labeling changes as provided in your letter faxed December 15, 2000 and to review and discuss our labeling counterproposal.

Outcomes expected from the meeting:
For FDA to provide feedback on our counterproposal to FDA's proposed changes to Cytotec's label and to come to an agreement on labeling changes to be submitted as an amendment to s-037. We anticipate resolving all issues at the meeting's conclusion but remain open to the possibility of subsequent discussions.

Proposed agenda:

1. **Introduction**
2. **Company presentation of response to the December 15, 2000 letter.**
3. **Discussion**

Regulatory issues:

1. A counterproposal is provided in response to FDA's labeling proposal faxed December 15, 2000. We feel this amended proposal incorporates revisions as suggested by FDA as well as addressing the company's position. Are our proposed changes satisfactory for submission as an amended CBE supplement for production and manufacturing use?

Searle's Attendee List:

Dr. Michael Tansey- Sr. V.P. Medical Development
Dr. Richard Spivey- Sr. V.P. Regulatory Affairs
Dr. Felix Arellano- V.P. Global Drug Surveillance
Dr. Mary Jo Pritza- Regulatory Affairs Associate

FDA attendees:
Appropriate officers from the Division of Gastrointestinal and Coagulation Drug Products and from the Office of Drug Evaluation III, and officers from additional Divisions or ODE as required. We also request representatives from Reproductive and Urologic Drug Products to discuss pertinent labeling concerns.

Data for review:
Provided in the enclosed background package is attachment I) FDA's labeling proposal from December 15, 2000; attachment II) Searle's counterproposal and attached rationale; Appendix I) as requested by FDA, studies to support the labeling text provided in the uterine effects subsection.

Suggested dates for the meeting:
As suggested by FDA.

If you have any questions regarding this submission please contact the undersigned.

Sincerely,

Mary Jo Pritza MPH, PharmD.
Regulatory Affairs Associate
Worldwide Regulatory Affairs
Ph: 847-982-7831
Fax: 847-982-8090/8152
enclosure
cc: A. Kacuba

November 1, 2000

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23, 12420 Parklawn Drive
Rockville, MD 20857

CITIZEN PETITION

The American College of Obstetricians and Gynecologists (ACOG) submits this petition to request that the Commissioner of the Food and Drug Administration take administrative action.

ACTION REQUESTED

This petition requests that the Commissioner of the Food and Drug Administration take administrative action to require the withdrawal of the letter which G.D. Searle issued on August 23, 2000 regarding its product, misoprostol. ACOG asks the FDA to review Searle's label of March 6, 2000 and particularly of June 29, 2000 and to rescind any contraindications for use of misoprostol in pregnancy that are not warranted by scientific evidence. Based on ACOG's review of the data, Searle's contraindictions warrant analysis by FDA. ACOG requests that the re-labeling of misoprostol currently under review by the FDA conform with the agency's approval of the mifepristone-misoprostol combination on September 28, 2000, and ACOG's Statement of Grounds below.

STATEMENT OF GROUNDS

The American College of Obstetricians and Gynecologists is an organization representing more than 41,000 physicians dedicated to improving women's health care. ACOG is also the body which establishes standards of care for the ob-gyn profession. ACOG submits this recent review of actions by G.D. Searle regarding misoprostol and all adverse event data in the possession of the FDA:

> "On August 23, 2000, G.D. Searle & Co. issued a letter entitled "Important Drug Warning Concerning Unapproved Use of Intravaginal or Oral Misoprostol in Pregnant Women for Induction of Labor or Abortion." This letter cautions that Cytotec (misoprostol) is indicated for prevention of non-steroidal-antiinflammatory-drug-induced gastric ulcers and states, "...*Cytotec administration by any route is contraindicated in women who are pregnant because it can cause abortion.*" The letter further states that Searle has become aware of the drug's use for induction of labor or as a cervical ripening agent prior to termination of pregnancy. Moreover, the letter notes serious adverse events, including uterine hyperstimulation and uterine rupture, which have resulted in fetal and maternal death. Finally, the company cautions, "*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."

The American College of Obstetricians and Gynecologists (ACOG) is concerned by the content, timing, and tone of this letter. Given that misoprostol is commonly employed in conjunction with mifepristone (RU 486) to achieve nonsurgical early pregnancy terminations, the arrival of the Searle letter within weeks of the U.S. Food and Drug Administration's (FDA) approval of mifepristone could limit the use of this new option for reproductive choice. Also, although the letter correctly points out the potentially serious, but relatively rare, risks of misoprostol when employed for cervical ripening and labor induction, it fails to comment on the extensive clinical experience with this agent and the large body of published reports supporting its safety and efficacy when used appropriately. A recent review of the Cochrane Pregnancy and Childbirth group trials registry identified 26 clinical trials of misoprostol for cervical ripening or induction of labor or both (1). These studies indicate misoprostol is more effective than prostaglandin E_2 in achieving vaginal deliveries within 24 hours and reduces the need for and total amount of oxytocin augmentation. Although these studies do suggest misoprostol is associated with a higher incidence of uterine hyperstimulation and meconium-stained amniotic fluid, these complications were more common with higher doses (>25 μg) of misoprostol. Other recent reviews and clinical trials support these conclusions (2-4). No studies indicate that intrapartum exposure to misoprostol (or other prostaglandin cervical ripening agents) has any long-term adverse health consequences to the fetus in the absence of fetal distress, nor is there a plausible biological basis for such a concern.

A review of published reports and of MedWatch, the FDA medical products reporting program, indicates the vast majority of adverse maternal and fetal outcomes associated with misoprostol therapy resulted from the use of doses greater than 25 μg, dosing intervals more frequent than 3–6 hours, addition of oxytocin less than 4 hours after the last misoprostol dose, or use of the drug in women with prior cesarean delivery or major uterine surgery. Grand multiparity also appears to be a relative risk factor for uterine rupture.

Thus, based on recently published series and a detailed review of adverse outcomes reported to the FDA, the ACOG Committee on Obstetric Practice strongly endorses its previous conclusions, published in Committee Opinion Number 228 (November 1999), *Induction of Labor with Misoprostol,* which states, "*Given the current evidence, intravaginal misoprostol tablets appear effective in inducing labor in pregnant women who have unfavorable cervices*" (5). Nonetheless, the Committee would like to emphasize that the following clinical practices appear to minimize the risk of uterine hyperstimulation and rupture in patients undergoing cervical ripening or induction in the third trimester:

1) If misoprostol is to be used for cervical ripening or labor induction in the third trimester, one quarter of a 100μg tablet (ie, approximately 25μg) should be considered for the initial dose.
2) Doses should not be administered more frequently than every 3-6 hours.
3) Oxytocin should not be administered less than 4 hours after the last misoprostol dose.
4) Misoprostol should not be used in patients with a previous cesarean delivery or prior major uterine surgery.

The use of higher doses of misoprostol (eg, 50 μg every 6 hours) to induce labor may be appropriate in some situations, although there are reports that such doses increase the risk of complications, including uterine hyperstimulation and uterine rupture (6). There is insufficient clinical evidence to address the safety or efficacy of misoprostol in patients with multifetal gestations or suspected fetal macrosomia.

In conclusion, the ACOG Committee on Obstetric Practice reaffirms that misoprostol is a safe and effective agent for cervical ripening and labor induction when used appropriately. Moreover, misoprostol also contributes to the obstetrician-gynecologist's resources as an effective treatment for serious postpartum hemorrhage in the presence of uterine atony (7-12)."

ENVIRONMENTAL IMPACT

The proposed action is exempt from the requirement of an environmental impact statement under 21 CFR §§ 25.24 (a)(8) and (c)(6).

ECONOMIC IMPACT

No information is required at this time.

CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Ralph W. Hale MD

Ralph W. Hale, MD, FACOG
American College of Obstetricians and Gynecologists
PO Box 96920
Washington, DC 20090
(202) 863-2509

Attachments: References
G.D. Searle letter 8/23/00
Rep. Coburn letter 10/16/00

References

1. Hofmeyr GJ, Gulmezoglu AM. Vaginal misoprostol for cervical ripening and labour induction in late pregnancy (Cochrane Review). In: The Cochrane Library, Issue 3, 2000. Oxford: Update Software
2. Wing DA. Labor induction with misoprostol. Am J Obstet Gynecol 1999;181:339–345
3. Nunes F, Rodrigues R, Meirinho M. Randomized comparison between intravaginal misoprostol and dinoprostone for cervical ripening and induction of labor. Am J Obstet Gynecol 1999;181:626–629
4. Blanchette HA, Nayak S, Erasmus S. Comparison of the safety and efficacy of intravaginal misoprostol (prostaglandin E1) with those of dinoprostone (prostaglandin E2) for cervical ripening and induction of labor in a community hospital. Am J Obstet Gynecol 1999;180:1551–1559
5. American College of Obstetricians and Gynecologists. Induction of labor with misoprostol. ACOG Committee Opinion 228. Washington, DC: ACOG, 1999
6. American College of Obstetricians and Gynecologists. Induction of labor. ACOG Practice Bulletin 10. Washington, DC: ACOG, 1999
7. El-Refaey H, O'Brien P, Morafa W, Walder J, Rodeck C. Use of oral misoprostol in the prevention of postpartum haemorrhage. Br J Obstet Gynaecol 1997;104:336–339
8. O'Brien P, El-Refaey H, Gordon A, Geary M, Rodeck CH. Rectally administered misoprostol for the treatment of postpartum hemorrhage unresponsive to oxytocin and ergometrine: a descriptive study. Obstet Gynecol 1998;92:212–214
9. Bamigboye AA, Hofmeyr GJ, Merrell DA. Rectal misoprostol in the prevention of postpartum hemorrhage: a placebo-controlled trial. Am J Obstet Gynecol 1998;179:1043–1046
10. Surbek DV, Fehr PM, Hosli I, Holzgreve W. Oral misoprostol for third stage of labor: a randomized placebo-controlled trial. Obstet Gynecol 1999;94:255–258
11. Hofmeyr GJ, Nikodem VC, de Jager M, Gelbart BR. A randomised placebo controlled trial of oral misoprostol in the third stage of labour. Br J Obstet Gynaecol 1998;105:971–975
12. Bamigboye AA, Merrell DA, Hofmeyr GJ, Mitchell R. Randomized comparison of rectal misoprostol with Syntometrine for management of third stage of labor. Acta Obstet Gynecol Scand 1998;77:178–181

October 26, 2000

Janet Woodcock, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Woodmont Building 2, Room 6027
1451 Rockville Pike
Rockville, MD 20852

Dear Dr. Woodcock:

The American College of Obstetricians and Gynecologists Committee on Obstetric Practice has met regarding Cytotec (misoprostol). We are expediting the transmittal of the content of their review to the Food and Drug Administration so that the agency can consider it during its review of the labeling of misoprostol.

> "On August 23, 2000, G.D. Searle & Co. issued a letter entitled "Important Drug Warning Concerning Unapproved Use of Intravaginal or Oral Misoprostol in Pregnant Women for Induction of Labor or Abortion." This letter cautions that Cytotec (misoprostol) is indicated for prevention of non-steroidal-antiinflammatory-drug-induced gastric ulcers and states, "*...Cytotec administration by any route is contraindicated in women who are pregnant because it can cause abortion.*" The letter further states that Searle has become aware of the drug's use for induction of labor or as a cervical ripening agent prior to termination of pregnancy. Moreover, the letter notes serious adverse events, including uterine hyperstimulation and uterine rupture, which have resulted in fetal and maternal death. Finally, the company cautions, "*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.*"
>
> The American College of Obstetricians and Gynecologists (ACOG) is concerned by the content, timing, and tone of this letter. Given that misoprostol is commonly employed in conjunction with mifepristone (RU 486) to achieve nonsurgical early pregnancy terminations, the arrival of the Searle letter within weeks of the U.S. Food and Drug Administration's (FDA) approval of mifepristone could limit the use of this new option for reproductive choice. Also, although the letter correctly

points out the potentially serious, but relatively rare, risks of misoprostol when employed for cervical ripening and labor induction, it fails to comment on the extensive clinical experience with this agent and the large body of published reports supporting its safety and efficacy when used appropriately. A recent review of the Cochrane Pregnancy and Childbirth group trials registry identified 26 clinical trials of misoprostol for cervical ripening or induction of labor or both (1). These studies indicate misoprostol is more effective than prostaglandin E_2 in achieving vaginal deliveries within 24 hours and reduces the need for and total amount of oxytocin augmentation. Although these studies do suggest misoprostol is associated with a higher incidence of uterine hyperstimulation and meconium-stained amniotic fluid, these complications were more common with higher doses (>25 μg) of misoprostol. Other recent reviews and clinical trials support these conclusions (2-4). No studies indicate that intrapartum exposure to misoprostol (or other prostaglandin cervical ripening agents) has any long-term adverse health consequences to the fetus in the absence of fetal distress, nor is there a plausible biological basis for such a concern.

A review of published reports and of MedWatch, the FDA medical products reporting program, indicates the vast majority of adverse maternal and fetal outcomes associated with misoprostol therapy resulted from the use of doses greater than 25 μg, dosing intervals more frequent than 3–6 hours, addition of oxytocin less than 4 hours after the last misoprostol dose, or use of the drug in women with prior cesarean delivery or major uterine surgery. Grand multiparity also appears to be a relative risk factor for uterine rupture.

Thus, based on recently published series and a detailed review of adverse outcomes reported to the FDA, the ACOG Committee on Obstetric Practice strongly endorses its previous conclusions, published in Committee Opinion Number 228 (November 1999), *Induction of Labor with Misoprostol,* which states, "*Given the current evidence, intravaginal misoprostol tablets appear effective in inducing labor in pregnant women who have unfavorable cervices*" (5). Nonetheless, the Committee would like to emphasize that the following clinical practices appear to minimize the risk of uterine hyperstimulation and rupture in patients undergoing cervical ripening or induction in the third trimester:

1) If misoprostol is to be used for cervical ripening or labor induction in the third trimester, one quarter of a 100μg tablet (ie, approximately 25μg) should be considered for the initial dose.
2) Doses should not be administered more frequently than every 3-6 hours.
3) Oxytocin should not be administered less than 4 hours after the last misoprostol dose.

4) Misoprostol should not be used in patients with a previous cesarean delivery or prior major uterine surgery.

The use of higher doses of misoprostol (eg, 50 μg every 6 hours) to induce labor may be appropriate in some situations, although there are reports that such doses increase the risk of complications, including uterine hyperstimulation and uterine rupture (6). There is insufficient clinical evidence to address the safety or efficacy of misoprostol in patients with multifetal gestations or suspected fetal macrosomia.

In conclusion, the ACOG Committee on Obstetric Practice reaffirms that misoprostol is a safe and effective agent for cervical ripening and labor induction when used appropriately. Moreover, misoprostol also contributes to the obstetrician-gynecologist's resources as an effective treatment for serious postpartum hemorrhage in the presence of uterine atony (7-12)."

Please contact Debra Hawks at (202) 863-2445 if you have any questions.

Sincerely,

Stanley Zinberg, MD, MS, FACOG

cc: Susan Allen, MD
Victor Raczkowski, MD

Attachment: References

References

1. Hofmeyr GJ, Gulmezoglu AM. Vaginal misoprostol for cervical ripening and labour induction in late pregnancy (Cochrane Review). In: The Cochrane Library, Issue 3, 2000. Oxford: Update Software
2. Wing DA. Labor induction with misoprostol. Am J Obstet Gynecol 1999;181:339–345
3. Nunes F, Rodrigues R, Meirinho M. Randomized comparison between intravaginal misoprostol and dinoprostone for cervical ripening and induction of labor. Am J Obstet Gynecol 1999;181:626–629
4. Blanchette HA, Nayak S, Erasmus S. Comparison of the safety and efficacy of intravaginal misoprostol (prostaglandin E1) with those of dinoprostone (prostaglandin E2) for cervical ripening and induction of labor in a community hospital. Am J Obstet Gynecol 1999;180:1551–1559
5. American College of Obstetricians and Gynecologists. Induction of labor with misoprostol. ACOG Committee Opinion 228. Washington, DC: ACOG, 1999
6. American College of Obstetricians and Gynecologists. Induction of labor. ACOG Practice Bulletin 10. Washington, DC: ACOG, 1999
7. El-Refaey H, O'Brien P, Morafa W, Walder J, Rodeck C. Use of oral misoprostol in the prevention of postpartum haemorrhage. Br J Obstet Gynaecol 1997;104:336–339
8. O'Brien P, El-Refaey H, Gordon A, Geary M, Rodeck CH. Rectally administered misoprostol for the treatment of postpartum hemorrhage unresponsive to oxytocin and ergometrine: a descriptive study. Obstet Gynecol 1998;92:212–214
9. Bamigboye AA, Hofmeyr GJ, Merrell DA. Rectal misoprostol in the prevention of postpartum hemorrhage: a placebo-controlled trial. Am J Obstet Gynecol 1998;179:1043–1046
10. Surbek DV, Fehr PM, Hosli I, Holzgreve W. Oral misoprostol for third stage of labor: a randomized placebo-controlled trial. Obstet Gynecol 1999;94:255–258
11. Hofmeyr GJ, Nikodem VC, de Jager M, Gelbart BR. A randomised placebo controlled trial of oral misoprostol in the third stage of labour. Br J Obstet Gynaecol 1998;105:971–975
12. Bamigboye AA, Merrell DA, Hofmeyr GJ, Mitchell R. Randomized comparison of rectal misoprostol with Syntometrine for management of third stage of labor. Acta Obstet Gynecol Scand 1998;77:178–181

TOM A. COBURN, M.D.
2D DISTRICT, OKLAHOMA

COMMITTEE ON COMMERCE
SUBCOMMITTEES:
HEALTH AND ENVIRONMENT
ENERGY AND POWER

Congress of the United States
House of Representatives
Washington, DC 20515–3602

215 STATE STREET, SUITE 816
MUSKOGEE, OK 74401
(918) 687-2533
(918) 682-8503 (FAX)

120 S. MISSOURI, ROOM 105
CLAREMORE, OK 74017
(918) 341-9336
(918) 341-9437 (FAX)

34 "A" STREET N.E., ROOM 202
MIAMI, OK 74354
(918) 542-5337
(918) 542-5367 (FAX)

October 16, 2000

Ralph W. Hale, MD, FACOG
Executive Vice President
American College of Obstetricians and Gynecologists
409 12th St. SW
Washington DC 20024-2188

Dear Dr. Hale,

Thank you for your letter stating ACOG's opposition to H.R. 5385 and S. 3157, the RU-486 Patient Health and Safety Act. Of course, I am not surprised by ACOG's opposition to this legislation because I am familiar with July 27, 2000 communication from ACOG to the FDA regarding the patient protection guidelines the FDA was reportedly considering. As you can see, my bill is nothing other than an attempt to codify most of those very same guidelines.

Each one of those guidelines has but one purpose: the protection of patient health and safety. It was a sad day when the FDA approved RU-486 — the first drug ever approved for the specific purpose of ending a human life. But that was made even worse by the fact that the FDA succumbed to the political pressure brought by ACOG and other elements of the abortion lobby by dropping most of the proposed patient protections, and thereby recklessly exposing women to avoidable risk.

Let us review the patient protection standards to which you objected and which the FDA dropped under that pressure, evidently in response to those objections.

1) Limit distribution of the drug only to licenced physicians. The point of this, obviously, is to ensure that mifepristone is administered only under a doctor's direct supervision. The FDA actually retained this standard, but your objection to it raises very troubling concerns about ACOG's commitment to patient protection.

2) Require the physician to be "trained and authorized by law" to provide surgical abortions. I am surprised that ACOG would object either to training or legal authorization for a physician. The legal authorization is a matter of state law. As for training in abortion procedures, the real issue in connection with a mifepristone/misoprostol abortion is the ability to handle complications, and especially the ability to perform a dilatation and curettage in the event of an incomplete abortion — a rather common complication, according to the clinical trials. I have dealt with this in my bill by adding to the original FDA proposal a distinct requirement that the prescribing physician be qualified to handle the complications of an incomplete abortion or an ectopic pregnancy.

429 CANNON HOUSE OFFICE BUILDING
WASHINGTON, DC 20515
(202) 225-2701 FAX: (202) 225-3038

E-mail: rep.coburn@mail.house.gov
Web site: www.house.gov/coburn

My bill does not address the paradox that the FDA has approved a drug which, used by itself, is not efficacious in achieving the intended purpose of a completed abortion, and which becomes effective only when used in combination with another drug whose manufacturer has warned is unsafe in that application. The FDA cannot escape the logical dilemma of having approved a drug that is either ineffective (when used without misoprostol) or unsafe (when used with misoprostol).

Your justification for authorizing the use of misoprostol for chemically inducing abortion is that without misoprostol, mifepristone is ineffective. That is what is known as circular reasoning.

The evidence that we have from the clinical trials about the safety of the mifepristone/ misoprosol combination for abortion is not entirely encouraging. There were no deaths among the sample population, but the rate of incomplete abortions was nearly 8 percent and the incidence of hemorrhaging was 5 percent. These are both potentially serious complications with rates of occurrence that are too high to be dismissed as "rare." In France, where far more stringent safety precautions are in effect, one death and two near-fatal cardiac arrests were recorded within the first two years of availability. In 1991, in response to concerns about such complications, France banned the use of mifepristone by women over 35 and by smokers. The U.S. clinical trials reportedly did not include smokers or women over 35 among the subjects, but neither of these conditions is listed in the label, the prescriber's agreement, the patient agreement, or the medication guide as a contraindication. Undoubtedly, some women from both of those risk categories will be likely to receive the drug combination because neither they nor their doctors have any way of knowing these factors pose an additional risk.

You will note that my legislation does not at all address the question of the use of misoprostol to induce labor. As a practitioner, I am grateful to Searle for calling attention to the risks and contraindications of induction with misoprostol. But I am also cognizant of the benefits of using misoprostol for induction in some cases. The freedom of doctors to weigh the risks and benefits and then to act in the best interest of their patients is not at all affected by my legislation and is irrelevant to the conditions under which mifepristone was approved.

I have no doubt that if women were asked whether their doctor should have to be able to read a sonogram, handle complications, and get them admitted to a hospital in case of emergency, they would not hesitate to demand those levels of competence. Nor do I have any doubt that women would expect their doctors to be trained in the use of a potentially risky drug. In light of the very real and very serious risks to maternal health associated with this method of abortion, I remain amazed and dismayed that ACOG opposes the elementary patient protection standards that I have proposed. I encourage you to reconsider your position.

Sincerely,

Tom A. Coburn, M.D.
Member of Congress

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,

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

cc:
Archival NDA 19268/S-037
HFD-180/Div. Files
HFD-180/A.Kacuba
HFD-180/P.Levine
HFD-103/F.Houn
HFD-103/V.Raczkowski
HFD-103/B.Collier
HFD-180/L.Talarico
HFD-180/S.Aurecchia
HFD-180/S.Kress
HFD-002/M.Lumpkin
HFD-005/J.Axelrad
GCF-1/A.Wion
GCF-1/S.Ray
DISTRICT OFFICE

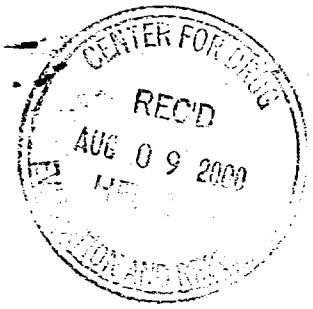
Drafted by: A.Kacuba/September 22, 2000
Initialed by: S.Aurecchia/ September 27, 2000
Initialed by: B.Collier/September 25, 2000
Initialed by: F.Houn/September 28, 2000
Initialed by: M.Lumpkin/September 28, 2000
Initialed by: J.Axelrad/September 28, 2000
Initialed by: A.Wion/September 28, 2000
Final: AK/September 28, 2000 AK 9-28-00
Filename: c:\mydocuments\Paul\19268-S-037-final-NA-letter.doc

NOT APPROVABLE (NA)

SEARLE

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077
PHONE (847) 982-7000
FAX (847) 982-4701

**SPECIAL LABELING SUPPLEMENT-
CHANGES BEING EFFECTED**



August 8, 2000

Lilia Talarico, M.D., Director
Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research (HFD-180)
Document Control Room 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

19-268 SLR-1
NDA NO. REF NO.
NDA SUPPL FOR Labelling

Re: NDA 19-268/S-033
Cytotec® (misoprostol)

Dear Dr. Talarico:

We acknowledge receipt of your approval letter dated June 22, 2000 for labeling changes under our supplemental New Drug Application (S-031) for Cytotec (misoprostol) tablets.

In addition to the changes approved under S-031, we have incorporated additional revisions to the labeling of Cytotec, including a new subsection and added text under the *Precautions* section of the product labeling. These additional revisions, which are described in detail below, are the subject of this Changes Being Effected Supplement pursuant to 21 CFR §314.70(c)(2)(i). Twelve (12) copies of the final printed labeling (FPL) (A05450-3) for Cytotec (misoprostol) tablets are enclosed. This version of the FPL incorporates both the changes approved by the agency under S-031 and the additional revisions covered by this CBE supplement. This version of the revised labeling will be placed into production use in September, 2000.

(1) The following change addresses the requirement for labeling under 21 CFR §201.57(f)(7). A new subsection has been added to the *Precautions* section of the label to address the recognized use of Cytotec in labor and delivery. Searle does not support

nor plan to study the use of misoprostol as a cervical ripening agent for the induction of labor, but is aware of a recognized medical practice of using this agent in this manner outside its labeled indication (Attachment 1). To appropriately address this usage the following text is now included in the label:

(2) Under same cover, we are submitting changes to the **Pregnancy** subsection to accurately reflect the most current data as supported by Adverse Event Reports submitted to the FDA. The approved labeling reads:

> One case of amniotic fluid embolism, which resulted in maternal and fetal death, has been reported with use of misoprostol during pregnancy.

We have amended that text to now read:

[redacted]

A copy of the most recently approved labeling (S-031) marked-up with the changes in the new labeling (Attachment 2), as well as supporting documentation, is included for your information.

Please direct any comments or questions concerning this submission to my attention.

Sincerely,

Mary Jo Pritza, M.P.H., PharmD.
Regulatory Affairs Associate

Ph:847-982-7831
Fax: 847-982-8090

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY
APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
G. D. Searle & Co.	August 8, 2000
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
(847) 982-7831	(847) 982-8090

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
4901 Searle Parkway Skokie, IL 60077	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) **NDA 19-268**

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY	
misoprostol	Cytotec®	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*) (±)methyl 11a, 16-dihydroxy-16-methyl-9-oxyprost-13^{E}-en-1-oate		CODE NAME (*If any*)
DOSAGE FORM: Tablet	STRENGTHS: 100 mcg/200 mcg	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE:
For the prevention of NSAID induced gastric ulcers in patients at high risk of complications from gastric ulcers

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☒ LABELING SUPPLEMENT ☐ CHEMISTRY, MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Special labeling Supplement S-033 Final Printed Labeling

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at this site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
	1. Index
X	2. Labeling (check one) ☐ Draft Labeling ☒ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.5 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) Supplement S-033

RTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Mary Jo Pritza, MPH, PharmD., Associate Worldwide Regulatory Affairs	08/08/2000

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
4901 Searle Parkway Skokie, IL 60077	(847) 982-7831

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

ase **DO NOT RETURN** this form to this address.

FORM FDA 356h (4/97)

4.268/SLR-037
CBE

A05450-3

SEARLE

Cytotec®

(misoprostol)

not approved

Revised: Jun. 29, 2000

DRAFT

DRAFT

DRAFT

REPRINTS INCLUDED

IN REFERENCE LISTING

(DRAFT LABELING IS SHOWN BECAUSE THESE ARE DOUBLE-SIDED PAGES)

7 DOUBLE SIDED PAGES

LeWiNe

NDA 19-268/S-031

G.D. Searle & Company
Attention: Mary Jo Pritza
Regulatory Affairs Associate
4901 Searle Parkway
Skokie, IL 60077

JUN 22 2000

Dear Dr. Pritza:

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

We acknowledge receipt of your submission dated April 12, 2000. Your submission of April 12, 2000 constituted a complete response to our December 17, 2000 action letter.

This supplemental new drug application provides for the addition of statements regarding uterine perforation and uterine rupture to the boxed CONTRAINDICATIONS AND WARNINGS, and to the WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of the package insert.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted April 12, 2000). Accordingly, the supplemental application is approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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

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

Sincerely,

6-22-00

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

NDA 19-268/S-031

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

MAY 2 3 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 [redacted] 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 [redacted]" from the second sentence of the first paragraph.

3. Delete the term [redacted] 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:

cc:
Archival NDA 19-268
HFD-180/Division file
HFD-180/P.Levine
/L.Talarico

5-23-00

Drafted by: PEL-05/12/00
Initialed by: BKS/May 22, 2000
LT/May 23, 2000
Final: BKS/May 23, 2000
Filename: DHCP letter 051100.doc

GC/ADVICE 5/24/00

VENABLE
ATTORNEYS AT LAW

VENABLE, BAETJER, HOWARD & CIVILETTI, LLP
Including professional corporations
1201 New York Avenue, N.W., Suite 1000
Washington, D.C. 20005-
(202) 962-4800 (202) 962-8300 FAX
MARYLAND • WASHINGTON, DC • VIRGINIA

FAX COVER SHEET

ATE: February 24, 2000

ient Number: 18581.121056

O:

Name	Company	Fax #	Telephone #
Jennifer Mercier	Food & Drug Administration	301-827-4272	301-827-4260
Murray Lumpkin, M.D.	Food & Drug Administration	301-594-6197	301-594-5400
Florence Houn, M.C.	Food & Drug Administration	301-480-3761	301-827-3144
Lilia Talarico, M.D.	Food & Drug Administration	301-443-9285	301-827-7310
Lisa Rarick, M.D.	Food & Drug Administration	301-827-4267	301-827-4260
Susan Allen, M.D.	Food & Drug Administration	301-827-4267	301-827-4260
Seth Ray, J.D.	Food & Drug Administration	301-480-2255	301-827-1148

ROM:

Name: Geoffrey M. Levitt Telephone No.: 202-962-4923

OTAL NUMBER OF PAGES (EXCLUDING COVER PAGE): 5

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

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(f)

February 24, 2000

Ms. Jennifer Mercier
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration HFD-580
5600 Fishers Lane
Rockville, Maryland 20857

VIA TELEFAX 301-827-4267

RE: NDA 19-268/Cytotec® (misoprostol)

Dear Ms. Mercier:

We appreciate your sending us the minutes of our November 18, 1999 meeting with FDA on Cytotec labeling issues raised by the pending NDA for mifepristone. We would, however, like to clarify the record in two respects. First, the second-to-last bullet in your minutes under the heading "Discussion" states: "Searle's main concern is the legal responsibilities they would acquire with this product's [*i.e.*, mifepristone's] approval and cross-labeling to their product." In fact, Searle does not acknowledge that it would "acquire" any "legal responsibilities" as a result of FDA's approval of mifepristone. Instead, as we made clear at our meeting, Searle does not support or condone such approval, and has had no involvement with the development of mifepristone or with the inclusion of our product, misoprostol, in the proposed mifepristone label. Therefore the approval of mifepristone would not, and could not, create any new legal responsibility for Searle, although it might expose Searle to lawsuits alleging such responsibility. Rather, our chief concern, as we have noted to the agency, is the health and safety implications of approving mifepristone for co-administration with misoprostol in the absence of adequate safety studies, as far as Searle is aware, investigating such co-administration.

We would appreciate it if this letter of clarification were appended to all copies of the minutes of this meeting.

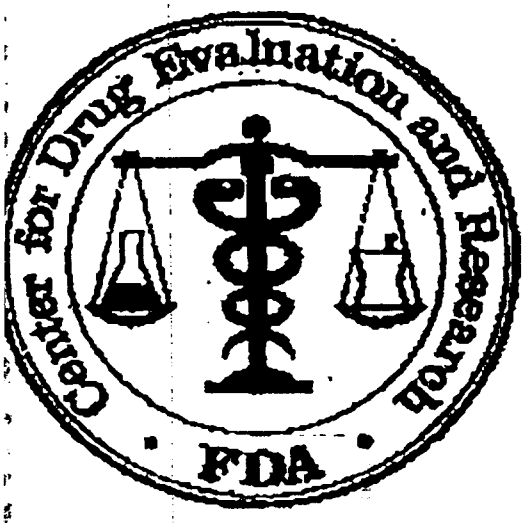
Sincerely,

Robert L. Bogomolny

Robert L. Bogomolny

cc: Murray Lumpkin, M.D.
Florence Houn, M.D.
Lilia Talarico, M.D.
Lisa Rarick, M.D.
Susan Allen, M.D.
Seth Ray, J.D.

Geoff Levitt



FOOD AND DRUG ADMINISTRATION
DIVISION OF REPRODUCTIVE
AND UROLOGIC DRUG PRODUCTS
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

Date: Jan. 3, 00

TO:

Name: Bob Bogomolny

Fax No: 847-581-4033

Phone No:

FROM:

Name: Jennifer Mercier

Fax No: 301 827-4267

Phone No: 301 827-4260

Comments:

Meeting Minutes

Date: November 18, 1999 **Time:** 3:30-4:00 PM **Location:** Woodmont 2 Conference Room "C"

NDA 19-268 **Drug:** Cytotec™ (misoprostol)

DEC 22 1999

Indication: Prevention of NSAID-induced gastric ulcers in high risk patients

Sponsor: Searle

Type of Meeting: Labeling Meeting

Meeting Chair: Murray Lumpkin, M.D.

External Lead: Richard N. Spivey, Pharm.D., Ph.D.

Meeting Recorder: Jennifer Mercier, B.S.

FDA Attendees:
Murray Lumpkin, M.D. – Deputy Center Director, Center for Drug Evaluation and Research (CDER; HFD-002)
Florence Houn, M.D. – Director, Office of Drug Evaluation III (ODEIII; HFD-103)
Lilia Talarico, M.D. – Director, Division of Gastrointestinal and Coagulation Drug Products (DGCDP; HFD-180)
Lisa Rarick, M.D. – Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Seth Ray, J.D. - General Attorney, Office of Chief Counsel (OCC; GCF-1)
Jennifer Mercier, B.S. – Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:
Richard Spivey, Pharm.D., Ph.D. – Vice President, Worldwide Regulatory Affairs, Searle
Robert Bogomolny, J.D. – Corpoarte Senior Vice President, General Counsel & Corporate Secretary, Searle
Janice Toran, J.D. – Associate General Counsel, Law Department, Searle
Geoff Levitt – Searle

Meeting Objective: To discuss the Cytotec label and concerns regarding proposed label for mifepristone.

Background: Searle has been actively discussing the use of their product, Cytotec, in combination with mifepristone to induce abortion. Searle has never been involved with these studies and does not believe that their product should be specifically mentioned in the mifepristone label if ever approved by the FDA. In 1996, Searle discussed with the Agency a number of options they were considering to address their concerns about the use of Cytotec in combination with mifepristone. Since the Agency did not approve the mifepristone application in 1996, Searle has decided to request the Agency consider their new proposals.

Discussion:

- Concerns regarding proposed label:
  - their drug name, Cytotec, is proposed for concominant use in the mifepristone label
  - Searle's expanded liability if their drug product is mentioned in the mifepristone label
  - unconsented use of their drug product; Searle maintains their objection to their product being used in this manner

- Consequences of cross-labeling
  - new abortifaciant effects from approval of mifepristone for misoprostol; inadvertant/advertant exposure
  - Searle has made a corporate decision not to get involved in the abortion issue

- Searle is currently in discussion with HFD-180 regarding the labeling changes

- Searle's proposal to the cross-labeling issue

- Searle's main concern is the legal responsibilities they would acquire with this products approval and cross-labeling to their product
- Cytotec goes off patent in 6/2000

Action Items:

- Fax meeting minutes to sponsor within 30 days

-S-

Minutes Preparer

-S-

Concurrence, Chair

not legal respon rid acquire
hve health + safety
implics of this release
[illegible]

SEARLE **DESK COPY**

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077
PHONE (847) 982-7000
FAX (847) 982-4701

June 3, 1999

Lilia Talarico, M.D., Acting Director
Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research (HFD-180)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: **NDA 19-268/S-031: Cytotec® (misoprostol)**

Dear Dr. Talarico:

Please refer to our supplemental new drug applications dated October 13, 1998 for Cytotec (misoprostol) Tablets and [redacted] Tablets, and to FDA's correspondence of March 17, 1999, April 2, 1999, and April 9, 1999 concerning the October 13, 1998 application. This letter provides Searle's comments on the revised draft labeling enclosed by FDA with the April 9, 1999 letter.

Searle submitted supplemental applications to the above NDAs on October 13, 1998 to address reported adverse events of uterine rupture and perforation in connection with the misuse of misoprostol during pregnancy. These applications provide for the addition of statements regarding uterine rupture and perforation to the Contraindications and Warnings box and the Warnings, Precautions, and Adverse Reactions sections of the package inserts. In a response letter dated March 17, 1999, FDA approved the applications and provided revised labeling for both Cytotec [redacted] that included the following statements, among others:

C
C

- Anecdotal reports, primarily from Brazil, of congenital anomalies and reports of fetal death subsequent to use of misoprostol as an abortifacient have been received...

In Searle's view, the labeling proposed by FDA on March 17,1999 more effectively conveys the risks associated with the use of misoprostol by pregnant women than the revised draft labeling proposed by FDA on April 9,1999. Given the existence of these risks, the fact that Cytotec and ——— are contraindicated in pregnant women, and the fact that FDA and Searle are aware of instances of off-label use of misoprostol to induce labor and/or abortion, it would be prudent to include in the labeling of these products a specific statement warning against such use, as FDA did in the March 17,1999 version.

In addition, Searle does not believe that warnings about the risk of uterine rupture and perforation with use of misoprostol should be limited to the last two trimesters of pregnancy. Searle is aware of no research indicating that the risk of uterine rupture or perforation is in fact limited to the second and third trimesters of pregnancy. Nor is it clear from adverse event reports that instances of uterine rupture have not occurred in the first trimester. There have been reports of uterine rupture following use of Cytotec to induce an abortion where the gestational age was unknown. (See DER Nos. 916022-SK848; 916022-SK850) Even if these incidents occurred outside the first trimester, there is no scientific reason to conclude that misoprostol presents no risk of uterine rupture or perforation in the first trimester. Therefore, the language in the April 9, 1999 labeling that limits the risk of uterine rupture or perforation to situations where misoprostol is administered after the first trimester is misleading in that it implies that misoprostol administration during the first trimester is free of such risks.

For these reasons, Searle proposes to revise the April 9, 1999 draft labeling recommended by FDA as indicated in the enclosed mark-up. However, it appears that the specific wording of this change in the labeling may take additional time and further discussion to finalize with the agency. Therefore, as an interim measure, we also propose sending the attached "Dear Health Care Practitioner" letter for Cytotec. The letter would be targeted to the following audiences, the size of which is shown below:

- Obstetrics and Gynecological Physicians (31,000)
- Hospital Pharmacists
- Nurse Practitioners in Female Care (3,810)
- Nurse Practitioners in Women's Health (1,911)
- Nurse Practitioners in Reproductive Health (55)
- Family Planning Centers (2,118)
- Midwives (7,027)

Total 66,921

Please address any questions or concerns regarding this submission to my attention.

Sincerely,

Peter F. East

Peter F. East
Associate Director,
Regulatory Affairs
Tel.: (847) 982-4913
Fax: (847) 982-8152

This application contains the following items: *(Check all that apply)*

	1.	Index
X	2.	Labeling (check one) x Draft Labeling ☐ Final Printed Labeling
	3.	Summary (21 CFR 314.50 (c))
	4.	Chemistry section
		A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
		B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
		C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5.	Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6.	Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7.	Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8.	Clinical data section (e.g. 314.50 (d) (5), 21 CFR 601.2)
	9.	Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10.	Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11.	Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12.	Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13.	Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14.	A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15.	Establishment description (21 CFR Part 600, if applicable)
	16.	Debarment certification (FD&C Act 306 (k)(1))
	17.	Field copy certification (21 CFR 314.5 (k) (3))
	18.	User Fee Cover Sheet (Form FDA 3397)
	19.	OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Peter F. East	Peter F. East, Associate Director Regulatory Affairs	06/03/1999

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
4901 Searle Parkway Skokie, IL 60077	(847) 982-8606

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

DRAFTS

5 pages

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-268/S-031

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

APR - 9 1999

Dear Mr. East:

Please refer to your supplemental new drug application dated October 13, 1998, received October 15, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cytotec (misoprostol) Tablets and /[redacted].

These supplemental new drug applications provide for the addition of statements regarding uterine perforation/uterine rupture to the boxed CONTRAINDICATIONS AND WARNINGS and the WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of the package inserts and the patient information leaflet.

We also refer to our letter dated April 2, 1999 in which we stated that we would send revised draft wording for the package inserts and invited you to discuss the revised wording with us as necessary. Enclosed is the revised draft wording for the package inserts.

We remind you of our requests, stated in our April 2, 1999 letter, to: (1) not issue the "Dear Health Care Practitioner" letter or any other type of information concerning these supplemental applications until we have reached final agreement on the wording for the labeling; and (2) submit for our review, prior to dissemination, a copy of the revised "Dear Health Care Practitioner" letter based on the final wording of the package inserts.

If you have any questions, contact Brian Strongin, Project Manager, at (301) 827-7310.

Sincerely,

/S/

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

DRAFTS

33 pages

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-268/S-031

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

APR 2 1999

Dear Mr. East:

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

These supplemental new drug applications provide for the addition of statements regarding uterine perforation/uterine rupture to the boxed warning and the WARNINGS, PRECAUTIONS, AND ADVERSE REACTIONS sections of the package inserts.

We also refer to our letter dated March 17, 1999, in which we stated that these supplemental applications were approved.

Upon further review of these supplements, we have concluded that the labeling text for the package inserts attached to and subject of the March 17, 1999, letter is misleading and is not fully reflective of the underlying scientific data. The March 17, 1999, letter was, therefore, issued in error. We regret any inconvenience our error may cause you. We will send revised draft wording for the package insert to you within a week. We invite you to discuss the revised draft wording with us as necessary.

Until we can reach an agreement on final wording for the labeling, we request that the "Dear Health Care Practitioner" letter we discussed with you prior to the March 17, 1999, letter or any other type of information concerning these supplemental applications not be issued. We also request that you submit for our review prior to dissemination, a copy of a revised "Dear Health Care Practitioner" letter that will be based on the final wording of the package inserts.

If you have any questions, contact Bronwyn Collier, Associate Director for Regulatory Affairs, Office of Drug Evaluation III, at (301) 827-3143.

Sincerely,

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

If you have any questions, contact Bronwyn Collier, Associate Director for Regulatory Affairs, Office of Drug Evaluation III, at (301) 827-3143.

Sincerely,

— 4-2-99

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

cc:
Archival NDAs 19-268,
HFD-180/Div. Files
HFD-180/B.Strongin
HFD-180/K.Robie-Suh
HFD-180/L.Talarico
HFD-580/L.Rarick
HF-2/MedWatch
HFD-002/ORM
HFD-103/ADRA
HFD-40/DDMAC
HFD-613/OGD
HFD-95/DDMS
HFD-001/J.Woodcock
HF-28/OC/M.Friedman

DISTRICT OFFICE

Drafted by: bc/April 1, 1999
Initialed by: M.Lumpkin 4/1/99

L.Talarico
T.Rumble
final: BC/4/1/99
filename: 19268BC.DOC
GENERAL CORRESPONDENCE (GC)

Medical Officer's Consult of NDAs

NDA 19-268-S031

Requestor of Consult: Brian Strongin (HFD-580)

Name of Drug: Cytotec (Misoprostol)

Sponsor: G.D. Searle & Company

Clinical Use: Prevention of NSAID-induced gastric ulcers in-patients at high risk of complications from gastric ulcer

Dosage and Route of Administration: Oral—Cytotec (100 mcg and 200 mcg tablets)

Date Assigned: January 25, 1999

Material Reviewed: Labeling Supplement

Comments:

The use of misoprostol to induce labor is now established in the US obstetrical community. The sponsor, Searle, has not and will not seek an approved pregnancy indication. At least 19 prospective, randomized clinical trials involving more than 1,900 patients, receiving doses of misoprostol ranging from 25 to 200 micrograms, on a variety of dosing schedules have been performed to date. The majority of researchers have administered misoprostol in tablet form into the posterior fornix of the vagina.

In general, misoprostol has been found to be an effective agent for the induction of labor. When compared to placebo, misoprostol lowered overall Cesarean section rates, decreased oxytocin requirements, and achieved higher rates of vaginal delivery within 24 hours. Misoprostol compared favorably to intracervical and intravaginal PGE_2 preparations, which have approved indications, such as Prepidil gel, and Cervidil vaginal insert. Studies have demonstrated shorter times to delivery and reduced oxytocin requirements after misoprostol administration.

Common adverse reactions occurring with labor induction include uterine tachysystole (six or more uterine contractions in 10 minutes in consecutive intervals), meconium passage, and hyperstimulation syndrome with attendant Cesarean section. Uterine rupture has been reported in all PGE preparations used to ripen the cervix or to induce labor. To date, there has been no increase in neonatal morbidity after misoprostol administration when used to induce labor.

The sponsor recommends the following changes to the approved label:

1. **Contraindications and Warning** section **(Box Warning)**

   A. Cytotec

   [redacted]

   Comment: The above statements are substantially correct. Data has been reported which showed uterine rupture with intravaginal administration of misoprostol for both induction of labor and in induced abortion. The sponsor, although theoretically correct, should submit data to support oral administration of Cytotec as a documented cause of uterine rupture.

2. **Warning** section

   [redacted]

3. **Precautions** section, **Special Note for Women** subsection. Cytotec labeling

[ ]

Comment: This sentence is supported by the literature.

4. **Adverse reactions** section, Gynecological subsection

The following sentence was added to the Cytotec [ ]abeling:

> There have been reports in which intravaginal administration of misoprostol in pregnant women resulted in rupture of the uterus and death of the infant. (See Warnings).

Comment: This sentence is supported by the literature.

Conclusions:
Submitted changes to the draft label are documented in the reported literature for the off-labeled use of Cytotec for the induction of labor with an intravaginal application. Data is also submitted which supports the term "perforation" when Cytotec is given intravaginally to induce abortion. However, perforation implies more to "instrumentation" use, which is associated with abortion, while rupture of the uterus rarely occurs before the twentieth-eight week of gestation. The sponsor should submit data to support the inclusion of oral use when referring to either rupture or perforation.

In addition, I agree with the modified draft text for a "Dear Doctor" letter.

-S-

Phill H. Price, M.D.
January 28, 1999

I concur

-S-

I concur

-S-

2/5/99

cc: Controlled Correspondence (+ Incoming)
Cytotec (+ Incoming)

NDA 19-268/S-031

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

MAR 17 1999

Dear Mr. East:

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

We acknowledge receipt of your submission dated November 24, 1998.

These supplemental new drug applications provide for the addition of statements regarding uterine perforation/uterine rupture to the CONTRAINDICATIONS AND WARNINGS box, and the WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of the package inserts. Although these supplements also provided the draft text of a "Dear Health Care Practitioner" letter, we have administratively separated this part and will provide comments under a separate cover.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the enclosed labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package inserts, text for the patient package inserts). Marketing the products with FPL that is not identical to the approved labeling text may render the products misbranded and unapproved new drugs.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 19-268/S-031, ———————" Approval of these submissions by FDA is not required before the labeling is used.

Before the letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2

FDA
5600 Fishers Lane
Rockville, MD 20857

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

If you have any questions, contact Brian Strongin, Project Manager, at (301) 827-7310.

Sincerely,

3-17-99

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

Enclosure

cc:
Archival NDAs 19-268.
HFD-180/Div. Files
HFD-180/B.Strongin
HFD-180/K.Robie-Suh
HFD-180/L.Talarico
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-103/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-95/DDMS (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

BS 3-16-99

Drafted by: BKS/January 19, 1999
Initialed by: VR/March 12, 1999
final: BKS/March 16, 1999
filename:. 19268901.0

APPROVAL (AP)

DRAFT: LABELING

DRAFT

LABEZINT

17 pages
(double sided)

EUROPEAN CLINICAL RESEARCH AND MEDICAL AFFAIRS
G. D. Searle & Co. Ltd., High Wycombe, England

CLINICAL RESEARCH REPORT

A double blind parallel group placebo controlled study of the effect of misoprostol on the pregnant uterus when administered during the first trimester of pregnancy to patients prior to elective terminations

Protocol Numbers:	EC1-84-02-212 EG9-85-02-241
Joint Document Number:	EC1-85-06-212/241
Date:	20th December, 1985
Authors:	Helen E. Cohen, ECRMA John W. Chapman, ESE
Investigator:	Dr.med. T. Rabe,

Misoprostol effect on pregnant uterus
20th December 1985

APPROVAL AND RELEASE OF DOCUMENT

Document Number:	EC1-85-06-212/241
Protocol Numbers:	EC1-84-02-212 EG9-85-02-241
Release Date:	<>

H. Cohen — 20.12.85

Helen E. Cohen,
Manager, Clinical Research,
ECRMA

Date

J.W. Chapman — 23/12/85

John W. Chapman,
Senior Statistician,
ESE

Date

Misoprostol effect on pregnant uterus
20th December 1985

REVIEWED AND APPROVED BY:

Paul A. Nicholson,
Director, European Clinical
Research & Medical Affairs.

Date

John R. Shelton,
Manager, European Scientific
Evaluation.

23 Dec. 85
Date

Robert N. Fowler,
Senior Director,
International Clinical Research
& Medical Affairs.

2 Jan 86
Date

D. Nitzberg,
Director,
Medical Statistics

7 Jan 86

EC1-85-06-212/241

Misoprostol effect on pregnant uterus
20th December 1985

ABSTRACT

In this report, the effects of 800 mcg (2 x 400 mcg) misoprostol given orally on the pregnant uterus are compared with placebo in a double blind group comparative study. The study was set up to compare this dose of misoprostol with placebo administered to 300 subjects the evening before elective termination of first trimester pregnancy. After 111 subjects had been recruited, the study was brought to an early close as it was apparent that misoprostol produced a marked effect on the pregnant uterus. A further 190 subjects were then recruited and treated according to an identical protocol with the exception that the dose of misoprostol was reduced to 400 mcg (2 x 200 mcg) given orally.

Eligible subjects were admitted to the clinic and given their test medication at 18.00 and 23.00 hours the evening before elective termination. Subjects were observed for bleeding, expulsion of products of conception and any adverse experiences. Subjects were taken to the operating theatre the next morning, given a cervical examination followed by dilatation and vacuum aspiration of the uterine contents. Subjects were observed for any post-operative complications.

Misoprostol effect on pregnant uterus
20th December 1985

During the observation period prior to cervical examination there were four incomplete abortions (7%) in subjects receiving misoprostol 2 x 400 mcg compared with none in subjects receiving placebo. This difference did not achieve statistical significance ($p = 0.061$). At cervical assessment, products of conception were visible in a further two subjects, giving a total of 6 subjects (11%) in the misoprostol group, compared with none in the placebo group showing evidence of expulsion of uterine contents during the study period. This difference was statistically significant ($p=0.014$).

Misoprostol 2 x 400 mcg also produced a statistically significant effect on bleeding prior to cervical assessment ($p<0.001$). In the misoprostol group 25 of the 56 subjects (45%) bled (7 mild, 12 moderate and 6 severe) compared with 2 of the 55 subjects (4%) in the placebo group where the bleeding in both cases was classified as mild. In no case was the severe bleeding considered to be life threatening, nor was any intervention required. A statistically significant effect was also found for bleeding at cervical assessment (41% misoprostol, 2% placebo, $p<0.001$), on the opening of the external cervical os (59% misoprostol, 11% placebo, $p<0.001$), the softening of the cervix (71% misoprostol, 51% placebo, $p=0.022$) and the incidence of abdominal pain (75% misoprostol, 20% placebo, $p<0.001$). No adverse haematological effects were noted, nor any other significant effects, observed.

Misoprostol effect on pregnant uterus
20th December 1985

Following the lower dose of misoprostol (2 x 200mcg), and before cervical assessment there were five subjects (5%) who experienced partial or complete abortions, compared with none in the placebo group ($p=0.031$). At cervical assessment, which was performed immediately prior to surgery, products of conception were visible in a further four subjects, giving a total of nine subjects (9%) in the misoprostol group and none in the placebo group who showed evidence of expulsion of uterine contents ($p=0.002$). The incidence of bleeding in the observation period after test medication was statistically significantly greater for misoprostol than for placebo ($p<0.001$). During this period 32 of the 96 subjects (33%) in the misoprostol group bled (16 mild, 9 moderate and 7 severe) compared with 1 of the 94 subjects (1%) in the placebo group where the bleed was classified as mild. The severe bleeding did not require any intervention.

At cervical assessment, there was a statistically significant effect of misoprostol 2 x 200 mcg on visible bleeding (33% misoprostol, 1% placebo, $p<0.001$), on the opening of the external cervical os (39% misoprostol, 7% placebo, $p<0.001$) and on the softening of the cervix (57% misoprostol, 33% placebo, $p<0.001$). The increased incidence of abdominal pain after misoprostol was also significant (43% misoprostol, 15% placebo, $p<0.001$). No adverse haematological effects were observed. No other significant

effects were demonstrated.

A formal comparison between the 2 x 400 mcg and 2 x 200 mcg doses has not been made although overall the effect of the lower dosage on abdominal pain was substantially reduced in incidence and severity. There was also less effect at this dosage on cervical dilatation and a slightly lower incidence of bleeding.

Misoprostol in the doses tested has a demonstrable effect on the uterus in the first trimester of pregnancy and its use during this time may cause the loss of the pregnancy.

TABLE OF CONTENTS

TABLE OF CONTENTS (continued)

LIST OF TABLES

LIST OF TABLES (continued)

LIST OF APPENDICES

Misoprostol effect on pregnant uterus
20th December 1985

1. INTRODUCTION

Misoprostol, a 15 de-oxy, 16-hydroxy, 16-methyl analogue of PGE_1, inhibits the secretion of acid and pepsin in the stomach of several species, exerts anti-ulcer activity in the upper gastrointestinal tract in animals and man and has been shown to have beneficial effects upon the integrity of the gastric mucosa.

Prostaglandins have been shown to exert a marked oxytocin-like effect on the pregnant uterus, but unlike oxytocin, which is effective predominantly at term, prostaglandins retain their activity irrespective of the stage of gestation.

Misoprostol has been evaluated in reproduction, fertility and teratology studies in rats and rabbits. In the two rat fertility studies the number of implantations was decreased at doses of 1600 mcg/kg and above. An increased number of resorptions was also noted in one rat study at doses of 1000 and 10000 mcg/kg. The recommended total daily dose for misoprostol for the treatment of duodenal or gastric ulcer is 800 mcg, and at this dose, by extrapolating the animal data, no effect on the pregnant uterus was expected.

Misoprostol effect on pregnant uterus
20th December 1985

In order to assess the effects of misoprostol in humans, a study was set up in pregnant patients prior to elective legal termination. The study follows protocol EC1-84-02-212 - "A double blind placebo controlled study to assess the effect of misoprostol on the pregnant uterus when given as two 400 mcg doses by mouth the evening before elective legal abortion during the first trimester of pregnancy' dated 8th November 1984 (Appendix 1). The protocol called for a total of 300 eligible subjects. However, the study was brought to a close after a recruitment of 111 subjects when evidence of activity on the pregnant uterus was apparent. A second study following protocol EG9-85-02-241 dated 2nd April 1985 (Appendix 2) was performed differing only from the above study by a reduced dosage to two 200 mcg doses of misoprostol. The results of both these studies are presented in the following report.

2. STUDY OBJECTIVE

To compare the effect of misoprostol and placebo on the pregnant uterus by assessing the incidence of partial or complete expulsion of products of conception, the incidence of bleeding and the effects of therapy on cervical dilatation and softening in the first trimester of pregnancy.

3. INVESTIGATORS

The study was co-ordinated and supervised by the principal investigator:

Dr. med. T. Rabe
Universitats Frauenklinik
Bergheimer Strasse
Heidelberg
West Germany

The study was performed at

Lindenfels Klinik
Lindenfels
West Germany

4. MATERIALS AND METHODS

The study was conducted in accordance with Searle Clinical Protocols EC1-84-02-212 and EG9-85-02-241. Examples of the protocols can be found in Appendices 1 and 2 respectively. The case report forms used were common to both studies and examples of these can be found in Appendix 3.

4.1 Study Design

This was a single centre, randomised, double blind, parallel group, placebo controlled study. Subjects were admitted to the clinic at about 17.00 hours the evening before elective abortion. Subjects satisfying the inclusion and exclusion criteria were allocated the next available study number.

A general history was taken which included the subject's date of birth, past medical history and all drugs taken in the last seven days.

The history also included gravidity, number of previous spontaneous and induced abortions and any previous gynaecological problems. Details concerning the menstrual cycle were recorded.

A synopsis of the current pregnancy included date of last menstrual period and estimated gestational age by dates confirmed by clinical assessments or scan. Greater confidence was placed in the clinical assessment or scan where this differed from the estimated dates. Any complications associated with the pregnancy were noted.

A general physical examination was performed, and subjects were checked for any visible vaginal bleeding and excluded if there was any indication of a spontaneous abortion.

A blood sample was taken for haemoglobin, haematocrit, red blood cell count, white blood cell count and platelets.

The subjects were given the first dose of test medication at 18.00 hours and, if tolerated, the second dose of test medication was administered at 23.00 hours. Any bleeding or expulsion of tissues during the period immediately following drug administration to the time of cervical assessment was noted. Any adverse events were also noted.

A blood sample was taken for repeat haematology next morning just before subjects were taken to the operating theatre. Inactin (thiobutabarbital) and atropine sulphate were administered and subjects were given a cervical examination to assess whether the cervical os was closed or open, whether the cervix was rigid, medium or soft, or whether there were signs of visible bleeding or products of conception. The size of the largest probe easily accepted before mechanical dilatation was noted and also the final size of the dilator used. An overall assessment of the dilatation procedure was made.

The uterine contents were evacuated by vacuum aspiration. Erogotren (ergometrine and ergocystine) and Orasthin (oxytocin and chlorobutanol) were administered to assist the evacuation. Any post-surgical complications were noted.

4.2 Study Materials

Tablets of misoprostol placebo (Lot 7279) and misoprostol 200 mcg (Lot 7280) were used in this study.

The tablets were provided in foil strips. A strip containing four tablets was packed in a catch cover labelled with instructions for usage. Two tablets were marked clearly to be taken at 18.00 hours and two at 23.00 hours.

When the study medication was reduced from 2 x 400 mcg to 2 x 200 mcg, the strip inside the catch cover contained two tablets. One tablet was marked 18.00 hours and one 23.00 hours. The instructions for usage were altered accordingly to one tablet to be taken at 18.00 hours and one at 23.00 hours.

The subjects were numbered consecutively from 1-112 in study EC1-84-02-212 (n=111) and 113-302 in study EG9-85-02-241 (n=190). There was no subject number 23 due to packaging problems and the drugs for this subject number were not delivered to the study site.

4.3 Study Population

The protocol for EC1-84-02-212 called for a total of 300 eligible subjects. After 111 subjects had been recruited, this study was brought to a close as it was clear that an effect on the pregnant uterus was detected. Study EG9-85-02-241 was started following an identical protocol but a reduced dosage of 2 x 200 mcg misoprostol. The study population criteria for both studies were identical.

Subjects were eligible for participation if they were pregnant females above 18 years of age and within 9-12 weeks of their last menstrual period confirmed by examination or ultrasound. These patients were scheduled for legal interruption of a first trimester pregnancy and had given informed consent to participate in the study.

Subjects were excluded if they showed any signs or symptoms of spontaneous abortion since the onset of pregnancy, if they had had previous cervical surgery, if they exhibited symptoms or had a history of cardio-vascular or pulmonary disease, ulcerative colitis or diabetes mellitus, disorders of blood coagulation, sickle cell anaemia, functional renal impairment, glomerulonephritis or epilepsy.

Subjects were ineligible if they were receiving treatment with any drug likely to increase or decrease the risk of abortion, had received any unlicensed drug within 30 days of the start of the study, had a known sensitivity to prostaglandins or were unwilling or unable to conform to the protocol.

5. STATISTICAL METHODS

The two studies presented in this report were analysed separately. The methods described below apply to both studies. Since the first study (the higher dose of misoprostol) was stopped early because of the number of spontaneous abortions observed in the misoprostol group, the statistical tests performed in the first study should be interpreted with caution.

The principal events used for assessing the effect on the pregnant uterus were the expulsion of products of conception and bleeding during the time between the first dose of study medication and the start of the operation. The other major response variables were the state of the os and the cervix and the presence or absence of visible products of conception and visible bleeding at the cervical assessment performed immediately prior to the operation.

Due to the low incidence of expulsion and visible products, the treatment comparison in respect of these variables was performed using Fisher's exact test. The treatment comparison for the other variables listed above was performed using the chi-squared test for a 2x2 contingency table with continuity correction. Where observed frequencies were small, response categories were combined prior to analysis. One-tailed tests were performed, as stated in the protocol, since spontaneous abortion, bleeding, open os, soft cervix and visible bleeding and products were expected to be extremely rare in the placebo group.

In the first study (higher dose of misoprostol) a secondary analysis was performed on the incidence of bleeding during the study to allow for the slight imbalance in the numbers of subjects who had previously experienced bleeding in the current pregnancy. The consistency of the treatment difference between those who had previously experienced bleeding and those who had not was tested using the Mantel-Haenszel procedure.

Secondary evidence of the effect on the pregnant uterus was provided by the size of the largest probe easily accepted before mechanical dilatation, the final size of dilator used and the overall assessment of the ease of the dilatation procedure. Analysis of the largest probe size easily accepted was performed by the Mann-Whitney test. The ease of the procedure was analysed by the chi-squared test for

trend in the 2x4 contingency table. This test is equivalent to a comparison of the mean outcome score in the two treatments (Armitage 1955). The final size of dilator used was analysed using the chi-squared test for the 2x2 table with continuity correction. Since the final size of dilator used was 11 mm for most subjects, all responses less than or equal to 11 mm and all responses greater than 11 mm were pooled prior to analysis. Two-tailed tests were performed since, for these secondary variables, treatment differences in either direction were possible.

The only spontaneously reported adverse experience for which the number of subjects was large enough for formal statistical analysis was abdominal pain. The numbers of subjects reporting no, mild, moderate or severe abdominal pain in the two treatment groups were compared by the chi-squared test for trend in the 2x4 contingency table. A two-tailed test was performed.

Each haematology variable was examined using shift tables. For each treatment group separately changes from pre-treatment to post-treatment relative to the normal range were tested by the Stuart-Maxwell test or McNemar test as appropriate. The treatment comparison was performed for both the number of subjects with a value which was above the normal range post-treatment but was not pre-treatment, and the number of subjects with a value which was below the normal range post-treatment but was not pre-treatment. Each

of these tests was performed using the chi-squared test for the 2x2 contingency table with continuity correction or Fisher's exact test as appropriate. Two-tailed tests were performed.

The Mann-Whitney test was performed using the procedure of SAS versions 4.07 and 4.10. The Mantel-Haenszel test, chi-squared tests for contingency tables, Stuart-Maxwell and McNemar tests were performed using in-house computer programs. All tests were performed at the 5% level of significance.

6. RESULTS EC1-84-02-212 (2 x 400 mcg)

The database used for the following analysis comprises details of 111 subjects. Listings of the data are included in Appendix 4 Main Data Listings, Appendix 5 Adverse Experiences and Appendix 6 Haematological Appendix.

6.1. Subject Enrollment

The first subject was admitted to the study on 20th January 1985 and the final one on 31st March 1985. All but one of the 111 subjects recruited fulfilled the admission criteria of the study. One subject was several months younger than the minimum age of 18 years but was inadvertently included in the study and allocated to the misoprostol treated group. Data on this under-age subject are included in the analyses.

Fifty six subjects were treated with misoprostol and 55 with placebo.

6.2. Admission Profile

Table 1 shows the age distribution and mean weight, height, pulse and blood pressure for each treatment group. The two groups were evenly matched with regard to these variables.

Details of obstetric and gynaecological history are given in Table 2. Six subjects in the misoprostol group and two in the placebo group had had previous spontaneous abortions. Eighteen subjects in the misoprostol group and 13 in the placebo group had had previous terminations. Twenty six subjects in the misoprostol group had had previous deliveries compared with 32 in the placebo group. The two groups were evenly matched, however, with regard to previous pregnancy (37 subjects on misoprostol, 36 subjects on placebo). An almost equal number of subjects in each group had had previous gynaecological surgery.

Misoprostol effect on pregnant uterus
20th December 1985

TABLE 1

ADMISSION PROFILE BY TREATMENT

		TREATMENT	
		MISOPROSTOL 2x400 mcg	PLACEBO
NUMBER OF SUBJECTS		56	55
AGE (YEARS)	<18	1	0
	18-20	9	13
	21-30	25	27
	31-40	19	13
	41-50	2	2
	MEDIAN AGE	29	28
	RANGE	17 - 44	18 - 43
WEIGHT (kg)	MEAN	59.8	60.4
	S.D.	8.4	9.4
HEIGHT (cm)	MEAN	164.0	163.7
	S.D.	6.0	6.3
PULSE (beats/min)	MEAN	78.0	78.2
	S.D.	9.1	7.2
SYSTOLIC BLOOD PRESSURE (mmHg)	MEAN	123.0	122.8
	S.D.	16.4	13.9
DIASTOLIC BLOOD PRESSURE (mmHg)	MEAN	79.6	79.5
	S.D.	8.7	7.9

TABLE 2

OBSTETRIC AND GYNAECOLOGICAL HISTORY BY TREATMENT

		TREATMENT	
		MISOPROSTOL 2x400 mcg	PLACEBO
NO. OF SUBJECTS		56	55
NO. OF PREVIOUS SPONTANEOUS ABORTIONS	0	50	53
	1	5	2
	2	1	0
NO. OF PREVIOUS INDUCED ABORTIONS	0	38	42
	1	15	10
	2	2	3
	3	1	0
NO. OF PREVIOUS DELIVERIES	0	30	23
	1	13	8
	2	7	15
	3	4	6
	4	1	3
	5	1	0
PREVIOUS PREGNANCY		37	36
NO PREVIOUS PREGNANCY		19	19
PREVIOUS GYNAECOLOGICAL SURGERY	YES	9	8
	NO	47	47

The gestational age, bleeding, vomiting and other complications in the current pregnancy are summarised in Table 3. All subjects were in the 9th to 12th week of pregnancy judged by clinical examination or ultrasound. In some cases this differed from the dates as judged by date of last menstrual period. There were 15 subjects in the misoprostol group who had experienced bleeding in the current pregnancy compared with eight in the placebo group.

Vomiting and other complications of pregnancy including nausea, abdominal pain, headache, etc. were fairly evenly distributed between the treatment groups. The full list is presented in Table 3.

6.3. Study Performance

6.3.1 Concurrent Medication

Medication used in the seven days prior to the study is shown in Table 4. Fifteen subjects in the misoprostol group and twelve in the placebo group had taken medication.

In the period between the first dose of study medication and the operation, additional medication was taken by three subjects, all in the misoprostol group. A tranquiliser,

TABLE 3

DETAILS OF CURRENT PREGNANCY BY TREATMENT

		TREATMENT	
		MISOPROSTOL 2x400 mcg	PLACEBO
NO. OF SUBJECTS		56	55
GESTATIONAL AGE (weeks) (a)	9	10	11
	10	19	10
	11	16	18
	12	11	16
BLEEDING	YES	15	8
	NO	41	47
VOMITING	YES	18	16
	NO	38	39
OTHER COMPLICATIONS:			
NAUSEA		8	7
ABDOMINAL PAIN		4	5
HEADACHE		5	2
BACK PAIN		2	3
VERTIGO		1	1
BREAST PAIN		1	1
WEIGHT DECREASE		1	0
NO. OF SUBJECTS WITH OTHER COMPLICATIONS		18	13

(a) Estimated by clinical examination or ultrasound.

TABLE 4

MEDICATION USED IN 7 DAYS PRIOR TO STUDY BY TREATMENT

MEDICATION	TREATMENT: MISOPROSTOL 2x400 mcg	PLACEBO
	0	1
AMOXYCILLIN	0	1
ANTIBIOTICS	1	0
ASPIRIN	1	0
BACITRACIN	0	1
BENACTYZINE HYDROCHLORIDE	1	0
BENZYL-DL-MANDELATE	0	1
BUTALBITAL	0	1
CAFFEINE	1	1
CARBROMAL	1	0
CHLORMADINONE ACETATE	0	1
CLOBAZAM	1	0
CLORAZEPATE POTASSIUM	0	1
CODEINE PHOSPHATE	1	1
CORTISONE	1	0
CROPROPAMIDE	1	0
CROTETHAMIDE	1	0
DIAZEPAM	1	0
DIHYDROERGOTAMINE	0	1
DIMENHYDRINATE	1	0
DIMEPROPION HYDROCHLORIDE	1	0
DIPHENYLPYRALINE	1	1
DIPYRONE SODIUM	1	0
ETENZAMIDE	1	1
ETHINYLOESTRADIOL	0	1
GUAIPHENESIN	0	1
METRAQUALONE	1	0
METOPROLOL TARTRATE	0	1
MURAMIDASE	0	1
NORETHISTERONE	0	1
NORFENEFRINE	0	1
OXAZEPAM	0	1
PAPAIN	0	1
PARACETAMOL	1	2
PHENYLTOLOXAMINE	0	1
PIRENZIPINE	1	0
PROPYPHENAZONE	1	2
QUINALBARBITONE	1	0
SALICYLAMIDE	0	1
THIAMINE	1	0
THYROXINE SODIUM	3	2
TROSPIUM CHLORIDE	1	0
VINYLBITONE	1	0
ORAL CONTRACEPTIVE	1	0
UNSPECIFIED	1	1
NO. OF SUBJECTS TAKING MEDICATION	15	12
TOTAL NO. OF SUBJECTS	56	55

clorazepate potassium, was given to two subjects and a combination of propyphenazone, drofenine hydrochloride and allobarbitione were given to a third subject for abdominal pain.

6.3.2 Study Medication and Timing

The first dose of study medication was taken between 18.00 and 18.30 in all cases. The second dose was taken between 23.00 and 23.45 in all cases except those subjects who did not receive a second dose. In the misoprostol group there were ten subjects who did not receive the second dose of study medication because they experienced bleeding or abdominal pain after the first dose. In addition, one subject took only half of the second dose (one tablet) because of abdominal pain. In the placebo group one subject did not receive the second dose because of abdominal pain.

The pre-operative cervical assessment was performed between 07.30 and 09.20 in all cases. The distribution of the time interval between the first dose of study medication and the pre-operative cervical assessment is shown in Table 5. The interval was between 13 hours 15 minutes and 15 hours 20 minutes for all subjects.

TABLE 5

INTERVAL FROM FIRST DOSE
TO PRE-OPERATIVE CERVICAL ASSESSMENT BY TREATMENT

		TREATMENT	
		MISOPROSTOL 2x400 mcg	PLACEBO
NUMBER OF SUBJECTS		56	55
TIME INTERVAL (HOURS)	>13-14	16	11
	>14-15	35	40
	>15-16	5	4
MINIMUM INTERVAL (HR.MIN)		13.15	13.30
MAXIMUM INTERVAL (HR.MIN)		15.15	15.20

6.4. Effect of Treatment on the Pregnant Uterus

During the time between the administration of the first dose of medication and the pre-operative cervical assessments, bleeding was observed in 25 of the 56 subjects in the misoprostol group and two of the 55 subjects in the placebo group. Eight of the subjects who experienced bleeding in the misoprostol group received only one dose of study medication. The subject identification number, the timing of medication and the onset of bleeding in relation to the first dose of medication are presented in Table 6. The earliest recorded onset of bleeding was 30 minutes after the initial dose of misoprostol.

In four subjects, numbers 56, 78, 81 and 110, all in the misoprostol treated group, products of conception were expelled spontaneously during the period between administration of the test medication and the pre-surgical cervical assessment. Two of these subjects (78, 81) received only one dose of study medication (Table 6). Although histopathological identification of the expelled tissue was requested in the protocol, this was not performed. The investigator used a clinical diagnosis of "incomplete abortion" for all four cases. It should be noted that from the history taken none of the four cases had had a previous spontaneous abortion. The timings of the expulsions are noted in Table 6.

TABLE 6

INDIVIDUAL SUBJECTS WHO EXHIBITED BLEEDING AND/OR EXPULSION OF PRODUCTS OF CONCEPTION PRIOR TO CERVICAL EXAMINATION, BY TREATMENT GROUP, TIME OF TEST MEDICATION AND ONSET OF RESPONSE

SUBJECT	TIME FIRST DOSE (hr)	TIME SECOND DOSE (hr)	ONSET OF BLEEDING (Hours since first dose)	EXPULSION OF PRODUCTS (Hours since first dose)
MISOPROSTOL 2x400 mcg				
PLACEBO				
--	—	—	—	

The observations concerning the expulsion of products of conception and the incidence and severity of bleeding during this period are summarised in Table 7 together with the results of the statistical analyses. The four expulsions of products of conception in the misoprostol group versus zero in the placebo group was not statistically significant using a one-sided test at the 5% level (p=0.061) (Table 7).

For bleeding, ignoring severity, the difference between the two groups was statistically significant (p<0.001). The severity of bleeding was judged subjectively by the investigator and according to his observations. Moderate or severe bleeding was noted only in the misoprostol treated group. The six subjects with severe bleeding included three of the four subjects who aborted. At no time was the bleeding considered life threatening, nor was it necessary to consider the need for transfusion or for earlier surgery.

Among those subjects who had previously experienced bleeding during the current pregnancy, 10 out of 15 (67%) in the misoprostol group and one out of eight (13%) in the placebo group exhibited bleeding during the study. Among subjects who had not previously experienced bleeding, 15 out of 41 (37%) in the misoprostol group and one out of 47 (2%) in the placebo group exhibited bleeding during the study. Although the incidence of bleeding appeared to be greater in those subjects who had previously experienced bleeding during the current pregnancy there was no evidence that the treatment

TABLE 7

POST-TREATMENT OBSERVATIONS AND PRE-OPERATIVE CERVICAL ASSESSMENT - SUMMARY OF RESULTS

		TREATMENT		STATISTICAL SIGNIFICANCE (one-sided)
		MISOPROSTOL 2x400 mcg	PLACEBO	
NO. OF SUBJECTS		56	55	
BETWEEN FIRST DOSE AND PRE-OPERATIVE ASSESSMENT:				
PRODUCTS OF CONCEPTION EXPELLED		4 (7%)	0 (0%)	p=0.061 (d)
BLEEDING	NONE	31 (55%)	53 (96%)	p<0.001 (e)
	MILD	7 (13%)	2 (4%)	
	MODERATE	12 (21%)	0 (0%)	
	SEVERE	6 (11%)	0 (0%)	
PRE-OPERATIVE CERVICAL ASSESSMENT:				
VISIBLE PRODUCTS OF CONCEPTION	PRESENT	6 (11%) (a)	0 (0%)	p=0.014 (d)
	ABSENT	50 (89%)	55 (100%)	
VISIBLE BLEEDING	PRESENT	23 (41%) (b)	1 (2%) (c)	p<0.001 (e)
	ABSENT	33 (59%)	54 (98%)	
EXTERNAL OS	OPEN	33 (59%)	6 (11%)	p<0.001 (e)
	CLOSED	23 (41%)	49 (89%)	
CERVIX	SOFT	40 (71%)	28 (51%)	p=0.022 (e)
	MEDIUM	16 (29%)	26 (47%)	
	RIGID	0 (0%)	1 (2%)	

(a) Includes the 4 subjects for whom products were expelled.
(b) Includes 22 subjects who bled between first dose and pre-operative assessment.
(c) Subject also bled between first dose and pre-operative assessment.
(d) Using Fisher's exact test.
(e) Using chi-squared test for 2x2 table.

difference was inconsistent in these two groups.

At the cervical examination, performed immediately before surgery (Table 7), products of conception were present in six subjects in the misoprostol group, which included the four for whom the products of conception were observed earlier, and zero in the placebo group. This difference was statistically significant (p=0.014). It should be noted that in cases where the products of conception had been expelled and were no longer visible at cervical assessment, the investigator indicated that the products were "present" so that this represents the total number of expulsions for the study.

Visible bleeding was observed in 23 subjects in the misoprostol group, 22 of whom had been noted to be bleeding prior to this assessment. Visible bleeding was observed in only one subject in the placebo group and the difference between the two treatment groups was statistically significant (p<0.001).

The external os was open in 33 subjects in the misoprostol group compared with six in the placebo group. The difference was statistically significant (p<0.001). The cervix was graded 'soft' for 40 subjects in the misoprostol group compared with 28 subjects in the placebo group. Combining the 'medium' and 'rigid' responses, the treatment difference was statistically significant (p=0.022).

The results for the dilatation procedure are summarised in Table 8. The largest probe easily accepted prior to mechanical dilatation tended to be greater in the misoprostol group (median 10 mm) than in the placebo group (median 8 mm). The difference between the two treatment groups was statistically significant ($p<0.001$). The final size of dilator used was 11 mm in the majority of subjects and there was no significant difference between the treatment groups ($p=0.97$).

In the overall assessment, the procedure was graded 'no effort' or 'easy' in 37 subjects in the misoprostol group compared with 16 in the placebo group. There was a significant difference between the two treatments in the ease of the procedure ($p<0.001$).

6.5. Adverse experiences

The incidence and severity of adverse experiences reported during the study are summarised in Table 9. The most commonly reported adverse experience was abdominal pain. This was reported by 42 subjects in the misoprostol group compared with 11 subjects in the placebo group. The difference between the two treatments was statistically significant ($p<0.001$). Other adverse experiences were of low incidence and included headache, vomiting, diarrhoea, flatulence, nausea and back pain.

TABLE 8

DILATATION PROCEDURE - SUMMARY OF RESULTS

		TREATMENT		STATISTICAL SIGNIFICANCE (two-sided)
		MISOPROSTOL 2x400 mcg	PLACEBO	
NO. OF SUBJECTS		56	55	
LARGEST PROBE EASILY ACCEPTED (mm)	3	0	1	p<0.001 (a)
	4	0	0	
	5	1	2	
	6	1	8	
	7	8	10	
	8	9	18	
	9	6	9	
	10	6	4	
	11	20	2	
	12	2	0	
	13	3	1	
MEDIAN SIZE		10	8	
FINAL SIZE OF DILATOR USED (mm)	11	46	46	p=0.97 (b)
	12	1	0	
	13	9	8	
	14	0	0	
	15	0	1	
EASE OF PROCEDURE	NO EFFORT	23 (41%)	3 (5%)	p<0.001 (c)
	EASY	14 (25%)	13 (24%)	
	NORMAL	15 (27%)	32 (58%)	
	DIFFICULT	4 (7%)	7 (13%)	

(a) Using Mann-Whitney test.
(b) Using chi-squared test for 2x2 table.
(c) Using chi-squared test for trend in 4x2 table.

TABLE 9

ADVERSE EXPERIENCES - INCIDENCE AND SEVERITY BY TREATMENT

ADVERSE EXPERIENCE	TREATMENT					
	MISOPROSTOL 2x400 mcg			PLACEBO		
	MILD	MOD.	SEV.	MILD	MOD.	SEV.
ABDOMINAL PAIN (a)	20	15	7	6	4	1
HEADACHE	2	1	0	2	1	1
VOMITING	1	3	0	1	0	0
DIARRHOEA	0	3	0	0	0	0
FLATULENCE	1	0	0	0	0	0
NAUSEA	0	1	0	0	0	0
BACK PAIN	0	0	0	0	1	0
NO. OF SUBJECTS WITH AN ADVERSE EXPERIENCE		43			17	
NO. WITH A MODERATE OR SEVERE ADVERSE EXPERIENCE		24			8	
NO. WITH A SEVERE ADVERSE EXPERIENCE		7			2	
TOTAL NO. OF SUBJECTS		56			55	

(a) Statistical significance of difference between treatments in abdominal pain, $p<0.001$ using two sided chi-squared test for trend in 4x2 table.

The relationship of each adverse experience to the study medication in the opinion of the investigator and clinical monitor is summarised in Appendix 5.

6.6. Haematological variables

Data listings for each haematological variable are included in Appendix 6. Each variable is summarised by a table showing the mean, s.d. and numbers outside the normal range by treatment group and time, and by a shift table showing the numbers of subjects who were below, within and above the normal range before and after medication by treatment group. These summary tables are included in Appendix 6.

There were statistically significant shifts in white blood count relative to the normal range in both the misoprostol group ($p<0.001$) and the placebo group ($p<0.001$). The changes were mainly from above the range before medication to within the range before the operation and there was no statistically significant difference between the treatment groups. No statistically significant shifts or differences between treatments were observed for any of the other haematological variables.

7. RESULTS EG9-85-02-241 (2 x 200 mcg)

The database used for the following analysis comprises details of 189 subjects, one of whom was admitted to the

study twice. Listings of the data are included immediately after the listings for study 212 in Appendices 4, 5 and 6.

7.1. Subject Enrollment

The first subject was admitted to the study on 17th April 1985 and the final one on 7th August 1985. All subjects recruited fulfilled the admission criteria of the study. Ninety six subjects were treated with misoprostol and 94 with placebo. One subject was recruited to the study twice. On the first occasion she received placebo (subject number 180) but she discharged herself from the clinic before the operation. She was readmitted three days later, allocated treatment number 185, misoprostol, but again discharged herself from the clinic before the termination was performed. This subject's data were retained in each treatment group for analysis. The outcome of this subject's pregnancy is as yet unknown. One other subject (number 224) changed her mind after receiving placebo and the abortion was not performed.

7.2. Admission Profile

Table 10 shows the age distribution and mean weight, height, pulse and blood pressure for each treatment group. The two groups were evenly matched with regard to these variables.

Details of obstetric and gynaecological history are given in Table 11. There were no marked differences between the two treatment groups.

TABLE 10

ADMISSION PROFILE BY TREATMENT

		TREATMENT	
		MISOPROSTOL 2x200 mcg	PLACEBO
NUMBER OF SUBJECTS		96	94
AGE (YEARS)	18-20	23	22
	21-30	44	46
	31-40	25	26
	41-50	4	0
	MEDIAN AGE	26	26
	RANGE	18 - 47	18 - 40
WEIGHT (kg)	MEAN	59.3	59.6
	S.D.	8.1	10.2
HEIGHT (cm)	MEAN	164.3	165.1
	S.D.	6.0	6.2
PULSE (beats/min)	MEAN	76.9	78.5
	S.D.	10.8	8.0
SYSTOLIC BLOOD PRESSURE (mmHg)	MEAN	123.1	121.9
	S.D.	13.9	13.3
DIASTOLIC BLOOD PRESSURE (mmHg)	MEAN	80.4	77.9
	S.D.	8.4	9.5

TABLE 11

OBSTETRIC AND GYNAECOLOGICAL HISTORY BY TREATMENT

		TREATMENT	
		MISOPROSTOL 2x200 mcg	PLACEBO
NO. OF SUBJECTS		96	94
NO. OF PREVIOUS SPONTANEOUS ABORTIONS	0	85	85
	1	9	8
	2	1	0
	3	0	0
	4	0	1
	5	1	0
NO. OF PREVIOUS INDUCED ABORTIONS	0	77	69
	1	16	22
	2	0	3
	3	3	0
NO. OF PREVIOUS DELIVERIES	0	50	54
	1	22	15
	2	15	20
	3	8	4
	4	1	0
	5	0	1
PREVIOUS PREGNANCY		56	58
NO PREVIOUS PREGNANCY		40	36
PREVIOUS GYNAECOLOGICAL SURGERY	YES	11	11
	NO	85	83

The gestational age, bleeding, vomiting and other complications in the current pregnancy are summarised in Table 12. All subjects were in the 9th to 12th week of pregnancy, judged by clinical examination or ultrasound. There were more subjects in the placebo group than in the misoprostol group who had other complications during their pregnancy. The difference was due largely to the number of subjects with nausea in the misoprostol group (37) compared with the placebo group (49). The full list of complications associated with the current pregnancy can be found in Table 12.

7.3. Study Performance

7.3.1 Concurrent Medication

Medication used in the seven days prior to the study is shown in Table 13. Twenty subjects in the misoprostol group and twenty six in the placebo group had taken medication. The pharmacological properties of some homeopathic medicines listed in Table 13 are not documented but as these were not taken by subjects showing a tendency to abort the pregnancy, they are not considered to have contributed to the study findings. In the period between the first dose of study medication and the operation, additional medication was taken by thirteen subjects. A tranquiliser, clorazepate potassium, was given to seven subjects in the misoprostol group and three in the placebo group. A combination of

TABLE 12

DETAILS OF CURRENT PREGNANCY BY TREATMENT

		TREATMENT	
		MISOPROSTOL 2x200 mcg	PLACEBO
NO. OF SUBJECTS		96	94
GESTATIONAL AGE (weeks) (a)	9	14	14
	10	26	31
	11	30	22
	12	26	27
BLEEDING	YES	15	15
	NO	81	79
VOMITING	YES	30	31
	NO	66	63
OTHER COMPLICATIONS:			
NAUSEA		37	49
ABDOMINAL PAIN		9	9
HEADACHE		4	9
BREAST PAIN		6	7
HYPOTENSION		1	3
BACK PAIN		1	3
SYNCOPE		1	2
DYSPEPSIA		2	1
ACUTE MASTITIS		2	1
ALOPECIA		0	1
VERTIGO		0	1
DIARRHOEA		1	0
FLATULENCE		0	1
OEDEMA		1	0
FEVER		1	0
		0	1
NO. OF SUBJECTS WITH OTHER COMPLICATIONS		51	66

(a) Estimated by clinical examination or ultrasound.

TABLE 13

MEDICATION USED IN 7 DAYS PRIOR TO STUDY BY TREATMENT
(Part 1 of 2)

MEDICATION	TREATMENT	
	MISOPROSTOL 2x200mcg	PLACEBO
ACONITE	1	0
AGNUS CASTUS	0	1
ALUMINIUM HYDROXIDE	0	2
ALUMINIUM HYDROXIDE GEL, DRIED	1	1
ALUMINIUM HYDROXIDE MAG. CARBONATE	1	0
AMITRIPTYLINE	0	1
AMPHO MORONAL	0	1
ASCORBIC ACID	1	0
ASPIRIN	1	4
BELLADONNA EXTRACT	3	0
BENZOCAINE	1	0
BIOTIN	0	1
BISMUTH ALUMINATE	1	0
BUTALBITAL	2	1
CAFFEINE	8	5
CALCIUM PANTOTHENATE	0	1
CHAMOMILE	1	0
CHLORDIAZEPOXIDE	0	1
CHLORPHENSIN	1	0
CHOLINE STEARATE	1	0
CODEINE PHOSPHATE	0	2
CONDURANGO TINCTURE	0	1
CYANOCOBALAMIN	0	1
DIAZEPAM	0	1
DIGOXIN	0	1
DIHYDROERGOTAMINE	0	1
DIMENHYDRINATE	0	2
DIPHENHYDRAMINE HYDROCHLORIDE	2	0
DIPYRONE SODIUM	0	1
ETHAMBUTOL	1	0
ETILEFRINE HYDROCHLORIDE	0	1
FERROUS SULPHATE	0	2
GUAIPHENESIN	1	0
GUANETHIDINE MONOSULPHATE	0	1
HORSE CHESTNUT SEED EXTRACT	0	1
HYDROCHLOROTHIAZIDE	0	1
HYDROXYEPHEDRINE	1	0
HYOSCINE BUTYLBROMIDE	0	1
HYPERICUM	1	0
IGNATIA	0	1
ISONIAZID	1	0

TABLE 13

MEDICATION USED IN 7 DAYS PRIOR TO STUDY BY TREATMENT
(Part 2 of 2)

MEDICATION	TREATMENT	
	MISOPROSTOL 2x200mcg	PLACEBO
LACTOSE	1	0
MAGNESIUM HYDROXIDE	1	3
MANDELIC ACID	2	1
MECLOZINE	1	0
METOCLOPRAMIDE HYDROCHLORIDE	1	2
METRONIDAZOLE	0	1
NEOMYCIN	1	0
NETTLE ROOT EXTRACT	0	1
NICOTINAMIDE	0	1
NITROXOLINE	0	1
OESTRIOL	1	0
OXAZEPAM	1	1
PARACETAMOL	3	3
PENICILLIN G POTASSIUM	0	1
PHENAZONE SALICYLATE	2	1
PHENOBARBITONE	1	0
PROGESTERONE	1	0
PROPYPHENAZONE	4	1
PYRIDOXINE HYDROCHLORIDE	0	3
RANITIDINE	1	1
RIBOFLAVINE	0	1
RIFAMPICIN	1	0
SALICYLAMIDE	2	1
SERINE	0	2
SULPHAMETHIZOLE	0	1
SULPHANILAMIDE	1	0
TETRACYCLINE	0	1
THIAMINE	2	1
THYROXINE SODIUM	3	2
TROSPIUM CHLORIDE	0	1
UNSPECIFIED	0	1
NO. OF SUBJECTS TAKING MEDICATION	20	26
TOTAL NO. OF SUBJECTS	96	94

propyphenazone, drofenine hydrochloride and allobarbitione were given to two subjects in the misoprostol group and one in the placebo group. These were administered mainly for abdominal pain and
anxiety.

7.3.2 Study Medication and timing

The first dose of study medication was taken between 18.00 and 18.15 in all cases. The second dose was taken between 23.00 and 24.00 in all cases except those subjects who did not receive a second dose. In the misoprostol group there were three subjects who did not receive the second dose of study medication. One was because of severe bleeding and pain, one was because of anxiety about severe bleeding and abortion (moderate bleeding was recorded) and for one the reason was not given although bleeding and abdominal pain were recorded. In the placebo group one subject did not receive the second dose because of anxiety about bleeding plus depression (no bleeding was recorded). This subject subsequently changed her mind and did not undergo abortion.

The pre-operative cervical assessment was performed between 06.25 and 11.00 in all cases. The distribution of the time interval between the first dose of study medication and the pre-operative cervical assessment is shown in Table 14. The interval was between 12 hours 25 minutes and 17 hours for all subjects.

TABLE 14

INTERVAL FROM FIRST DOSE
TO PRE-OPERATIVE CERVICAL ASSESSMENT BY TREATMENT

		TREATMENT	
		MISOPROSTOL 2x200 mcg	PLACEBO
NUMBER OF SUBJECTS		95 (a)	92 (b)
TIME INTERVAL (HOURS)	>12-13	3	2
	>13-14	38	39
	>14-15	51	48
	>15-16	2	2
	>16-17	1	1
MINIMUM INTERVAL (HR.MIN)		12.25	12.35
MAXIMUM INTERVAL (HR.MIN)		17.00	16.10

(a) 1 subject excluded, cervical assessment and operation not performed.
(b) 2 subjects excluded, cervical assessment and operation not performed.

7.4. Effect of Treatment on the Pregnant Uterus

During the period between the administration of the first dose of medication and the pre-operative cervical assessment, bleeding was observed in 32 of the 96 subjects in the misoprostol group and one of the 94 subjects in the placebo group. Three of the subjects who experienced bleeding in the misoprostol group received only one dose of study medication. The subject identification number, the timing of medication and the onset of bleeding in relation to the first dose of study medication is presented in Table 15. The earliest recorded onset of bleeding was 1 hour 30 minutes after the first dose of medication.

In five subjects, numbers 156, 157, 178, 186 and 271, all in the misoprostol treated group, products of conception were expelled spontaneously during the period between administration of the test medication and the pre-surgical cervical assessment. The timings for the expulsions are given in Table 15. All five of these subjects received both doses of study medication. Based on the history given, none of the five cases had had a previous spontaneous abortion.

The observations concerning the expulsion of products of conception and the incidence and severity of bleeding during

TABLE 15

INDIVIDUAL SUBJECTS WHO EXHIBITED BLEEDING AND/OR EXPULSION OF PRODUCTS OF CONCEPTION PRIOR TO CERVICAL EXAMINATION, BY TREATMENT GROUP, TIME OF TEST MEDICATION AND ONSET OF RESPONSE

SUBJECT	TIME FIRST DOSE (hr)	TIME SECOND DOSE (hr)	ONSET OF BLEEDING (Hours since first dose)	EXPULSION OF PRODUCTS (Hours since first dose)
MISOPROSTOL 2x200 mcg				
PLACEBO				
—	—	—	—	

this period are summarised in Table 16 together with the results of the statistical analysis. The five expulsions in the misoprostol group versus zero in the placebo group was statistically significant using a one-sided test at the 5% level (p=0.031). In common with study 212, histopathological identification of the expelled tissue as being all or part of the products of conception was not performed. Based on a clinical diagnosis alone, three were believed to be incomplete and two complete.

For bleeding, ignoring severity, the difference between the two treatment groups was statistically significant (p<0.001). The seven subjects who were judged to have had severe bleeding included four of the five subjects in the misoprostol group who aborted. The remaining subject experienced moderate bleeding. The severe bleeding was not considered to be life threatening and no intervention was required.

At the cervical examination, performed immediately before surgery (Table 16), products of conception were visible in nine subjects in the misoprostol group, including the five in whom the products of conception were earlier expelled, and zero in the placebo group. This difference was statistically significant (p=0.002). Visible bleeding was observed in 31 subjects in the misoprostol group, 30 of whom had been noted to be bleeding prior to this assessment. Visible bleeding was observed in only one subject in the

TABLE 16

POST-TREATMENT OBSERVATIONS AND PRE-OPERATIVE CERVICAL ASSESSMENT - SUMMARY OF RESULTS

		TREATMENT		STATISTICAL SIGNIFICANCE (one-sided)
		MISOPROSTOL 2x200 mcg	PLACEBO	
NO. OF SUBJECTS		96	94	
BETWEEN FIRST DOSE AND PRE-OPERATIVE ASSESSMENT:				
PRODUCTS OF CONCEPTION EXPELLED		5 (5%)	0 (0%)	p=0.031 (e)
BLEEDING	NONE	64 (67%)	93 (99%)	p<0.001 (f)
	MILD	16 (17%)	1 (1%)	
	MODERATE	9 (9%)	0 (0%)	
	SEVERE	7 (7%)	0 (0%)	
PRE-OPERATIVE CERVICAL ASSESSMENT: (a)				
VISIBLE PRODUCTS OF CONCEPTION	PRESENT	9 (9%) (b)	0 (0%)	p=0.002 (e)
	ABSENT	86 (91%)	92 (100%)	
VISIBLE BLEEDING	PRESENT	31 (33%) (c)	1 (1%) (d)	p<0.001 (f)
	ABSENT	64 (67%)	91 (99%)	
EXTERNAL OS	OPEN	37 (39%)	6 (7%)	p<0.001 (f)
	CLOSED	58 (61%)	86 (93%)	
CERVIX	SOFT	54 (57%)	30 (33%)	p<0.001 (f)
	MEDIUM	38 (40%)	57 (62%)	
	RIGID	3 (3%)	5 (5%)	

(a) 1 subject excluded from misoprostol group and two subjects excluded from placebo group - cervical assessment and operation not performed.
(b) Includes the 5 subjects for whom products were expelled.
(c) Includes 30 subjects who bled between first dose and pre-operative assessment.
(d) Subject also bled between first dose and pre-operative assessment.
(e) Using Fisher's exact test.
(f) Using chi-squared test for 2x2 table.

placebo group and the difference between the two treatment groups was statistically significant ($p<0.001$).

The external os was open in 37 subjects in the misoprostol group compared with six in the placebo group. The difference was statistically significant ($p<0.001$). The cervix was graded 'soft' for 54 subjects in the misoprostol group compared with 30 subjects in the placebo group. Combining the 'medium' and 'rigid' responses, the treatment difference was statistically significant ($p<0.001$).

The results for the dilatation procedure are summarised in Table 17. The largest probe easily accepted prior to mechanical dilatation tended to be greater in the misoprostol group (median 9 mm) than in the placebo group (median 8 mm). The difference between the two treatment groups was statistically significant ($p<0.001$). The final size of dilator used was 11 mm in the majority of subjects and there was no significant difference between the treatment groups ($p=0.38$).

In the overall assessment, the procedure was graded 'no effort' or 'easy' in 43 subjects in the misoprostol group compared with 15 in the placebo group. There was a significant difference between the two treatments in the ease of the procedure ($p<0.001$).

TABLE 17

DILATATION PROCEDURE - SUMMARY OF RESULTS

		TREATMENT		STATISTICAL SIGNIFICANCE (two-sided)
		MISOPROSTOL 2x200mcg	PLACEBO	
NO. OF SUBJECTS		95 (a)	92 (b)	
LARGEST PROBE EASILY ACCEPTED (mm)	5	0	1	p<0.001 (c)
	6	2	6	
	7	17	30	
	8	21	34	
	9	14	6	
	10	4	3	
	11	30	7	
	12	0	0	
	13	7	5	
MEDIAN SIZE		9	8	
FINAL SIZE OF DILATOR USED (mm)	9	2	0	p=0.38 (d)
	10	0	0	
	11	74	79	
	12	0	0	
	13	19	13	
EASE OF PROCEDURE	NO EFFORT	21 (22%)	1 (1%)	p<0.001 (e)
	EASY	22 (23%)	14 (15%)	
	NORMAL	43 (45%)	61 (66%)	
	DIFFICULT	9 (9%)	16 (17%)	

(a) 1 subject excluded, cervical assessment and operation not performed.
(b) 2 subjects excluded, cervical assessment and operation not performed.
(c) Using Mann-Whitney test.
(d) Using chi-squared test for 2x2 table.
(e) Using chi-squared test for trend in 4x2 table.

TABLE 18

ADVERSE EXPERIENCES - INCIDENCE AND SEVERITY BY TREATMENT

ADVERSE EXPERIENCE	TREATMENT					
	MISOPROSTOL 2x200 mcg			PLACEBO		
	MILD	MOD.	SEV.	MILD	MOD.	SEV.
ABDOMINAL PAIN (a)	29	6	6	12	1	1
NAUSEA	0	0	1	2	0	0
HEADACHE	0	0	0	0	1	1
VOMITING	1	0	0	1	0	0
BACK PAIN	1	1	0	0	0	0
HYPOTENSION	0	1	0	0	0	0
NO. OF SUBJECTS WITH AN ADVERSE EXPERIENCE	42			17		
NO. WITH A MODERATE OR SEVERE ADVERSE EXPERIENCE	13			5		
NO. WITH A SEVERE ADVERSE EXPERIENCE	6			2		
TOTAL NO. OF SUBJECTS	96			94		

(a) Statistical significance of difference between treatments in abdominal pain, $p<0.001$, using two-sided chi-squared test for trend in 4x2 table.

7.5. Adverse experiences

The incidence and severity of adverse experiences reported during the study are summarised in Table 18. The most commonly reported adverse experience was abdominal pain. It was reported by 41 subjects in the misoprostol group compared with 14 subjects in the placebo group. The difference between the two treatments was statistically significant ($p<0.001$). Other adverse experiences were of low incidence and included nausea, headache, vomiting, back pain and hypotension.

The relationship of each adverse experience to the study medication in the opinion of the investigator is summarised in Appendix 5.

7.6. Haematological variables

Data listings for each haematological variable are included in Appendix 6. Each variable is summarised by a table showing the mean, s.d. and numbers outside the normal range by treatment group and time, and by a shift table showing the numbers of subjects who were below, within and above the normal range before and after medication by treatment group. These summary tables are also included in Appendix 6.

There were statistically significant shifts in haemoglobin, haematocrit and red blood count relative to the normal range in

both the misoprostol group and the placebo group. In all cases the changes were mainly from below the range before medication to within the range before the operation and there were no significant differences between the treatment groups.

There were statistically significant shifts in white blood count relative to the normal range in both the misoprostol group and the placebo group. The changes were mainly from above the range before medication to within the range before the operation and there was no statistically signficant difference between the treatment groups.

8. COMPARISON OF 2 x 400 mcg AND 2 x 200 mcg

The major findings for the two studies are presented in Table 19. No formal comparison of the results for 2 x 400 mcg and 2 x 200 mcg has been made, since the studies were performed at different times.

However, allowing for the differences in responses in the respective placebo groups, it would appear that overall the effect of the 200 mcg dose is less marked than that of the 400 mcg dose with respect to the incidence (Table 19) and severity (Tables 9, 18) of abdominal pain, the effect on the external os and the ease of the dilatation procedure. Some reduction in the incidence of bleeding was noted but the overall effect on the expulsion of products and the softening of the cervix was unchanged.

Misoprostol effect on pregnant uterus
20th December 1985

TABLE 19

COMPARISON OF RESULTS FOR 2 x 400 mcg AND 2 x 200 mcg

	MISOPROSTOL 2x400mcg	MISOPROSTOL 2x200mcg	PLACEBO 2x400mcg	PLACEBO 2x200mcg
Overall incidence Partial or Complete Expulsion of Products	11%	9%	0%	0%
Bleeding visible at Cervical Assessment	41%	33%	2%	1%
External Os Open	59%	39%	11%	7%
Cervix Soft	71%	57%	51%	33%
Dilatation Procedure (No effort or Easy)	66%	45%	29%	16%
Abdominal Pain	75%	43%	20%	15%

9. STUDY DEVIATIONS

There were two study deviations. One concerned the lack of histopathological examination of the products of conception. The diagnosis concerning the complete or incomplete abortion was based on clinical grounds alone.

The second concerned the inclusion of one subject into the study twice. Subject number 180 took study medication (placebo) but decided against surgery. She was readmitted to the study as subject number 185, took study medication (misoprostol) and again decided against surgery.

10. DISCUSSION

The information available from the use of misoprostol in animal reproductive studies, at doses representative of those used in man, did not indicate that misoprostol would cause an effect on the pregnant uterus. However natural prostaglandins e.g. PGE_2 and PGF_2 have been used to ripen the cervix at term, to terminate first trimester pregnancy and to soften the cervix pre-operatively. Recognising that the available data in rodents might not represent the situation in man, a study was set up at the Lindenfels Clinic, West Germany to investigate the effect of misoprostol, a PGE_1 analogue, in subjects about to undergo legal elective termination of their pregnancy. Subjects between the 9th and 12th week were selected because it was

routine at the clinic for these late first trimester pregnant patients to remain in hospital for three days, allowing appropriate pre-operative and post-operative supervision.

Based on the experience of this clinic, the expected incidence of spontaneous bleeding of any significance or the spontaneous expulsion of products of conception during the period of hospitalisation would be almost zero. It was clear therefore after observing several cases of incomplete abortions and a high incidence of bleeding in the subjects included in the study, that the drug did indeed have an effect on the pregnant uterus. The study was brought to a close after 111 subjects were recruited, the code was broken and it was evident from the results that misoprostol did show "uterotropic" activity. This uterotropic activity was also shown when a further 191 subjects were treated with misoprostol 2 x 200 mcg or placebo. A dose response relationship could only have been investigated if patients had been randomised to the different dosage regimens within the same study. In this report, containing two studies each placebo-controlled, it is not possible to make any formal comparisons. However it was clear that if the differences in placebo responses are taken into account, the lower dosage overall appears to have less activity particularly with respect to the incidence and severity of abdominal pain, the opening of the external os and the ease with which dilatation could be performed. Some reduction in bleeding

was noted.

Since one 200 mcg or 400 mcg dose was sufficient to cause bleeding and abdominal cramps within a very short time of tablet ingestion in a few subjects, there is a suggestion that some subjects are particularly sensitive to the effect of misoprostol. Others showed no signs or symptoms clearly indicative of a prostaglandin effect, even after both doses had been taken.

In conclusion, the administration of one or two doses of misoprostol, in a dosage regimen normally used for the treatment of duodenal or gastric ulcer, can cause the loss of a pregnancy. The effect on the developing foetus is unknown. Misoprostol should not be used in pregnant patients.

11. REFERENCES

1. Armitage, P. (1955).
Tests for linear trends in proportions and frequencies.
Biometrics, 11, 375-386.

Misoprostol effect on pregnant uterus
20th December 1985

APPENDIX 1

STUDY PROTOCOL

EC1-84-02-212

International Clinical Research
and Medical Affairs

G. D. Searle & Co.

Clinical Research Report

A DOUBLE BLIND PLACEBO CONTROLLED STUDY OF THE UTERINE CONTRACTILITY STIMULATING POTENTIAL OF MISOPROSTOL WHEN ADMINISTERED BY MOUTH AT VARYING DOSES PRIOR TO ELECTIVE LEGAL ABORTION OR IN NONPREGNANT FEMALES

PROTOCOL #IC4-84-02-048; REPORT NO. IB2-86-06-124

PRINCIPAL INVESTIGATOR:

Nils Wiqvist, M.D.
Professor and Chairman
University of Goteborg
Department of Obstetrics and Gynecology
Sahlgren's Hospital
S-413 45
Goteborg, Sweden

August 20, 1986

Misoprostol Uterine Contractility
Stimulating Potential
August 20, 1986

Report Prepared by:

Johann Rothwangl, M.D.
Associate Director,
International Clinical Research

Reviewed and Approved By:

P.P. Paul A. Nicholson, M.D.
Vice President,
International Clinical Research

Statistical Analysis Provided By:

Lawrence G. Deysach, M.A.
Supervisor
Medical Statistics Department

Misoprostol Uterine Contractility
Stimulating Potential
August 20, 1986

ABSTRACT

The present placebo-controlled and open label study was intended to evaluate the potential of misoprostol to increase uterine contractility and tonus.

This trial included subjects in the first trimester of their pregnancy who were scheduled for a legal abortion and one nonpregnant subject.

A total of 22 subjects were enrolled, of whom eight received placebo, and nine received misoprostol in a double blind fashion. In the open label study five patients received misoprostol.

A microballoon catheter was introduced into the uterus one hour before drug administration to measure baseline uterine activity. After drug administration, uterine contractility was recorded for a minimum of 4 hours.

Placebo had no effect on uterine activity. Misoprostol at 200 mcg and 400 mcg doses always increased uterine tonus and frequency of contractions.

Misoprostol Uterine Contractility
Stimulating Potential
August 20, 1986

TABLE OF CONTENTS

APPENDICES

Misoprostol Uterine Contractility
Stimulating Potential
August 20, 1986

1. INTRODUCTION

Misoprostol, a synthetic methyl ester analog of prostaglandin E_1, has been shown to significantly inhibit gastric acid output in humans (1,2). The compound has also been shown to have mucosal cytoprotective properties and in peptic ulcer healing trials it has been statistically significantly superior to placebo (3,4,5,6,7,).

Natural and synthetic prostaglandins are known to affect the female reproductive systems. The effects of misoprostol on the pregnant uterus were evaluated in women in their first trimester prior to elective termination of pregnancy. In separate studies, two doses of 400 mcg or two doses of 200 mcg misoprostol were administered 5 hours apart. Expulsion of the products of conception occurred in 6/56 (11%) of the 2 x 400 mcg subjects and 9/96 (9%) of the 2 x 200 mcg subjects and none of the 55 and 94 placebo subjects. This was statistically significant ($p=0.014$ and $p=0.002$, respectively). Bleeding was also significantly greater after misoprostol than placebo ($p<0.001$ in both studies), but did not require medical intervention in any case. Bleeding occurred in 41% (23/56) of the misoprostol subjects who received 2 x 400 mcg compared with 2% (1/55) of the placebo subjects. Following the 2 x 200 mcg misoprostol dosage, 33% (32/96) experienced

bleeding compared with 1% (1/94) of the placebo group (8).

The results of the first of these separate studies became available before the present study, originally designed for 16 subjects, was half completed. As a result, this study was amended to allow for investigating the uterotropic potential of lower doses of misoprostol, and of misoprostol on the non-pregnant uterus. The study as originally planned was never completed. The results for the first half of the study supplied convincing evidence that misoprostol at 800 mcg (given in two 400 mcg doses 4 hours apart) is uterotropic.

2. STUDY OBJECTIVES

To measure changes in uterine contractility due to administration of misoprostol in pregnant women admitted for legal abortion and in nonpregnant women.

3. MATERIALS AND METHODS

The study was conducted in accordance with protocol IC4-84-02-048, "A Double-Blind Placebo Controlled Study of the Uterine Contractility Stimulating Potential of Misoprostol When Administered by Mouth at a Dose of 400 mcg Twice (4 Hour Interval) Prior to Elective Legal Abortion During the First Trimester of Pregnancy." The protocol, dated September 28, 1984, was amended

February 19, 1985, April 16, 1985, and May 24, 1985. A copy of the protocol and amendments is attached as Appendix I. The study was initiated on February 6, 1985, and the last subject was studied on January 8, 1986.

3.1 Investigator

The principal investigator was Nils Wiqvist, M.D., Professor and Chairman of the Department of Obstetrics and Gynecology, University of Goteborg, Sahlgren's Hospital, Goteborg, Sweden. All the laboratory determinations were performed by the laboratory at Sahlgren's Hospital.

3.2 Subjects

Subjects were eligible for admission if they were of legal age, during their first trimester of pregnancy confirmed by a urine test, and had intrauterine pregnancy confirmed by physical examination. They had to be scheduled for legal interruption of a first trimester pregnancy.

Subjects were excluded from the study if they showed signs or symptoms of spontaneous abortion, had a history of sensitivity to prostaglandins, or had a history or symptoms of cardiovascular or

pulmonary disease, inflammatory bowel disease, diabetes mellitus, disorders of blood coagulation, sickle cell anemia, functional renal impairment or glomerulonephritis, or epilepsy.

In the open label study, nonpregnant subjects could be enrolled if they met all the other criteria not pertaining to pregnancy.

3.3 Study Plan

Subjects were to be studied as outpatients. They were to be admitted to the hospital early in the morning and discharged late in the evening. Prestudy laboratory tests consisting of hematology and urinalysis were to be obtained prior to insertion of the microballoon.

Uterine contractility was to be recorded by the microballoon or microtransducer technique. Following one hour of recording basal contractility, 200 mcg or 400 mcg misoprostol or placebo were to be administered by mouth. In the double-blinded part of the study, this was to be followed by a second dose 4 hours after the first dose. In the open label study, only Subjects 103 and 104 were to receive two doses. Monitoring of uterine contractility was to continue for 2 hours following the last oral dose. Termination of pregnancy was

then to be completed in accordance with the routine of the hospital.

3.4 Study Drug

In the double-blind study, Subjects 001-008, inclusive, received 400 mcg misoprostol or placebo twice daily, 4 hours apart.

The bulk lot used in this study was misoprostol 200 mcg, lot RCT 7288. Placebo lot number was RCT-7398.

Subjects 009-016 were to receive 200 mcg twice daily, 4 hours apart. The drug was packaged in individual bottles for each subject containing either four 200 mcg tablets of misoprostol or placebo. The drug was from the same lot as for subjects 001-008.

For the open label study, drug was supplied in individual bottles containing two 200 mcg tablets of misoprostol. The bulk lot used in this study was misoprostol 200 mcg, lot RCT 7361.

The individual bottles of study drug were labeled with the appropriate subject study number and packaging lot numbers.

4. RESULTS

All 22 subjects participating in this study were Caucasian, with a mean age for the group of 25 years. None had cramps, bleeding, or signs/symptoms of threatened abortion at the onset of the study. The age, height, weight, and blood pressure of each subject is given in Table 1.

The first 8 subjects were entered according to the original study plan and received medication according to the randomization schedule prepared prior to study initiation. When the decision was made to study a lower dose of misoprostol the blind was broken for these 8 subjects, 4 of whom showed uterine contractions and 4 did not. The 4 with contractions were on misoprostol 800 mcg, and the 4 without contractions were on placebo (Table II). By a Fisher's Exact Test, the p-value associated with this all-or-none result is 0.028. This, along with evidence from an independent clinical trial carried out in Germany briefly described in the Introduction, indicates that misoprostol at 800 mcg is uterotropic in pregnant women in their first trimester.

For Subjects 101, 102, 103, 104 and 105, the drug was administered in an open label fashion. Subject 101 was

Exhibit 89

CLINICAL STUDY SYNOPSIS

A DOUBLE BLIND PLACEBO CONTROLLED STUDY OF THE UTERINE CONTRACTILITY STIMULATING POTENTIAL OF MISOPROSTOL WHEN ADMINISTERED BY MOUTH AT VARYING DOSES PRIOR TO ELECTIVE LEGAL ABORTION OR IN NONPREGNANT FEMALES
[REPORT: IB2-86-06-124]

INVESTIGATOR	o Dr. Nils Wiqvist
STUDY SITE	o University of Goteborg Sahlgren's Hospital Goteborg, Sweden
OBJECTIVE	o To evaluate the uterotropic effect of misoprostol given twice by mouth at doses of 400 mcg, 4 hours apart in pregnant women during the first trimester, who are scheduled for legal abortion o To evaluate the uterotropic effect of misoprostol given twice by mouth at doses of 200 mcg, 4 hours apart in pregnant women during the first trimester, who are scheduled for legal abortion o To evaluate the uterotropic effect of misoprostol in non-pregnant women
STUDY DESIGN	o Randomized double blind, placebo controlled or open label
POPULATION	o Twenty-one pregnant (first trimester) females, scheduled for legal abortion o one non-pregnant female
TEST DRUG	o Misoprostol 400 mcg administered twice, 4 hours apart o Misoprostol 200 mcg administered twice, 4 hours apart o Misoprostol 200 mcg or 400 mcg administered once
EVALUATION CRITERIA	o Increase in uterine tonus and frequency of contractions measured by the microballoon technique was considered a positive response
RESULTS	o All 14 subjects who had received active drug, regardless whether a 200 mcg dose or a 400 mcg dose was administered, responded with an increase in uterine tonus and increased frequency of contractions o Subjects who had received placebo had identical tracings before and after drug administration o One subject complained of mild nausea after administration of a second 200 mcg dose of misoprostol. This was the only adverse experience reported.
CONCLUSION	o Misoprostol given once or twice (4 hours apart) at 200 mcg or 400 mcg doses causes an increase in frequency of contractions and tonus of the pregnant and nonpregnant uterus

Misoprostol Uterine Contractility Stimulating Potential
August 20th 1986

INVESTIGATOR SIGNATURE PAGE

A DOUBLE-BLIND PLACEBO CONTROLLED STUDY OF THE UTERINE CONTRACTILITY STIMULATING POTENTIAL OF MISOPROSTOL WHEN ADMINISTERED BY MOUTH AT VARYING DOSES PRIOR TO ELECTIVE LEGAL ABORTION OR IN NONPREGNANT FEMALES

PROTOCOL NUMBER: IC4-84-02-048

REPORT NUMBER: IB2-86-04-124

I confirm my participation as a Clinical Investigator in the above study, and my contribution to the data in the final report. A copy of this report has been received.

..... Dec 16, 1986

Investigator Signature Date

Name: Professor N Wiqvist

Address: Department of Obstetrics & Gynaecology
University of Göteborg
S-413 45
Göteborg
SWEDEN

Misoprostol Uterine Contractility
Stimulating Potential
August 20, 1986

Table I

EVALUATION OF UTERINE CONTRACTILITY - CYTOTEC

CHARACTERISTICS

SUBJECT NUMBER	AGE	SEX	RACE	HEIGHT (CM)	WEIGHT (KG)	TEMP (C)	PULSE (NO/MIN)	BLOOD PRESSURE (MM/HG)
1144- 1	24	FEMALE	CAUCASIAN	165.00	59.00	37.0	70	110/ 70
1144- 2	36	FEMALE	CAUCASIAN	160.00	81.00	37.3	82	115/ 80
1144- 3	24	FEMALE	CAUCASIAN	168.00	54.00	36.9	75	120/ 70
1144- 4	20	FEMALE	CAUCASIAN	168.00	63.00	36.8	75	110/ 70
1144- 5	17	FEMALE	CAUCASIAN	161.00	52.00	37.1	80	130/ 70
1144- 6	36	FEMALE	CAUCASIAN	167.00	64.00	36.9	75	130/ 70
1144- 7	26	FEMALE	CAUCASIAN	171.00	66.00	37.0	80	120/ 65
1144- 8	20	FEMALE	CAUCASIAN	160.00	52.00	36.8	70	125/ 75
1144- 9	21	FEMALE	CAUCASIAN	160.00	62.00	37.0	75	120/ 70
1144- 10	22	FEMALE	CAUCASIAN	163.00	53.00	36.9	75	115/ 75
1144- 11	20	FEMALE	CAUCASIAN	162.00	54.00	36.9	75	115/ 70
1144- 12	17	FEMALE	CAUCASIAN	163.00	61.00	37.0	80	110/ 70
1144- 13	22	FEMALE	CAUCASIAN	172.00	74.00	36.9	75	115/ 70
1144- 14	20	FEMALE	CAUCASIAN	172.00	53.00	37.1	80	120/ 75
1144- 15	22	FEMALE	CAUCASIAN	173.00	58.00	36.9	68	135/ 65
1144- 16	28	FEMALE	CAUCASIAN	171.00	64.00	37.4	64	110/ 70
1144-101	43	FEMALE	CAUCASIAN	166.00	57.00	37.1	80	120/ 80
1144-102	28	FEMALE	CAUCASIAN	173.00	68.00	37.0	64	115/ 70
1144-103	29	FEMALE	CAUCASIAN	164.00	63.00	37.0	76	115/ 65
1144-104	25	FEMALE	CAUCASIAN	164.00	57.00	37.1	70	115/ 70
1144-105	25	FEMALE	CAUCASIAN	167.00	70.00	36.9	74	105/ 65
1144-909	24	FEMALE	CAUCASIAN	160.00	56.00	36.9	72	110/ 60
N	22			22	22	22	22	22/ 22
MEAN	25.0			165.909	60.955	37.00	74.3	117.3/ 70.2
SD	6.5			4.587	7.587	0.15	5.1	7.5/ 4.8
CV %	25.9			2.765	12.448	0.40	6.8	6.4/ 6.8

Misoprostol Uterine Contractility
Stimulating Potential
August 20, 1986

Table II

TREATMENT GROUP AND OUTCOME
DOUBLE BLIND 2 X 400 MCG

SUBJECT NO.	DATE OF PROCEDURE	TREATMENT - DOSE	OUTCOME: CONTRACTIONS SEEN
1	2/06/85	PLACEBO	NO
2	1/31/85	MISOPROSTOL 2 X 400 MCG	YES
3	2/11/85	PLACEBO	NO
4	2/14/85	MISOPROSTOL 2 X 400 MCG	YES
5	2/18/85	MISOPROSTOL 2 X 400 MCG	YES
6	4/03/85	PLACEBO	NO
7	4/09/85	PLACEBO	NO
8	4/22/85	MISOPROSTOL 2 X 400 MCG	YES

TREATMENT GROUP AND OUTCOME
DOUBLE BLIND 2 X 200

SUBJECT NO.	DATE OF PROCEDURE	TREATMENT - DOSE	OUTCOME: CONTRACTIONS SEEN
9	5/13/85	MISOPROSTOL 2 X 200 MCG	YES
909	5/14/85	MISOPROSTOL 2 X 200 MCG	YES
10	5/22/85	PLACEBO	NO
11	5/28/85	MISOPROSTOL 2 X 200 MCG	YES
12	9/04/85	PLACEBO	NO
13 *	9/09/85	MISOPROSTOL 2 X 400 MCG	YES
14	10/14/85	MISOPROSTOL 2 X 200 MCG	YES
15	10/17/85	PLACEBO	NO
16	12/19/85	PLACEBO	NO

TREATMENT GROUP AND OUTCOME
OPEN LABEL

SUBJECT NO.	DATE OF PROCEDURE	TREATMENT - DOSE	OUTCOME: CONTRACTIONS SEEN
101 **	6/07/85	MISOPROSTOL 1 X 400 MCG	YES
102	6/19/85	MISOPROSTOL 1 X 400 MCG	YES
103	6/24/85	MISOPROSTOL 2 X 200 MCG	YES
104	6/25/85	MISOPROSTOL 2 X 200 MCG	YES
105	1/08/86	MISOPROSTOL 1 X 200 MCG	YES

* SUBJECT 13 RECEIVED INCORRECT DOSE
** SUBJECT 101 NON-PREGNANT

not pregnant. Subjects 102, 103, and 104 were in their early stages of pregnancy (1-8 weeks), whereas subject 105 had been pregnant for 11-12 weeks (Table II).

By the end of the study all 14 subjects taking misoprostol had exhibited contractions while none of the 8 subjects on placebo had an increase in uterine activity. Based on these data, the 95% confidence interval for the probability of placebo inducing contractions is from 0.0% to 36.9%, and for misoprostol (all doses combined) causing contractions is from 76.8% to 100.0%. Together with the evidence from the German study, these results indicate that misoprostol, given at 200 mcg doses or higher, is uterotropic.

5. EVALUATION OF SAFETY

5.1 ADVERSE EXPERIENCES

One subject complained of mild nausea. This occurred after the second 200 mcg dose of misoprostol was administered and lasted for about 40 min. No other adverse experiences were reported. (Table III).

Table III
EVALUATION OF UTERINE CONTRACTILITY - CYTOTEC
ADVERSE EXPERIENCES BY EVENT

ADVERSE EXPERIENCE	SUBJECT	AGE	SEX	TREATMENT
NAUSEA	1164- 11	20	FEMALE	MISOPROSTOL 2 X 200 MCG

SEVERITY	DURATION DAYS	HRS	MIN	DRUG RELATED OPINIONS INVESTIGATOR	SPARLE
MILD	0	0	40	YES	YES

5.2 CLINICAL LABORATORY FINDINGS

Only pretreatment laboratory tests were obtained. Minor deviations from the norm were considered clinically not significant. (Appendix III a-e).

6. STUDY DEVIATIONS

The first subject who entered the study was assigned subject number 2 and given test article for subject number 2. The second subject entered into the studyt was then assigned subject number 1 and given test article for subject number 1. Subject 014 received 5 mg Terbutaline orally 15 minutes prior to administration of the second dose of the test article. This did not appear to have any effect on the uterine tonus.

Subject 009 received the appropriate dose but the subsequent subject studied, received drug from the same container. This subject was assigned study #909.

Subject 013 was given 400 mcg of misoprostol twice instead of 200 mcg.

Subject 105 received only one 200 mcg dose of misoprostol (was also 8-16 weeks pregnant).

7. CONCLUSIONS

Misoprostol, administered orally once or twice four hours apart, at 200 mcg or 400 mcg doses, causes an

increase in frequency of contractions and tonus of the pregnant uterus.

The one nonpregnant subject studied also exhibited uterotropic activity secondary to misoprostol.

8. REFERENCES

1. Akdamar, K.; Agrawal, N.; and Ertan, A.: Inhibition of Nocturnal Gastric Secretion in Normal Human Volunteers by Misoprostol: A synthetic Prostaglandin E_1 Methyl Ester Analog, Amer. J. Gastroenterol. 77(12):902-904, 1982.

2. Ramage, J.K.; Denton, A.; and Williams, J.G.: Inhibition of Food Stimulated Acid Secretion by Misoprosotol, an Orally Active Synthetic E_1 Analogue Prostaglandin, Br. J. Clin. Pharmac. 19:9-12, 1985.

3. Hunt, J.N.; Smith, J.L.; Jiang, C.L.; and Kessler, L.: Effect of Synthetic Prostaglandin E_1 Analog on Aspirin-Induced Gastric Bleeding and Secretion, Dig. Dis. Scis. 28(10):897-902, 1983.

4. Cohen, M.M.; Clark, L.; Armstrong, L; and D'Souza, J.: Reduction of Aspirin-Induced Fecal Blood Loss with Low-Dose Misoprostol Tablets in Man, Dig. Dis. Scis. 30(7):605-611, 1985.

5. Multiclinic, Double-Blind, Controlled Comparison of Two Dosage Regimens of Misoprostol and Placebo with Antacid PRN in the Treatment of Duodenal Ulcer in Outpatients. G.D. Searle & Co. Protocol No. MED-81-02-016; Report No. N19-84-06-016, February, 1984.

6. A Multicenter, Double-Blind Trial of Misoprostol and Placebo in the Treatment of Duodenal Ulcer in Outpatients. G.D. Searle & Co. Protocol No. MED-80-02-092; Report No. N18-84-06-182, November, 1984.

7. A Multicentre, International, Double-Blind, Parallel Group Comparison of Two Dosage Regimens of Misoprostol and Cimetidine in the Treatment of Duodenal Ulcer in Outpatients. G.D. Searle & Co., Protocol No. ECR-81A-0012,; Report No. E20-84-06-012, July, 1984; amended June, 1985.

8. Data on File, G.D. Searle & Co. EC1-85-06-212/241.

APPENDIX I

PROTOCOL PLUS AMENDMENTS

SAFETY STUDY

A DOUBLE BLIND PLACEBO CONTROLLED STUDY OF THE UTERINE CONTRACTILITY STIMULATING POTENTIAL OF MISOPROSTOL WHEN ADMINISTERED BY MOUTH AT A DOSE OF 400 MCG TWICE (4 HOUR INTERVAL) PRIOR TO ELECTIVE LEGAL ABORTION DURING THE FIRST TRIMESTER OF PREGNANCY

IC4-84-02-048

NILS WIQVIST, M.D.

PROFESSOR CHAIRMAN

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

UNIVERSITY OF GOTEBORG

SAHLGREN'S HOSPITAL

S-413 45

GOTEBORG, SWEDEN

PHONE: 031/60 10 00

FRANCIS B. O'BRIEN, JR., M.D.
ASSOCIATE DIRECTOR
OBSTETRICS & GYNECOLOGY
CLINICAL RESEARCH

RESEARCH & DEVELOPMENT
DIVISION OF G.D. SEARLE & CO.
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60048
U.SA

PHONE: 312-982-4621 (OFFICE)
PHONE: 312-367-0076 (HOME)

TABLE OF CONTENTS

1. FULL STUDY TITLE

A double blind placebo controlled study of the uterine contractility stimulating potential of misoprostol when administered by mouth at a dose of 400 mcg twice (4 hour interval) prior to elective legal abortion during the first trimester of pregnancy.

2. STATEMENT OF INVESTIGATOR

The study will be conducted at the University of Goteborg, Department of Obstetrics and Gynecology, Sahlgren's Hospital, S-413 45 Goteborg, Sweden by Professor Wiqvist.

3. ETHICS

In performing this study, both the investigator and G.D. Searle endorse, as a minimum, the standards for conduct of clinical research activities as set forth in the Declaration of Helsinki (Appendix I).

The investigator will obtain and document informed consent from each subject in this study. Informed consent should, as a minimum, be obtained in accordance with the Declaration of Helsinki.

Further, it is understood that consent is a matter solely within the realm of investigator subject relationship and not subject to influence by the sponsor.

Approval for the study must be obtained from the government authority of the country concerned where such approval is required. Written notification of approval for the study must also be obtained from an ethical committee or peer review board prior to shipment of drug and will include date of approval and signature of the chairman.

Where an ethical committee is not available or peer review not possible, the investigator will provide a signed statement indicating that the study will be conducted in accordance with the laws and regulations governing clinical research in the country in which the study is to be conducted.

4. BACKGROUND AND RATIONALE

Misoprostol is a novel synthetic prostaglandin E_1 analogue with gastric antisecretory and cytoprotective

properties(1). It has been shown to be a potent inhibitor of gastric secretion in animals (2,3,4) and to prevent the development of acute upper gastrointestinal ulceration in the rat, cat and guinea pig(3). In the dog it significantly strengthens the integrity of the gastric mucosa against hydrogen ion back difusion induced by aspirin(5,6,7). It is thought to inhibit gastric secretion by both local and systemic actions. Studies suggest that the mechanism of gastric secretory inhibition is mediated by a direct action on the parietal cells (3).

Misoprostol in antisecretory doses in animals appeared to have little effect upon the cardiovascular system, respiratory function, platelet aggregation and gastrointestinal motility. In pharmacological exploratory screening tests misoprostol was devoid of Central Nervous System (C.N.S.), anticholinergic, antiarrhythmic, prostaglandin antagonistic, estrogenic, estrogen antagonistic, progestational, progesterone antagonistic, androgenic and androgen antagonistic activities(3). After daily administration of up to 300 mcg/kg of misoprostol in dogs for 12 months there was no evidence of bone abnormalities on microscopic examination of long bones or differences in serum calcium or alkaline phosphatase values between control and treated groups (1).

Misoprostol has been administered to man in single doses as high as 600 mcg and in multiple doses up to 400 mcg four times daily(total of 1600 mcg daily) for 14 consecutive days. Although transient diarrhea was recorded with the latter dose regimen the drug was continued(1).

In animal experimentation, E_1 prostaglandins have demonstrated the ability to induce contractions in the pregnant uterus and this has been applied clinically to humans. E_1 analogues are used at low doses to soften the cervix and facilitate dilatation prior to first trimester surgical termination of pregnancy and at higher doses to induce the termination.

This protocol outlines a double blinded placebo controlled study to evaluate the uterine contracility stimulating potential of misoprostol when administered by mouth at a dose of 400 mcg twice (4 hours apart) immediately prior to elective legal abortion during the first trimester of pregnancy.

The methodology used in this study has been reported in

the literature (6-15).

The investigator is requested to become familiar with the data in the Misoprotol Investigational Brochure before commencing the study. (Appendix II).

5. OBJECTIVE

To compare the uterine contractility stimulating action of misoprostol and placebo in women admitted for legal abortion in the 11th - 12th week of pregnancy. Two oral doses of 400 mcg of misoprostol will be given 4 hours apart and prior to evacuation of the uterus by vacuum aspiration.

6. SUMMARY OF TRIAL DESIGN

Subjects for this study will be women who have been scheduled for legal interruption of first trimester pregnancy. They will be studied on an out-patient basis as admitted to the hospital early in the morning and discharged from the hospital late in the evening. Uterine contractility will be recorded by the micro-balloon technique or micro-transducer. Following one hour of recording basal contractility 400 mcg will be administered by mouth followed by a second dose of 400 mcg 4 hours later. Monitoring of uterine contractility will continue for two hours following the last oral dose. Termination of pregnancy will then be completed in accordance with the routine of the hospital. They will be discharged from the hospital approximately three hours following the surgical intervention.

7. STUDY POPULATION

7.1 Description

Each patient will be given two 200 mcg tablets of misoprostol orally twice (4 hours apart) or placebo in a double blind controlled study. This means that the patients will obtain either two tablets of misosprostol or 2 tablets of placebo. The tablets will be coded by the Searle Company. Patients will be randomized into groups of 4 subjects , two of whom will receive misoprostol tablets and the remaining two will receive placebo tablets. Following analysis of the uterine contractility curves an additional group of four subjects will be included in the study, etc. until significant information is obtained concerning the effect of misoprostol on uterine contractility.

7.2 Inclusion Criteria

7.2.1 Of legal age to sign consent.

7.2.2 Between 11 and 12 weeks inclusive since onset of last normal menses.

7.2.3 Diagnosis of pregnancy confirmed by blood pregnancy test.

7.2.4 Diagnosis of intrauterine pregnancy confirmed by physical examination

7.2.5 Scheduled for legal interruption of a first trimester pregnancy.

7.3 Exclusion Criteria

7.3.1 Subjects showing signs or symptoms of spontaneous abortion

7.3.2 Subjects who have history of sensitivity to prostaglandins

7.3.3 Subjects exhibiting symptoms or having a history of cardiovascular or pulmonary disease, inflammatory bowel disease (ulcerative colitis,Crohn's disease) diabetes mellitus, disorders of blood coagulation, sickle cell anemia, functional renal impairment or glomerulonephritis, or epilepsy.

7.3.4 Subjects who have received antiabortion therapy during the current pregnancy

8.1 TEST MATERIAL

8.1 Supplies

The investigator (or his designate) will dispense randomized containers which will have a label upon which the subject number is imprinted and the directions: two tablets stat and two tablets in 4 hours. The containers will be filled either with 4 200 mcg misoprostol tablets or 4 matching placebo tablets. The statement: "for investigational use only" will be imprinted on the label.

9. RANDOMIZATION PROCEDURE

Subjects will be randomly allocated to one of two treatment groups according to a computer generated randomization list prepared prior to the start of the study. The randomization of the two treatments in the randomization list will be balanced in blocks of 4.

10. STUDY PLAN

10.1 Treatment Period

10.1.1 Status of Subjects

The subjects will be studied as outpatients.

10.1.2 Diet

The subjects will be permitted an early morning breakfast only.

10.1.3 Concurrent Medication

The subjects will not be permitted any additional medication before completion of uterine contractility measurements. Any routine preoperative medication may be given as is the local custom. All concurrent medications will be recorded as to name, dose, route and time of administration.

Every attempt should be made to discontinue concurrent medications unless the investigator feels that it would be in appropriate.

10.1.4 Activity

Activity will be permitted in so far as it does not intefere with the measurement of the uterine contractility.

10.2. Admission to the Study

Subject satisfying the inclusion and exclusion criteria will be allocated to the next available study number.

10.2.1 General History

Details of the subject history will be recorded on the case report forms prior to receiving the first dose of the study medication.

The history will include:

Age, gravidity, parity, date of first day of last normal menses. Drug allergies, serious systemic diseases (including those listed under exclusion criteria)

Synopsis of current pregnancy with emphasis on GI disturbances and uterine bleeding and/or cramps.

Medication taken during the pregnancy to date including vitamins, iron, over the counter medications.

10.2.3 Physical examination

A general physical examination should be done and special details should be recorded for the pelvic examination, including size of the uterus and the condition of the cervix. In addition, weight,blood pressure and urinary sugar and albumin tests should be done on or immeditely prior to admission to the hospital.

10.2.4 Clinical Laboratory Tests

All clinical laboratory determinations should be performed in the same laboratory for the same subject throughout the study. A list of normal values for the laboratory should be provided to the sponsor prior to the beginning of the study.

A blood sample will be collected for each subject on entry into the study for

hemoglobin, hematocrit, RBC, WBC, differential(blood smear and platelet estimation). A urine sample will be collected for protein(albumin), sugar, and acetone.

The results will be recorded on the appropriate clinical report form(CRF). If there are any abnormalities in any of the clinical laboratory test results prior to entry into the study that the investigator considers to be clinically significant that subject will be excluded from entering the study.

10.3 Clinical observations

For the interval between admission and the beginning of the abortion procedure, the subject will be observed for signs and symptoms of spontaneous abortion. All tissue which is spontaneously expelled from the uterus should be placed in a fixative and sent to the laboratory for proper histopathological identification of such tissue as being all or part of the products of conception. The macroscopic evaluation of an experienced observer concerning the source of the tissue should also be recorded on the case report form.

10.4 Recording of Uterine Contractility

Uterine contractility will be recorded by the microballoon technique or by a microtransducer. Following cleansing of the vagina the catheter will be introduced into the extra-amniotic space so that the tip of the catherter is approximately half way between the internal os and fundus. The catheter will be secured in position by two or three gauze pads and also taped to the thigh of the patient. Following connection of the catheter to the recording instrument basic contractility will be recorded for one hour at which time 400 mcg of misoprostol will be administered by mouth and will be followed by 4 hours of recording. A second dose of misoprostol will be given followed by two

hours of recording. Since the patient will undergo surgical intervention with inhalation anesthesia in the afternoon, they will not be given food or drink so that the contractility curves will remain undisturbed. The patient will remain in the dorsal position as much as possible and occasions of urination will be noted on the chart.

STUDY MANAGEMENT

11.1 Monitoring

The Searle Monitor will visit the investigator to monitor all aspects of the study. The investigator agrees to allow the monitor access to case record forms, drug supplies, drug inventory, etc., to allow such monitoring to be purposeful.

11.2 Code Breaks

The details of the specific treatment(s) randomly allocated to a subject will be contained in a sealed label, imprinted with the subject's study number.

This sealed label may be opened if it becomes necessary for the investigator to know the specific treatment received by the subject for therapeutic reasons.

The date and reason for breaking the code must be written on the adverse experience form which the investigator should sign and return to Searle.

All labels, whether opened or sealed, should be returned to the Searle Monitor at the end of the study.

11.3 Adverse Experiences

11.3.1 General

All adverse experiences will be recorded on the appropriate case report form.

They will be graded by the

investigator as mild, moderate or severe and as bearing the following causal relationship to treatment:

1. Mild
2. Moderate
3. Severe

Grade	Definition
Mild:	Annoying, but not requiring special medical management or attention.
Moderate:	Tolerable, but requiring medical management.
Severe:	Necessitating discontinuation of drug.

For this study, diarrhea is defined as the occurrence of 3 or more watery and/or loose stools within a 24 hour interval.

11.3.2 Serious or Unexpected Adverse Experiences

Any adverse experiences of a serious or unexpected nature, whether or not considered to be drug related, must be communicated to Searle immediately upon discovery of the events.

The investigator will be required to provide sufficient information to allow an FDA 1639 (CSM yellow card or local

country equivalent) to be completed. The monitor will advise the investigator regarding the information and documentation required.

11.3.3 Follow-up on Adverse Experiences

Any abnormal laboratory values, clinical findings or adverse experiences which are of clinical significance in the opinion of the clinical investigator must be followed with appropriate medical management until resolved. A rechallenge will be considered if it is both safe and ethical.

11.4 Withdrawal from study

The subject may express the intention of withdrawing from the study. If the subject means that she wishes only to stop taking the test medication but wishes to proceed with the scheduled abortion, then the subject in effect will be continued in the study with appropriate documentation of discontinuation of administration of the test article and the subject's reason if she wishes to give one.

If the subject wishes to have the measurements of uterine contracility discontinued, then the catheters will be removed and appropriate documentation of the event made, indicating time of discontinuation of measurement and any reason the patient may give for her decision to withdraw.

If the subject means that she has changed her mind and has decided to not have the previously scheduled pregnancy termination, the investigator will document that event and any stated reason the subject may wish to give. He will also remove any catheters that have been placed and not administer any more misoprostol. The time of those events are to be documented.

Animal teratology studies suggest that no adverse teratological experience is to be anticipated. Please refer to the Investigation Brochure for a summary of those studies.

Arrangements should be made to get follow-up information on the outcome of the pregnancy. If the subject refuses to comply with that request, a note should be made on the proper case report form.

11.5 Reporting Obligations

11.5.1 Case Report Forms

Searle case report forms are printed on NCR (no carbon required) paper to permit multiple copies. The bottom copy will be retained by the investigator for his files.

Data collected on each subject will be recorded on the case report forms provided. The investigator will be responsible for insuring that all the questions on the case report forms are answered fully. If certain data are not available, not done, or not applicable, the investigator will enter "N.Av.", "N.D.", or "N.Ap", respectively in the appropriate spaces.

The 24 hour clock should be used for all times entries (00.00-24.00).

Completed case report forms should be signed and dated by the registered investigator and be available for review.

The case report forms will be reviewed and evaluated for completeness and forms with errors or omissions will be returned to the investigator for correction. Changes or additions to the data must be made in the following manner: the original entry will be crossed out with a single line drawn through the error (not erased or whited out) so as to leave the original entry still legible. The correction should be entered in ink,

initialled and dated by the person making the correction. Only the registered investigator(s) may correct the data on the top copy form. The monitoring team may only enter corrections based on information received from the investigator.

In addition to the standard Searle Case Report Forms(CRF), the investigator will submit to Searle copies of the tracings made and a summary of the criteria used to determine the presence or absence of contractions.

11.5.2 Drug Inventory

The investigator (or his designate) will be responsible for dispensing and accounting for clinical supplies according to the local practice. A record of the drugs dispensed will be kept on the Drug Inventory form (Appendix 2). This form will be available to the Searle monitor for checking.

Under no circumstances will the investigator supply investigational drug to other investigators or clinics or allow the investigational drug to be used other than as directed by this protocol without prior authorization by Searle.

Clinical supplies assigned to a subject participating in the study and not consumed by that subject must be entered on the drug inventory form. These supplies must not be dispensed again even to the same subject.

At the end of the study or during a monitoring visit all returned or undispensed drugs will be checked against the drug inventory and any discrepancies must be resolved. When a satisfactory resolution has occurred, the unused drug will be removed and returned to Searle for destruction.

11.5.3 Investigator's Final Reporting

Accurate and complete case report forms for all participating subjects must be submitted to G.D.Searle within three months of the final

drug administration.

Any omissions in study paperwork must be explained and the required information, if available, submitted in an alternate form acceptable to Searle.

All significant adverse experiences must be described, with the investigator's opinion as to whether or not they were related to drug administration.

11.5.4 Maintenance of Records

The investigator will retain a copy of all the case report forms in accordance with the FDA or local regulations whichever are more stringent.

The FDA regulations are as follows: For two years following the date a New Drug Application (NDA) is approved or for two years after the U.S. Food and Drug Administration (FDA) has been notified that applicable clinical investigations have been discontinued or the governing Investigational New Drug Exemption (IND) is terminated.

If an application has been submitted but not approved the investigator is to maintain these records for a period of five years after the U.S. NDA was submitted.

The investigator is recommended to contact Searle before disposing of any study records.

11.5.5 Changes to the Protocol

Changes to the protocol require a protocol amendment and a new completed approval signature list. Changes to the protocol which materially affect the subject will require ethical committee review or peer review approval.

Changes to the protocol must be communicated to all the appropriate drug authorities.

12. STUDY EVALUATION

12.1 ANALYTIC CONSIDERATIONS

The procedures described in this protocol have been published in the scientific literature. However, definitive criteria for analysis cannot be stated beforehand. The principal investigator will set forth the criteria used as stated in the section under reporting obligations.

12.2 BIOSTATISTICAL CONSIDERATIONS

Any statistical methology that may be used will be determined after actual data have been received by Searle but before any breaking of the code.

Tabulations of adverse experiences recorded during the study will be made.

13. APPROVAL SIGNATURE LIST

Nils Wiqvist, M.D.
Professor and Chairman
Department of Obstetrics and Gynecology
University of Goteborg
Sahlgren's Hospital
Goteborg, Sweden

11 Sept. 84
Date

Francis B. O'Brien, Jr., M.D.
Associate Director
Obstetrics & Gynecology
Clinical Research
Searle Research and Development
Division of G.D.Searle & Co.
Skokie, Illinois 60077

26 SEP 84
Date

Robert N. Fowler, M.D.
Senior Director
International Clinical Research
Searle Research and Development
Division of G.D.Searle & Co.
Skokie, Illinois 60077

1 Oct 84
Date

Kenneth P. Tempero, M.D.
Senior Vice-President
Clinical Research &
Medical Affairs
Searle Research and Development
Division of G.D.Searle & Co.
Skokie, Illinois 60077

9/25/84
Date

14. REFERENCES

1. Investigational Brochure for Misoprostol (SC-29333) January 1983.

2. Dajani, E.Z.; Driskill, D.; Bianchi, R.; Collins, P. and Pappo, R.: SC 29333: A potent inhibitor of canine gastric secretion. Am. J. Dig. Dis. 21:1049-1057, 1976.

3. Dajani, E.Z. and Cook, D.L.: Sc-29333: A gastric antisecretory agent biological studies. G.D. Searle & Co. BRD-77D-1147, December 1977.

4. Colton, D.G.; Driskill, D.R.; Phillips, E.L.; Poy, P. and Dajani, E.Z.: Effect of SC 29333. An inhibitor of gastric secretion, on canine gastric mucosal blood flow and serum gastrin levels. Arch. Int. Pharmacodyn. Therap. 236:86-95, 1978.

5. Dajani, E.Z.; Callison, D. and Bertermann, R.: Effects of E-prostaglandins on canine gastric potential difference. Am. J. Dig. Dis. 23: 436-442, 1978.

6. Wiqvist,N.,Lindblom,B.,Wikland,M.Wilhemlsson,L.,. 1st Symposium on the Importance of Prostaglandins in Obstetrics and Gynecology, Are ,Sweden, April 12-16, 1981, Acta Obstet Gynecol Scand Suppl 0(113):23-30,1983

7. Wikland,M.,Lindblom,B.,Wihelmsson,L.Wiqvist,N.,Oxytocin Prostaglandins and Contractility of the Human Uterus at Term Pregnancy,Acta Obstet Scand, 6:467-472,1983

8. Wikland,M.,Lindblom,B.,Wilhemlmsson,L.,Wiqvist,N., Differentiated Contractile Properties of Isthmic and Corporal Segments of the Pregnant Human Uterus,21st Scandinavian Congress of Obstetrics and Gynecology, Gothenberg,Sweden June 8-12,1980, Acta Obstet Gynecol Scand Suppl. 0(93):25,1980

9. Wilhelmsson,L.,Wikland,M.,Wiqvist,N.,Prostaglandin E-2 Thromboxane A-2 and Prostaglandin I-2 Have Potent and Differentiated Actions on Human Uterine

Contractility,Prostaglandins,21(2):277-287,1983.

10. Wikland,M.,Lindblom,B.,Wiqvist,N.,Myometrial Response to Prostaglandins during Labor, Gynecol Obstetr Invest,17(30):131-138,1984

11. Wiqvist,N.,Lindbolm,B.,Wikland,M.,Wilhelmsson,L., Prostaglandins and Uterine Contratility,Acta Obstet Gynecol Scand [Suppl] 113:23-29,1983

12. Wikland,M.,Lindblom,B.,Wilhelmsson,L.,Wiqvist,N., Oxytocin, Prostaglandins, and Contractility of the Human Uterus at Term, Acta Obstet Gynecol Scand, 61:467-472,1982

13. Green,K.,Granstrom,E.,Bygdeman,M.,Wiqvist,N., Kinetic and Metabolic Studies of 15-methyl Prostaglandin F2alpha administrered Intra-amniotically for Induction of Abortion, Prostaglandins 11:699-671,1976

14. Wiqvist,N.,Beguin,P.,Bydgeman,M.,Toppozada,M., 15 (S)-Methyl-Prostaglandin F2alpha: Myometrial Response and Abortifacient Efficacy, Adv Biosci 9:831,842,1973

15. Wiqvist,N.,Martin,J.N.,Bygdeman,M.,Green,K., Prostaglandin Analogues and Uterotonic Potency: a Comparative Study of Seven Compounds, Prostaglandins 9:255-269,1975

APPENDIX I

DECLARATION OF HELSKINKI

DECLARATION OF HELSINKI

RECOMMENDATIONS GUIDING MEDICAL DOCTORS IN BIOMEDICAL RESEARCH

Adopted by the 18th World Medical Assembly

Helsinki, Finland, 1964

and as revised at Tokyo, 1975

GUIDING PRINCIPLES

WORLD MEDICAL ASSOCIATION - DECLARATION OF GENEVA

"The health of my patient will be my first consideration"

INTERNATIONAL CODE OF MEDICAL ETHICS

"Any art or advice which could weaken physical or mental resistance of a human being may be used only in his or her interest."

These standards are guides only and cannot relieve doctors from criminal, civil or ethical responsibilities under the laws of their own countries

1. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment, and guidance.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study of the subject's physical and mental integrity and on the personality of the subject.

7. Doctors should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Doctors should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the doctor is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The doctor should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the doctor should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. in that case the informed consent should be obtained by a doctor who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain permission from the responsible relative replaces that of the subject in accordance with legislation.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined With Professional Care
(Clinical Research)

1. In the treatment of the sick person, the doctor must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomforts of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the doctor/patient relationship.

5. If the doctor considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (1, 2).

6. The doctor can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-Therapeutic Biomedical Research I

(Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers--either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

APPENDIX II

INVESTIGATIONAL BROCHURE

(SEPARATE ATTACHMENT)

APPENDIX III

CASE REPORT FORMS

(TO BE ATTACHED LATER)

Stimulating Potential Of Cytotec™

IC4-84-02-048
Admission Criteria

SEARLE

Do NOT place on other NCR forms while filling in - Use black ballpoint or type. CRF 1 of 9

Investigator Name			Study Site
Nils Wiqvist, M.D.			Goteborg, Sweden
Subject First Name	M.I.	L.I.	Subject Study No.

I. Informed Consent

Was written informed consent obtained?

☐ No DO NOT ADMIT TO STUDY. ☐ Yes - Date Obtained Da | Mo | Yr

II. Inclusion Criteria

If any one of the criteria listed below is checked "No", DO NOT ADMIT subject to study.

	NO	YES
1. The subject is of legal age of consent	☐	☐
2. The subject's onset of last normal senses is between 11 and 12 weeks inclusive (uterus is 11-12 weeks in size)	☐	☐
3. The subject has a diagnosis of pregnancy that has been confirmed by blood pregnancy test	☐	☐
4. The subject has a diagnosis of intrauterine pregnancy that has been confirmed by physical examination	☐	☐
5. The subject is scheduled for legal interruption of a first trimester pregnancy	☐	☐

III. Exclusion Criteria

If any one of the criteria listed below is checked "Yes", DO NOT ADMIT subject to study.

	NO	YES
1. The subject shows signs or symptoms of spontaneous abortion	☐	☐
2. The subject has a history of sensitivity to prostaglandins	☐	☐
3. The subject exhibits symptoms or has a history of cardiovascular or pulmonary disease, inflammatory bowel disease (ulcerative colitis, Crohn's disease) diabetes mellitus, disorders of blood coagulation, sickle cell anemia, functional renal impairment or glomerulonephritis, epilepsy	☐	☐
4. The subject has received antiabortion therapy during the current pregnancy	☐	☐

Principal Investigator's Signature	Date Da	Mo	Yr

Evaluation Of Uterine Contractility Stimulating Potential Of Cytotec™

IC4-84-02-048
Medical History - Part 1

SEARLE

Do NOT place on other NCR forms while filling in - Use black ballpoint or type.

Investigator Name	Study Site
Nils Wiqvist, M.D.	Goteborg, Sweden
Subject First Name / M.I. / L.I.	Subject Study No.

I. Date of Visit

Da | Mo | Yr

II. Subject Data

1. Date of Birth	2. Sex	3. Race
Da - Mo - Yr	Female	☐ Caucasian ☐ Negro ☐ Oriental ☐ Other, specify. _____

III. Initial Medical History

Does subject have a history of, or currently have, an abnormality or disease in any of the following systems? If yes, describe.

System	No	Yes - Description
1. Neurologic		
2. Psychiatric		
3. Cardiovascular		
4. Bronchopulmonary		
5. Gastrointestinal		
6. Urogenital		
7. Hepatic		
8. Hematologic		
9. Endocrine		
10. Musculoskeletal		
11. Dermatologic		
12. Immunologic Include Drug Allergy		
13. Chronic Addiction Alcohol, Tobacco, Caffeine		

Principal Investigator's Signature	Date Da / Mo / Yr

Investigator Name	Study Site
Nils Wiqvist, M.D.	Goteborg, Sweden
Subject First Name / M.I. / L.I.	Subject Study No.

IV. History Of Present Pregnancy

1. Date of the first day of the last normal menstrual period: Da _____ Mo _____ Yr _____

2. Gravidity _____ _____ Parity _____ _____

3. Has bleeding occured since the last menstrual period? ☐ No ☐ Yes-If so, give date:
Date: Da _____ Mo _____ Yr _____

4. Has cramping occurred since the last menstrual period? ☐ No ☐ Yes

Principal Investigator's Signature	Date Da / Mo / Yr

Stimulating Potential Of Cytotec™

IC4-84-02-048
Physical Examination - Part 1

SEARLE

Do NOT place on other NCR forms while filling in - Use black ballpoint or type.

Investigator Name			Study Site
Nils Wiqvist, M.D.			Goteborg, Sweden
Subject First Name	M.I.	L.I.	Subject Study No.

I. Date of Visit

Da | Mo | Yr

II. Subject Data

1. Height	2. Weight	3. Temperature	4. Pulse	5. Sitting Blood Pressure
cm.	kg.	°C	/min.	mm H

III. Physical Examination

Describe abnormal findings.

Examination	Not Done	Normal	Abnormal	Description
1. Eyes Include Funduscopic				
2. Ears, Nose, Throat				
3. Neck Include Thyroid				
4. Heart				
5. Lungs				
6. Abdomen Include Liver & Spleen				
7. Rectum				
8. External Genitalia				
9. Lymph Nodes				
10. Extremities Include Peripheral Pulses				
11. Neurologic				
12. Skin Include Accessory Structures				

Principal Investigator's Signature	Date
	Da / Mo / Yr

Investigator Name	Study Site
Nils Wiqvist, M.D.	Goteborg, Sweden
Subject First Name / M.I. / L.I.	Subject Study No.

IV. Pelvic Examination

Size of Uterus:
☐ 11-12 weeks ☐ Other, specify: _____

	General Condition	Any Abnormalities? No	Yes - Describe
1. Cervix	☐ Soft ☐ Medium ☐ Rigid		
2. External/OS	☐ Closed ☐ Open		
3. Adnexa	☐ Normal ☐ Abnormal - Describe _____		

V. Medication

List all medications taken during pregnancy, to date.
Include over the counter preparations.

☐ None

Drug Name Generic Preferred	Dose	Regimen	Start Date Da / Mo / Yr	Stop Date Da / Mo / Yr	Reason for Therapy
				☐ Continuing	
				☐ Continuing	
				☐ Continuing	
				☐ Continuing	
				☐ Continuing	

Principal Investigator's Signature	Date Da / Mo / Yr

Evaluation Of Uterine Contractility Stimulating Potential Of Cytotec™

IC4-84-02-048

Pre-Operative Laboratory Data

SEARLE

Do NOT place on other NCR forms while filling in - Use black ballpoint or type. CRF 6 of 9

Investigator Name	Study Site
Nils Wiqvist, M.D.	Goteborg, Sweden
Subject First Name / M.I. / L.I.	Subject Study No.
Laboratory Site	

I. Hematology

Values within the normal range do not require explanation.

Date Sample Collected | Da | Mo | Yr | Date Sample Analyzed | Da | Mo | Yr

Test	Not Done	Value	TO BE COMPLETED FOR OUT OF RANGE VALUES ONLY: Clinically Significant Abnormality? No	Yes	Description	Monitor Evaluat No	Yr
1. Hemoglobin							
2. Hematocrit							
3. RBC x 10^6							
4. WBC x 10^3							
5. Polys/Neutrophils							
6. Bands							
7. Lymphocytes							
8. Monocytes							
9. Eosinophils							
10. Basophils							
11. Platelet Estimate							

II. Urinalysis

Values within the normal range do not require explanation.

If the value is other than negative, enter in the space provided.

Date Sample Collected | Da | Mo | Yr | Date Sample Analyzed | Da | Mo | Yr

Test	Not Done	Value	TO BE COMPLETED FOR OUT OF RANGE VALUES ONLY: Clinically Significant Abnormality? No	Yes	Description	Monitor Evaluat No	Yr
1. Acetone		☐ Negative					
2. Albumin		☐ Negative					
3. Glucose		☐ Negative					

Searle Monitor's Signature	Date Da / Mo / Yr	Principal Investigator's Signature	Date Da / Mo / Yr

Stimulating Potential Of Cytotec™

IC4-84-02-048
Administration of Drug and Procedure

SEARLE

Do NOT place on other NCR forms while filling in - Use black ballpoint or type.

CRF 7 of 9

Investigator Name	Study Site
Nils Wiqvist, M.D.	Goteborg, Sweden
Subject First Name / M.I. / L.I.	Subject Study No.

I. Date of Procedure

Da | Mo | Yr

II. Administration Record Of Study Test Article

1. Insertion of Microballoon/Transducer	_____ (Military Time)
2. Starting of recording	_____ (Military Time)
3. First dose of study test article	_____ (Military Time)
4. Second dose of study test article	_____ (Military Time)
5. Termination of recording	_____ (Military Time)
6. Vacuum Aspiration started	_____ (Military Time)

III. Surgical Procedure

Time surgical procedure began: _____ (Military Time)
Time surgical procedure ended: _____ (Military Time)

IV. Complications During Surgery

☐ None

V. Adverse Experiences

Were there any adverse experiences?

☐ No ☐ Yes-complete Adverse Experience Form

Principal Investigator's Signature	Date
	Da / Mo / Yr

Investigator Name	Study Site
Nils Wiqvist, M.D.	Goteborg, Sweden
Subject First Name / M.I. / L.I.	Subject Study No.

I. Uterine Tracings

Attatch to this form.

Principal Investigator's Signature	Date Da / Mo / Yr

Stimulating Potential Of Cytotec™

IC4-84-02-048
End of Study Participation

SEARLE

Do NOT place on other NCR forms while filling in - Use black ballpoint or type. CRF 9 of 9

Investigator Name	Study Site
Nils Wiqvist, M.D.	Goteborg, Sweden
Subject First Name / M.I. / L.I.	Subject Study No.

I. Date and Time of Last Dose of Study Test Article

Date	Military Time
Da / Mo / Yr	

II. Date and Reason Subject Ended Participation in Study

1. Date Da____ Mo____ Yr____

2. Reason
Check one box only.

- ☐ Subject Completed Study
  or
- ☐ Adverse Experience — Complete Adverse Experience Form.
  or
- ☐ Protocol Deviation — Explain ____
  or
- ☐ Other Reason — Explain ____

III. Concurrent Medication

List all concurrent medication taken during the course of the study (including pre-operative medications.)

☐ None

Drug Name Generic Preferred	Dose	Regimen	Start Date Da / Mo / Yr	Stop Date Da / Mo / Yr	Reason for Therapy
				☐ Continuing	
				☐ Continuing	
				☐ Continuing	
				☐ Continuing	
				☐ Continuing	

Principal Investigator's Signature	Date Da / Mo / Yr

Evaluation Of Uterine Contractility Stimulating Potential Of Misoprostol
1C4-84-02-048

SEARLE

Adverse Experiences Form

Use black ballpoint or type. Do NOT place on other NCR forms while filling in

Investigator Name	Study Site
Subject First Name M.I. L.I.	Study Number

I.

No	Description of Event	Began Day / Mo / Yr / Military Time	Ended Day / Mo / Yr / Military Time	Attributed to Treatment No / Yes / Unknown	Severity* Mild / Mod / Sev	Outcome**	Monitor's Evaluation No / Yes / Unknown / Not An Adv. Ex.
1.			☐ Continuing			☐ A ☐ S ☐ R ☐ D	
2.			☐ Continuing			☐ A ☐ S ☐ R ☐ D	
3.			☐ Continuing			☐ A ☐ S ☐ R ☐ D	

* Key for Severity
Mild - Annoying but not requiring special medical management Mod. - Tolerable, but requiring medical management or attention Sev. - Necessitating discontinuation of drug

** Key for Outcome
A - Alive with sequelae R - Recovered S - Still under treatment, follow-up is required D - Died - Give date and cause in Investigator's Comments section.

A38

II. Was subject discontinued from study because of an adverse experience?

☐ No ☐ Yes If yes, identify event(s) by number _____

If subject continued in study, was the study drug(s) reduced in dosage?

☐ No ☐ Yes ☐ Not Applicable

III. Investigator's Comments
Include any medication given for treatment of adverse experience(s). Identify event by number.

☐ No Comment

IV. Searle Monitor's Comments

☐ No Comment

Monitor's Signature	Date	Principal Investigator's Signature	Date

Description of Serious Adverse Events Reported Following Cytotec Administration For Induction of Labor or Abortion

Case	Indication	Gestational Age	Mode of Drug Delivery	SAE	Country
SK 848 (aka SK 850)	Abortion	<20 weeks	Intravaginal	Uterine rupture	USA
SK 651	Abortion	20 weeks	Intravaginal	Uterine rupture	S. Africa
SK 161	Labor induction	Term	Intravaginal	Uterine rupture	USA
SK 162	Labor induction	Term	Intravaginal	Uterine rupture	USA
SK 733	Abortion	≤ 8-26 weeks	Oral + intravaginal	Uterine perforation	Brazil
SK 735	Abortion	≤ 8-26 weeks	Oral + intravaginal	Uterine perforation	Brazil
SK 736	Abortion	≤ 8-26 weeks	Oral + intravaginal	Uterine perforation	Brazil
SK 024	Abortion	18 weeks	Intravaginal	Uterine rupture	UK
SK 994	Labor induction	39 weeks	Intravaginal	Uterine rupture	USA
SK 060	Labor induction	40+ weeks	Intravaginal	Uterine rupture	USA
SK 323	Suicide attempt	31 weeks	Oral	Vaginal hemorrhage, hyperthermia, abortion, fetal death	USA
SK 567	Abortion	10-11 weeks	Oral	Severe vaginal bleeding	USA
SK 586	Abortion	23 weeks	Oral	Fetal death	USA
MedWatch 22753	Abortion	Unknown	Unknown	Hemorrhage, surgery required	USA
SK 495	Labor induction	36 weeks	Oral + intravaginal	Hyperthermia, hypotension, fetal death	USA
SK 452	Labor induction	41 weeks	Intravaginal	Amniotic fluid embolism, maternal and fetal death	USA
SK 133	Prophylaxis post-partum hemorrhage	41 weeks	Oral	Hyperthermia	Singapore

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

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 (FL)	**Uterine rupture.**	Unk	Unk	Unk	Vaginal	Induce abortion
961022-SK850	1996	US (FL)	**Uterine rupture.**	Unk	Unk	Unk	Vaginal	Induction of labor
970714-SK994	1996	US (FL)	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 (CA)	**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 (CA)	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.

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)

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)

List faxed to Debra Hawks 9/18/00 BC

Attn: Medwatch - reporting

1-800-332-0178

This Fax contains 2 pages including this page.

2 of 2
MER#74036

RECEIVED AT DRUG SAFETY SURVEILLANCE

14-JAN-1998-0154

UNTARY reporting
professionals of adverse
and product problems

MEDWATCH

EDICAL PRODUCTS REPORTING PROGRAM

CDER

Page ___ of ___

FDA Use Only

Triage unit sequence # 75828

ent information

entifier	2. Age at time of event: 26yo or Date of birth:	3. Sex ☒ female ☐ male	4. Weight ___ lbs or ___ kgs

erse event or product problem

erse event and/or ☐ Product problem (e.g., defects/malfunctions)

es attributed to adverse event (check all that apply)

n ___ (mo/day/yr)

hreatening

pitalization – initial or prolonged

☐ disability

☐ congenital anomaly

☒ required intervention to prevent permanent impairment/damage

☐ other: ___

10/21/97

4. Date of this report (mo/day/yr) 11/17/97

e event or problem

10/21 Misoprostol 50mg placed in upper vagina by MD

at 2340 2nd dose of Misoprostol placed per vagina by MD

pt experienced abd pain monitors showed no contractions. pt had vag bleeding MD confirmed suspected rupture

10/22 10am pt taken to surgery.

Called 2/10/98

vant tests/laboratory data, including dates

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM
HF-2

JAN 14 1998

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

previous C-section 38.4 wks c̄ fetal demise
EDC 10/30/97

C. Suspect medication(s)

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

#1 Misoprostol 100mg tab

#2

2. Dose, frequency & route used

#1 50mcg per vag

#2

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

#1 10/21/97

#2

4. Diagnosis for use (indication)

#1 Induction of labor 2° fetal demise

#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)

previous C-section

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

REC'D.

4. Operator of device

☐ health professional

☐ lay user/patient

☐ other:

5. Expiration date (mo/day/yr)

6.

model #

JAN 14 1998

catalog #

serial #

MEDWATCH CTU

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 #

2. Health professional? ☑ yes ☐ no

3. Occupation

Pharmacist

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

332

FDA

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

SUMMIT PHARMACY Fax 510-869-6753

RECEIVED AT DRUG SAFETY SURVEILLANCE
14-JAN-1998-0154

VOLUNTARY report of professionals of adverse events and product problems

Individual Safety Report
3015209-1-00

MEDWATCH
FDA MEDICAL PRODUCTS REPORTING PROGRAM (HFE-

Page ___ of ___

Patient information

Patient identifier / confidence

2. Age at time of event: 26yo or Date of birth:

3. Sex: ☒ female ☐ male

4. Weight: ___ lbs or ___ kgs

Adverse event or product problem

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

Outcomes attributed to adverse event (check all that apply)

☐ death ___ (mm-dd-yyyy)
☐ life-threatening
☐ hospitalization – initial or prolonged
☐ disability
☐ congenital anomaly
☒ required intervention to prevent permanent impairment/damage
☐ other: ___

Date of event (mm/dd/yy): 10/21/97

4. Date of this report (mm/dd/yy): 11/7/97

Describe event or problem

on 10/21 Misoprostol 50mg placed ~~PARA~~ in upper vagina by MD

at 2340 2nd dose of Misoprostol placed per vagina by MD

pt experienced abd pain minimal shortly after contractions. pt had vag bleeding MD confirmed suspected rupture

10/22 10am pt taken to surgery.

Relevant tests/laboratory data, including dates

MEDWATCH THE FDA MEDICAL PRODUCTS REPORTING PROGRAM
HF-2

JAN 14 1998

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

primary C-section
EDC 10/30/97 38.4 wks c fetal demise

C. Suspect medication(s)

1. Name (give labeled strength & manufacturer, if known)
#1 Misoprostol 100mg tab
#2

2. Dose, frequency & route used
#1 50mcg per vag
#2

3. Therapy dates (if unknown, give duration)
#1 10/21/97
#2

4. Diagnosis for use (indication)
#1 Induction of labor 2° fetal demise
#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)
primary C-section

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address
75827
REC'D.
JAN 14 1998
MEDWATCH CTU
4. Operator of device
☐ health professional
☐ lay user/patient
☐ other:
5. Expiration date (mm-dd-yy)
6. model # / catalog # / serial # / lot # / other #
7. If implanted, give date (mm-dd-yy)
8. If explanted, give date (mm-dd-yy)
9. Device available for evaluation? (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on ___ (mm-dd-yy)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name & address
phone
2. Health professional? ☒ yes ☐ no
3. Occupation: pharmacist
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. ☐

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

332

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

RECEIVED AT DRUG SAFETY SURVEILLANCE K. / FAX NO. 7373704000

04-DEC-1997-0395

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

OL
lth
events a
Pag

Individual Safety Report

3007564-3-00

10-0291 Expires 12/31/98
See placement on reverse

36

A. Patient information

1. Patient Identifier	2. Age at time of event: or Date of Birth:	3. Sex	4. Weight
In confidence	35	☒ female ☐ male	192 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 11/15/97 (Fetal) (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): 11/15/97

4. Date of this report (mo/day/yr): 12/4/97

5. Describe event or problem

G5P2 gestational diabetic (diet controlled) admitted for induction of labor @1745 11/14/97

Given cytotec 25mcg (¼x100mcg) vaginally @1935 (contractions = 0, membranes intact, closed thick cervix).

Given second cytotec 25mcg vaginally @2320 (contractions = 4/10min, cervix finger tip dil and thick. At 0208 ROM, cervix 2-3 cm, no contractions reported

@0218 pt c/o pain, fetus presenting breech - off monitor moving to L&D.

@0239 on monitor - FHT 130 but not presenting @ cervix - MD responded & ultrasound etc.

@0306 - Stat C-section & uterine rupture fetus + placenta in abdominal cavity. fetus expired. Mom ~~went~~ underwent hysterectomy & survived.

6. Relevant tests/laboratory data, including dates

Uterine tissue showed infect c/s scar anteriorly & large rupture of posterior wall which was noted to contain multiple transmural fibroids.

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

Gestational diabetic (diet controlled)

Patient was VBAC (previously tested)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
- #1 Misoprostil 100 mg tablet C.D. Searle
- #2

2. Dose, frequency & route used
- #1 25mcg - x2 - vaginal
- #2

3. Therapy dates (if unknown, give duration)
- #1 11/14 - 11/15
- #2

4. Diagnosis for use (indication)
- #1 Cervical ripening
- #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)
- – –

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

RECD. DEC 08 1997 MEDWATCH CTU

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)

E. Reporter (see confidentiality section on back)

[redacted]

☒ yes ☐ no | Pharmacist

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

☐ user facility
☐ distributor

FDA

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.

Approved by FDA on September 17, 1993

3477116-X-00-01

U.S. REPORTING

Drug Experience Report

Searle Research and Development

MFR report # 000302-SK676

UF/Dist 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 (mo/day/yr) ☐ life-threatening ☑ hospitalization - initial or prolonged ☐ disability ☐ congenital anomaly ☐ required intervention to prevent permanent impairment/damage ☑ other: Medically Significant

3. Date of event (mo/day/yr): Unknown

4. Date of this report (mo/day/yr): MAR 13 2000

5. Describe event or problem

Plaut, M.M., MD, Schwartz, M.L., MD, Lubarsky, S.L., MD. Uterine Rupture Associated With The Use Of Misoprostol In The Gravid Patient With A Previous Cesarean Section. Am J Obstet Gynecol 1999; 180 (6) 1535 - 1542.

In this article we report 7 cases of uterine rupture after the use of misoprostol in gravid patients with a previous cesarean section.

Patient 1: "A 26-year-old woman, gravida 6, para 3-0-2-3, underwent induction of labor a 39 weeks 6 days' gestation because of maternal exhaustion after repeated visits to the labor and delivery suite for prodromal labor. Her first baby had been born vaginally. Her second child was delivered by low transverse cesarean section because of a footling breech presentation. The third was a successful VBAC after oxytocin induction at 41 weeks. The current pregnancy was complicated by laparotomy at 8 weeks' gestation for diagnosis of tubo-ovarian torsion. She had diet-controlled gestational diabetes and smoked 1 pack of cigarettes a day.

At the time of the decision to induce labor, she was having only sporadic contractions and had a Bishop score of 4. Misoprostol, 25 mcg (one quarter of a 100 mcg tablet prepared by the pharmacy), was placed in the

(continues...)

6. Relevant test/laboratory data, including dates

CENTER FOR ... REC'D MAR 16 2000 CDR EVALUATION AND RESEARCH

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

CONCOMITANT ILLNESSES: CESAREAN SECTION NOS; PREG STATE, INCIDENTAL; CEPHALIC VERSION NOS; ABNORMAL GTT IN PREG; TORSION OF OVARY OR TUBE; HISTORY OF TOBACCO USE

DSS

MAR 17 2000

C. Suspect medication(s)

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

#1 MISOPROSTOL

#2

2. Dose, frequency & route used

#1 25.000 MCG VAG

#2

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

#1 2 DOSES

#2

4. Diagnosis for use (indication)

#1 MEDICAL INDUCTION LABOR

#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)

OXYTOCIN	Unknown - Unknown
ANAESTHETICS	Unknown - Unknown

G. All manufacturers

1. Contact office - name/address

Dennis P. Miley, M.D.
G.D. Searle and Co.
9855 Woods Drive
Skokie, Illinois 60077

2. Phone number: (847) 581-7874

3. Report source (check all that apply)

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

4. Date received by manufacturer (mo/day/yr): MAR 2 2000

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
FETAL DISTRESS
DRUG EXPOSURE DURING PREGNANCY

9. Mfr. report number: 000302-SK676

E. Initial reporter

1. Name, address & phone #

MM Plaut MD
12607 SE Mill Plain Blvd.

Vancouver, WA 98684
UNITED STATES

Telephone Nr: Unknown

MAR 16 2000

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.

000302-SK676

000302-SK676

MISOPROSTOL

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

U.S. REPORTING
RLE **Drug Experience Report**
Searle Research and Development

Approved by FDA on September 17, 1993

MFR report # 000302-SK676
UF/Distr report #
FDA Use Only

000302-SK676

B. Adverse event or product problem (continued)

5. Describe event or problem

posterior vaginal fornix. At 4.5 hours later the cervix was unchanged, and her contractions were every 4 to 7 minutes. A second 25 mcg misoprostol was given intravaginally. After 3 more hours intravenous oxytocin was begun and gradually increased during the next 9 hours to 10 mU/min. During this time she had spontaneous rupture of membranes with clear fluid; she received an epidural anesthetic, and the cervix became completely dilated. The fetal heart tracing remained reactive, with intermittent variable decelerations to 90/min. No tachysystole was noted.

Shortly after pushing began, the fetal heart rate dropped abruptly to 60/min, and the fetal head could no longer be palpated in the vagina. She was immediately brought to the operating department, where laparotomy was performed while she was under general anesthesia. The baby was free in the abdominal cavity, and a 4-cm defect in the dome of the bladder was noted. The infant weight 3969 g and had Apgar scores of 1, 4, 4, 4, and 8 at 1, 5, 10, 15, and 20 minutes, respectively. The arterial cord blood pH was 6.78. Both the bladder and uterine defects were easily repaired, and the estimated blood loss was 750 mL. Mother and baby recovered quickly and went home together on the third postoperative day. The baby was nursing well and had no obvious sequelae." This is the first of 7 reports. The other reports are uterine rupture (000303-SK965, 000303-SK967, 000303-SK968, 000303-SK972, 000303-SK975, 000303-SK976).

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

REPRINT
INCLUDED IN REFERENCE
LIST

8 pages

PRINT DATE: 14-MAR-2000 07:46:28

Approved by FDA on September 17, 1993

Individual Safety Report

3477115-8-00-01

U.S. REPORTING

Drug Experience Report

Searle Research and Development

• 1 of 2

Mfr report # 000303-SK965

UF/Diet report #

FDA Use Only

000303-SK965

A. Patient information

1. Patient Identifier	2. Age at time of event: / or Date of birth:	3. Sex	4. Weight
--- In confidence	36 Yrs	☑ 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 ____ (mo/day/yr)
☐ life-threatening
☑ hospitalization - initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☑ other: Medically Significant

3. Date of event (mo/day/yr): Unknown

4. Date of this report (mo/day/yr): MAR 13 2000

5. Describe event or problem

Plaut, M.M., MD, Schwartz, M.L., MD, Lubarsky, S.L., MD. Uterine Rupture Associated With The Use Of Misoprostol In The Gravid Patient With A Previous Cesarean Section. Am J Obstet Gynecol 1999; 180 (6) 1535 - 1542.

In this article we report 7 cases of uterine rupture after the use of misoprostol in gravid patients with a previous cesarean section.

Patient 2: "A 36-year-old woman, gravida 4, para 2-0-1-1, underwent induction of labor at 39 weeks 6 days' gestation because of suspected macrosomia. Her previous deliveries had both been by low transverse cesarean section, the first because of breech presentation and the second because of fetal distress. The first child died of cardiac defects. During the current pregnancy she had undergone a successful version from breech presentation at 37 weeks' gestation.

At the time of induction she had a Bishop score of 4 and occasional mild contractions. Two 25 mcg doses of misoprostol were placed in the posterior fornix 3 hours apart. This procedure caused her to enter labor, and 9 hours after the second dose the cervix was 6 cm dilated.

An epidural catheter was placed, and artificial rupture

(continues...)

6. Relevant test/laboratory data, including dates

CENTER FOR DRUG EVALUATION AND RESEARCH REC'D MAR 16 2000 CDR

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

CONCOMITANT ILLNESSES: CESAREAN SECTION NOS; PREG STATE, INCIDENTAL; EXCESSIVE FETAL GROWTH; PREG W POOR OBSTETRIC HX

DSS

MAR 17 2000

C. Suspect medication(s)

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

#1 MISOPROSTOL

#2

2. Dose, frequency & route used

#1 25.000 MCG VAG

#2

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

#1 2 DOSES

#2

4. Diagnosis for use (indication)

#1 MEDICAL INDUCTION LABOR

#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)

ANAESTHETICS Unknown - Unknown

G. All manufacturers

1. Contact office - name/address

Dennis P. Miley, M.D.
G.D. Searle and Co.
9855 Woods Drive
Skokie, Illinois 60077

2. Phone number: (847) 581-7874

3. Report source (check all that apply)

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

4. Date received by manufacturer (mo/day/yr): MAR 2 2000

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
FETAL DISTRESS
DRUG EXPOSURE DURING PREGNANCY

9. Mfr. report number: 000303-SK965

E. Initial reporter

1. Name, address & phone #

MM Plaut MD
12607 SE Mill Plain Blvd.
Vancouver, WA 98684
UNITED STATES

Telephone Nr: Unknown

MAR 16 2000

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.

000303-SK965

Approved by FDA on September 17, 1993

Individual Safety Report
3477115-8-00-02

U.S. REPORTING

Drug Experience Report

Searle Research and Development

MFr report # 000303-SK965

UF/Dist report #

FDA Use Only

000303-SK965

B. Adverse event or product problem (continued)

5. Describe event or problem

of membranes revealed clear fluid. Up to this time the tracing had been reassuring, and there was no uterine tachsystole. During the next 1.5 hours she made rapid progress and had some repetitive decelerations, some of which appeared to be late decelerations. Shortly after complete dilation occurred, there was a sudden bradycardia to 60/min. which lasted 5 minutes. When this bradycardia recurred, she was brought to the operating department, and laparotomy while she was under the existing epidural anesthesia revealed a large clot overlying the previous uterine incision. Blunt dissection through the hematoma revealed complete separation of the incision. Delivery was assisted by upward vaginal pressure because of low fetal station.

The baby weighed 4160 g and Apgar scores were 1, 4, 5, and 8 at 1, 5, 10 and 15 minutes, respectively. The arterial cord blood pH was 6.98. A cervical laceration related to delivery and the uterine rupture site were repaired without significant difficulty. There was an irregular shape to the fundus, thought to be caused by either a fundal myoma or a septate uterus. The estimated blood loss was 2000 mL; 1 U packed red blood cells was transfused during surgery. Both mother and baby did well and went home on the third postoperative day.' This is the second of 7 reports. The other reports are uterine rupture (000302-SK676, 000303-SK967, 000303-SK968, 000303-SK972, 000303-SK975, 000303-SK976).

Approved by FDA on September 17, 1993

Individual Safety Report — CHARLE

3477110-9-00-01

U.S. REPORTING

Drug Experience Report

Searle Research and Development

Page 1 of 2

Mfr report # 000303-SK967

UF/Dist report #

FDA Use Only

000303-SK967

A. Patient information

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

In confidence

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: Medically Significant

3. Date of event (mo/day/yr): Unknown

4. Date of this report (mo/day/yr): MAR 13 2000

5. Describe event or problem

Plaut, M.M., MD, Schwartz, M.L., MD, Lubarsky, S.L., MD. Uterine Rupture Associated With The Use Of Misoprostol In The Gravid Patient With A Previous Cesarean Section. Am J Obstet Gynecol 1999; 180 (6) 1535 - 1542.

In this article we report 7 cases of uterine rupture after the use of misoprostol in gravid patients with a previous cesarean section.

Patient 3: "A 27-year-old woman, gravida 2, para 0-1-0-1, underwent induction of labor at 38 weeks because of insulin-dependent diabetes after an amniocentesis confirmed fetal lung maturity. Her previous delivery was a low transverse cesarean section performed because of intrauterine growth restriction and transverse lie at 33 weeks. At the time of induction she had a Bishop score of 6 and no significant contractions. She received 1 dose of 25 mcg misoprostol intravaginally, which caused regular contractions. After 6 hours with no cervical change, oxytocin was begun at 1 mU/min and increased during the next hour to 3 mU/min. The tracing remained reactive without decelerations or tachysystole.

One hour after oxytocin was started, the patient had acute onset of severe abdominal pain. Cervical examination revealed no change, and the fetal heart rate

(continues...)

6. Relevant test/laboratory data, including dates

CENTER FOR DRUG EVALUATION AND RESEARCH REC'D MAR 16 2000 CDR

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

CONCOMITANT ILLNESSES: CESAREAN SECTION NOS; PREG STATE, INCIDENTAL; DIABETES MELLITUS

DSS

MAR 17 2000

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.

C. Suspect medication(s)

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

#1 MISOPROSTOL

#2

2. Dose, frequency & route used

#1 25.000 MCG VAG

#2

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

#1 1 DOSE

#2

4. Diagnosis for use (indication)

#1 MEDICAL INDUCTION LABOR

#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)

OXYTOCIN Unknown - Unknown

G. All manufacturers

1. Contact office - name/address

Dennis P. Miley, M.D.
G.D. Searle and Co.
9855 Woods Drive
Skokie, Illinois 60077

2. Phone number: (847) 581-7874

3. Report source (check all that apply)

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

4. Date received by manufacturer (mo/day/yr): MAR 2 2000

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
DEATH NEONATAL
FETAL DISTRESS
DRUG EXPOSURE DURING PREGNANCY

9. Mfr. report number: 000303-SK967

E. Initial reporter

1. Name, address & phone #

MM Plaut MD
12607 SE Mill Plain Blvd.
Vancouver, WA 98684
UNITED STATES

Telephone Nr: Unknown

MAR 16 2000

2. Health professional? ☑ yes ☐ no

3. Occupation: MD

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

Approved by FDA on September 17, 1993

3477110-9-00-02

U.S. REPORTING

RLE **Drug Experience Report**

Searle Research and Development

Page 2 of 2

Mfr report # 000303-SK967

UF/Distr report #

FDA Use Only

000303-SK967

B. Adverse event or product problem (continued)

5. Describe event or problem

was difficult to auscultate but was noted to be 130/min by ultrasonography. Uterine rupture was suspected on the basis of physical examination and fetal heart rate decelerations. Emergency laparotomy was performed with the patient under general anesthesia, revealing complete separation of the uterine scar, with fetus and placenta both free in the abdominal cavity. The baby weighed 2860 g and had Apgar scores of 1, 5, 6, 6, and 7 at 1, 5, 10, 15, and 20 minutes, respectively. Cord pH was unobtainable because the blood clotted. The uterine defect was easily repaired, and the estimated blood loss was 1400 mL.

The mother's postoperative course was uncomplicated, and she was discharged on the fourth postoperative day. The baby subsequently died in the intensive care unit." This is the third of 7 reports. The other reports are uterine rupture (000302-SK676, 000303-SK965, 000303-SK968, 000303-SK972, 000303-SK975, 000303-SK976).

DSS
MAR 17 2000

MAR 16 2000

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.

Approved by FDA on September 17, 1993

Individual Safety Report

3477108-0-00-01

U.S. REPORTING

Drug Experience Report

Searle Research and Development

Page 1 of 2

Mfr report # 000303-SK968

UF/Distr report #

FDA Use Only

000303-SK968

A. Patient information

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

In confidence

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: Medically Significant

3. Date of event (mo/day/yr): Unknown

4. Date of this report (mo/day/yr): MAR 13 2000

5. Describe event or problem

Plaut, M.M., MD, Schwartz, M.L., MD, Lubarsky, S.L., MD. Uterine Rupture Associated With The Use Of Misoprostol In The Gravid Patient With A Previous Cesarean Section. Am J Obstet Gynecol 1999; 180 (6) 1535 - 1542.

In this article we report 7 cases of uterine rupture after the use of misoprostol in gravid patients with a previous cesarean section.

Patient 4: "A 29-year-old woman, gravida 5, para 1-0-3-1, with a history of chronic hypertension had labor induced at 37 weeks' gestation because of increased blood pressure. Her previous low transverse cesarean section at 36 weeks was done because of preeclampsia and failed induction of labor. The Bishop score was 4, and 1 dose of 25 mcg misoprostol initiated regular contractions. Six hours later she was having mild contractions, but no cervical change had occurred. Oxytocin was begun, and during the next 12 hours it was increased to 18 mU/min. The tracing had been reactive without decelerations, and there was no tachysystole. She began reporting extreme pain; the cervix was 1 cm dilated and 75% effaced. Oxytocin was stopped; a few minutes later a bradycardia to 60/min occurred, and she was brought for immediate cesarean section while she was under general anesthesia.

(continues...)

6. Relevant test/laboratory data, including dates

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 16 2000
CDR

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

CONCOMITANT ILLNESSES: CESAREAN SECTION NOS; PREG STATE, INCIDENTAL; MILD/NOS PRE-ECLAMPSIA; HYPERTENSION NOS

DSS

MAR 17 2000

C. Suspect medication(s)

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

#1 MISOPROSTOL

#2

2. Dose, frequency & route used

#1 25.000 MCG UNK

#2

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

#1 1 DOSE

#2

4. Diagnosis for use (indication)

#1 MEDICAL INDUCTION LABOR

#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)

OXYTOCIN Unknown - Unknown

G. All manufacturers

1. Contact office - name/address

Dennis P. Miley, M.D.
G.D. Searle and Co.
9855 Woods Drive
Skokie, Illinois 60077

2. Phone number: (847) 581-7874

3. Report source (check all that apply)

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

4. Date received by manufacturer (mo/day/yr): MAR 2 2000

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
FETAL DISTRESS
DRUG EXPOSURE DURING PREGNANCY

9. Mfr. report number: 000303-SK968

E. Initial reporter

1. Name, address & phone #

MM Plaut MD
12607 SE Mill Plain Blvd.
Vancouver, WA 98684
UNITED STATES

Telephone Nr: Unknown

MAR 16 2000

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.

Approved by FDA on September 17, 1993

3477100-0-00-02

U.S. REPORTING

SEARLE

Drug Experience Report

Searle Research and Development

Mfr report #
000303-SK968
UF/Diet report #
FDA Use Only

B. Adverse event or product problem (continued)

5. Describe event or problem

Uterine rupture from the previous incision to the left cornu was found, with the baby's arm extending through the laceration. The baby weighed 2890 g and had Apgar scores of 3 and 9 at 1 and 5 minutes. The arterial cord blood pH was 7.04. The estimated blood loss was 1200 ml, and the defect was easily repaired. Mother and baby did well and were discharged on the fourth postoperative day...Maternal complications: none" This is the fourth of 7 reports. The other reports are uterine rupture (000302-SK676, 000303-SK965, 000303-SK967, 000303-SK972, 000303-SK975, 000303-SK976).

000303-SK968

Approved by FDA on September 17, 1993

3477106-7-00-01

U.S. REPORTING

Drug Experience Report

Searle Research and Development

1 of 1

MFR report # 000303-SK972

UF/Dist report #

FDA Use Only

A. Patient information

1. Patient identifier	2. Age at time of event: UNK 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 ____ (mo/day/yr)
- ☐ life-threatening
- ☑ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☑ other: Medically Significant

3. Date of event (mo/day/yr): Unknown

4. Date of this report (mo/day/yr): MAR 13 2000

5. Describe event or problem

Plaut, M.M., MD, Schwartz, M.L., MD, Lubarsky, S.L., MD. Uterine Rupture Associated With The Use Of Misoprostol In The Gravid Patient With A Previous Cesarean Section. Am J Obstet Gynecol 1999; 180 (6) 1535 - 1542.

In this article we report 7 cases of uterine rupture after the use of misoprostol in gravid patients with a previous cesarean section.

Patient 5 "...a subsequent medical records review of this time period revealed 3 more cases of uterine rupture associated with misoprostol use in patients with previous cesarean sections. In 1 of these (patient) 5) a woman with a previous low transverse cesarean delivery had a cesarean section performed at 5 cm dilatation because of failure of labor to progress. At surgery a fetal hand and head were found to be outside the uterine cavity.... Maternal complications: none. Neonatal outcome: good..." This is the fifth of 7 reports. The other reports are uterine rupture (000302-SK676, 000303-SK965, 000303-SK967, 000303-SK968, 000303-SK975, 000303-SK976).

6. Relevant tests/laboratory data, including dates

Cord pH 7.27

CENTER FOR DRUG EVALUATION AND RESEARCH REC'D MAR 16 2000 CDR

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

CONCOMITANT ILLNESSES: CESAREAN SECTION NOS; PREG STATE, INCIDENTAL

DSS

MAR 17 2000

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.

C. Suspect medication(s)

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

#1 MISOPROSTOL

#2

2. Dose, frequency & route used

#1 UNKNOWN UNK

#2

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

#1 UNKNOWN

#2

4. Diagnosis for use (indication)

#1 MEDICAL INDUCTION LABOR

#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)

OXYTOCIN Unknown - Unknown

G. All manufacturers

1. Contact office - name/address

Dennis P. Miley, M.D.
G.D. Searle and Co.
9855 Woods Drive
Skokie, Illinois 60077

2. Phone number: (847) 581-7874

3. Report source (check all that apply)

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

4. Date received by manufacturer (mo/day/yr): MAR 2 2000

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
DRUG EXPOSURE DURING PREGNANCY

9. Mfr. report number: 000303-SK972

E. Initial reporter

1. Name, address & phone #

MM Plaut MD
12607 SE Mill Plain Blvd.
Vancouver, WA 98684
UNITED STATES

Telephone Nr: Unknown

MAR 16 2000

2. Health professional? ☑ yes ☐ no

3. Occupation: MD

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

000303-SK972

MISOPROSTOL

PRINT DATE: 14-MAR-2000 07:48:55

Approved by FDA on September 17, 1993

3477103-1-00-01

U.S. REPORTING

Drug Experience Report

Searle Research and Development

Page 1 of 2

Mfr report # 000303-SK975

UF/Dist report #

FDA Use Only

000303-SK975

A. Patient information

1. Patient identifier: --- In confidence

2. Age at time of event: UNK or Date of birth:

3. Sex: ☑ female ☐ male

4. Weight: 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 ____ (mo/day/yr)
☐ life-threatening
☑ hospitalization - initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☑ other: Medically Significant

3. Date of event (mo/day/yr): Unknown

4. Date of this report (mo/day/yr): MAR 13 2000

5. Describe event or problem

Plaut, M.M., MD, Schwartz, M.L., MD, Lubarsky, S.L., MD. Uterine Rupture Associated With The Use Of Misoprostol In The Gravid Patient With A Previous Cesarean Section. Am J Obstet Gynecol 1999; 180 (6) 1535 - 1542.

In this article we report 7 cases of uterine rupture after the use of misoprostol in gravid patients with a previous cesarean section.

Patient 6: "...a subsequent medical records review of this time period revealed 3 more cases of uterine rupture associated with misoprostol use in patients with previous cesarean sections....Two additional cases of scar separation (patients 6 and 7) are somewhat difficult to categorize; should they be called true uterine ruptures or symptomatic dehiscences? In both cases patients who were undergoing a trial of labor after a single previous low transverse cesarean section had emergency cesarean deliveries done because of sudden bradycardia at 9 to 10 cm dilatation. Both had intact visceral peritoneum but complete uterine wall separation beneath this. One had a stellate laceration involving the previous incision, and the other had a hematoma associated with the scar disruption. Maternal and fetal outcomes were good in both cases...Maternal complications: none" This is the sixth of 7 reports. The other reports are uterine

(continues...)

6. Relevant test/laboratory data, including dates

Cord pH 7.12

CENTER FOR DRUG EVALUATION AND RESEARCH REC'D MAR 16 2000 CDR

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

CONCOMITANT ILLNESSES: CESAREAN SECTION NOS; PREG STATE, INCIDENTAL

DSS

MAR 17 2000

C. Suspect medication(s)

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

#1 MISOPROSTOL

#2

2. Dose, frequency & route used

#1 UNKNOWN UNK

#2

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

#1 UNKNOWN

#2

4. Diagnosis for use (indication)

#1 MEDICAL INDUCTION LABOR

#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)

G. All manufacturers

1. Contact office - name/address

Dennis P. Miley, M.D.
G.D. Searle and Co.
9855 Woods Drive
Skokie, Illinois 60077

2. Phone number: (847) 581-7874

3. Report source (check all that apply)

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

4. Date received by manufacturer (mo/day/yr): MAR 2 2000

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
FETAL DISTRESS
DRUG EXPOSURE DURING PREGNANCY

9. Mfr. report number: 000303-SK975

E. Initial reporter

1. Name, address & phone #

MM Plaut MD
12607 SE Mill Plain Blvd.

Vancouver, WA 98684
UNITED STATES

Telephone Nr: Unknown

MAR 16 2000

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.

000303-SK975

Approved by FDA on September 17, 1993

3477103-1-00-02

U.S. REPORTING

Drug Experience Report

Searle Research and Development

Mfr report # 000303-SK975

UF/Dist report #

FDA Use Only

000303-SK975

B. Adverse event or product problem (continued)

5. Describe event or problem

rupture (000302-SK676, 000303-SK965, 000303-SK967, 000303-SK968, 000303-SK972, 000303-SK976).

DSS

MAR 17 2000

MAR 16 2000

Approved by FDA on September 17, 1993

3477100-6-00-01

U.S. REPORTING

Drug Experience Report

Searle Research and Development

Mfr report # 000303-SK976

UF/Diet report #

FDA Use Only

A. Patient information

1. Patient identifier	2. Age at time of event: UNK 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 ____ (mo/day/yr)
- ☐ life-threatening
- ☑ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☑ other: Medically Significant

3. Date of event (mo/day/yr)	4. Date of this report (mo/day/yr)
Unknown	MAR 13 2000

5. Describe event or problem

Plaut, M.M., MD, Schwartz, M.L., MD, Lubarsky, S.L., MD. Uterine Rupture Associated With The Use Of Misoprostol In The Gravid Patient With A Previous Cesarean Section. Am J Obstet Gynecol 1999; 180 (6) 1535 - 1542.

In this article we report 7 cases of uterine rupture after the use of misoprostol in gravid patients with a previous cesarean section.

Patient 7: "...a subsequent medical records review of this time period revealed 3 more cases of uterine rupture associated with misoprostol use in patients with previous cesarean sections....Two additional cases of scar separation (patients 6 and 7) are somewhat difficult to categorize; should they be called true uterine ruptures or symptomatic dehiscences? In both cases patients who were undergoing a trial of labor after a single previous low transverse cesarean section had emergency cesarean deliveries done because of sudden bradycardia at 9 to 10 cm dilatation. Both had intact visceral peritoneum but complete uterine wall separation beneath this. One had a stellate laceration involving the previous incision, and the other had a hematoma associated with the scar disruption. Maternal and fetal outcomes were good in both cases...Maternal complications: none." This is the seventh of 7 reports. The other reports are uterine

(continues...)

6. Relevant test/laboratory data, including dates

Cord pH 7.27

CENTER FOR DRUG EVALUATION AND RESEARCH REC'D MAR 16 2000 CDR

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

CONCOMITANT ILLNESSES: CESAREAN SECTION NOS; PREG STATE, INCIDENTAL

DSS

MAR 17 2000

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.

C. Suspect medication(s)

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

#1 MISOPROSTOL

#2

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1 UNKNOWN UNK	#1 UNKNOWN
#2	#2

4. Diagnosis for use (indication)	5. Event abated after use stopped or dose reduced
#1 MEDICAL INDUCTION LABOR	#1 ☐ yes ☐ no ☑ doesn't apply
#2	#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)	7. Exp. date (if known)	8. Event reappeared after reintroduction
#1 UNK	#1 UNK	#1 ☐ yes ☐ no ☑ doesn't apply
#2	#2	#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)

OXYTOCIN Unknown - Unknown

G. All manufacturers

1. Contact office - name/address

Dennis P. Miley, M.D.
G.D. Searle and Co.
9855 Woods Drive
Skokie, Illinois 60077

2. Phone number: (847) 581-7874

3. Report source (check all that apply)

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

4. Date received by manufacturer (mo/day/yr): MAR 2 2000

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
FETAL DISTRESS
DRUG EXPOSURE DURING PREGNANCY

9. Mfr. report number: 000303-SK976

E. Initial reporter

1. Name, address & phone #

MM Plaut MD
12607 SE Mill Plain Blvd.

Vancouver, WA 98684
UNITED STATES

Telephone Nr: Unknown

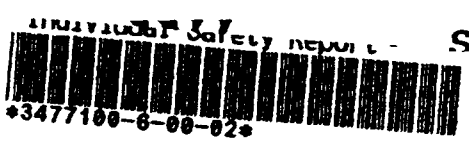
MAR 16 2000

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA
☑ yes ☐ no	MD	☐ yes ☐ no ☑ unk

000303-SK976

MISCARRIAGE

Approved by FDA on September 17, 1993



SEARLE

U.S. REPORTING

Drug Experience Report

Searle Research and Development

MIR report # 000303-SK976

UF/Dist report #

FDA Use Only

B. Adverse event or [illegible] (cont'd)

5. Describe event or problem

rupture (000302-SK676, 000303-SK965, 000303-SK967, 000303-SK968, 000303-SK972, and 000303-SK975).

DSS

MAR 17 2000

MAR 16 2000

PRINT DATE: 14-MAR-2000 11:20:04

Approved by FDA on September 17, 1993

3477097-9-00-01

U.S. REPORTING

E Drug Experience Report

Searle Research and Development

Page 1 of 1

Mfr report # 000308-SK953

UF/Dist report #

FDA Use Only

000308-SK953

A. Patient information

1. Patient identifier	2. Age at time of event: 28 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 ____ (mo/day/yr)
- ☐ life-threatening
- ☑ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☑ other: Medically Significant

3. Date of event (mo/day/yr): Unknown

4. Date of this report (mo/day/yr): MAR 14 2000

5. Describe event or problem

Blanchette, H.A., MD, Nayak, S., MD, Erasmus, S. Comparison Of The Safety And Efficacy Of Intravaginal Misoprostol (Prostaglandin E1) With Those Of Dinoprostone (Prostaglandin E2) For Cervical Ripening And Induction Of Labor In A Community Hospital. Am J Obstet Gynecol. 1999; 180 (6) 1551 - 1559.

"...28-year-old, gravida 3, para 2, with 2 previous low transverse cesarean births, 41 weeks' gestation ...In the first case 25 microg misoprostol was followed 4 hours later by 50 microg times 3 for a total of 4 doses, with subsequent use of oxytocin to a maximum dose of 34 mU/min 4.5 hours after the last misoprostol insertion. Amniotomy was then performed with the cervix dilated 3 cm. Cervical dilatation progressed to 5 cm with tachysystole for the next 2 hours 10 minutes, followed by a 13-minute fetal bradycardia. An emergency cesarean delivery was performed because of acute fetal distress 10 hours after the last misoprostol dose with delivery of an infant weighing 8 lb 4.5 oz and Apgar scores at 1 and 5 minutes of 2 and 7, respectively. This infant did well in the nursery. A low transverse uterine rupture with extension into the left broad ligament was diagnosed, necessitating an emergency hysterectomy and left salpingo-oophorectomy...." This is the first of 4 cases reported. The other cases are uterine rupture/ dehiscence (000308-SK954, 000308-SK957, 000308-SK959).

6. Relevant test/laboratory data, including dates

CENTER FOR DRUG EVALUATION AND RESEARCH REC'D MAR 16 2000 CDR

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

CONCOMITANT ILLNESSES: CESAREAN SECTION NOS; PREG STATE, INCIDENTAL

DSS

MAR 17 7000

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.

C. Suspect medication(s)

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

#1 MISOPROSTOL

#2

2. Dose, frequency & route used

#1 50.000 MCG VAG

#2

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

#1 4 DOSES

#2

4. Diagnosis for use (indication)

#1 MEDICAL INDUCTION LABOR

#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)

OXYTOCIN Unknown - Unknown

G. All manufacturers

1. Contact office - name/address

Dennis P. Miley, M.D.
G.D. Searle and Co.
9855 Woods Drive
Skokie, Illinois 60077

2. Phone number: (847) 581-7874

3. Report source (check all that apply)

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

4. Date received by manufacturer (mo/day/yr): MAR 8 2000

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
FETAL DISTRESS
DRUG EXPOSURE DURING PREGNANCY

9. Mfr. report number: 000308-SK953

E. Initial reporter

1. Name, address & phone #

H- Blanchette MD
Metro West Medical Ctr., OB/GI
115 Lincoln Street
Framingham, MA 01702
UNITED STATES

Telephone Nr: Unknown

MAR 16 2000

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA
☑ yes ☐ no	MD	☐ yes ☐ no ☑ unk

MLSOFMS.TOL

Individual Safety Report

3490309-0-00-01

PRINT DATE: 17-APR-2000 15:13:11

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

U.S. REPORTING

E

Drug Experience Report

Searle Research and Development

Approved by FDA on September 17, 1993

Page 1 of 2

MFr report #: 000405-SK976

UF/Dist report #:

FDA Use Only

000405-SK976

A. Patient information

1. Patient identifier	2. Age at time of event: UNK 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 (mo/day/yr) ☐ disability
☐ life-threatening ☐ congenital anomaly
☑ hospitalization - initial or prolonged ☐ required intervention to prevent permanent impairment/damage
☑ other: Medically Significant

3. Date of event (mo/day/yr): Unknown

4. Date of this report (mo/day/yr): APR 17 2000

5. Describe event or problem

Mathews, J.E., Mathai, M., George, A. Uterine rupture in a multiparous woman during labor induction with oral misoprostol. International Journal of Gynecology & Obstetrics 2000: 68: 43-44.

*A multipara with gestational diabetes and mild pregnancy-induced hypertension was admitted at 40 weeks for delivery. Previously, she had two normal deliveries and a post-abortal curettage. Her abdomen was pendulous; the fetal head was high and mobile. Her cervix was 2 cm long and 1 cm dilated.

Three doses of 100 mcg misoprostol (Cytotec - Searle, Chennai) were given orally at three hourly intervals after which she was transferred to the labor ward with labor pains. As uterine contractions were infrequent and the cervix 1 cm long and 2 cm dilated, a fourth dose of misoprostol was given. An apparently healthy infant was delivered 1 h later followed immediately by expulsion of the placenta, bloody hindwaters and clots.

After 3 h, she had sudden, heavy vaginal bleeding resulting in shock. Uterine rupture, confirmed at laparotomy, involved the cervix and the left uterine artery. Hysterectomy and ligation of the left hypogastric artery were done. The post-operative period

(continues...)

6. Relevant test/laboratory data, including dates

APR 19 2000

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

CONCOMITANT ILLNESSES: MULTIPARITY; ABNORMAL GTT IN PREG; TRANS HYPERTENSION PREG
Multipara - 2 normal deliveries and a post-abortal curettage
Gestational Diabetes
Mild pregnancy-induced hypertension

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.

C. Suspect medication(s)

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

#1 CYTOTEC

#2

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1 100.000 MCG Q1H PO	#1 4 DOSES
#2	#2

4. Diagnosis for use (indication)	5. Event abated after use stopped or dose reduced
#1 MEDICAL INDUCTION LABOR	#1 ☑ yes ☐ no ☐ doesn't apply
#2	#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)	7. Exp. date (if known)	8. Event reappeared after reintroduction
#1 UNK	#1 UNK	#1 ☐ yes ☐ no ☑ doesn't apply
#2	#2	#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)

G. All manufacturers

1. Contact office - name/address

Dennis P. Miley, M.D.
G.D. Searle and Co.
9855 Woods Drive
Skokie, Illinois 60077

2. Phone number: (847) 581-7874

3. Report source (check all that apply)
☐ foreign ☐ study ☑ literature ☐ consumer ☐ health professional ☐ user facility ☐ company representative ☐ distributor ☐ other:

4. Date received by manufacturer (mo/day/yr): APR 5 2000

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
DRUG EXPOSURE DURING PREGNANCY

9. Mfr. report number: 000405-SK976

E. Initial reporter

1. Name, address & phone #

JB Mathews MD
Dept. of Obstetrics & Gynecology
Christian Medical College Hosp.
Vellore,
INDIA

Telephone Nr: Unknown

DSS
APR 20 2000

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA
☑ yes ☐ no	MD	☐ yes ☐ no ☑ unk

Individual Safety Report

3490309-0-00-02

PRINT DATE: 17-APR-2000 15:13:11

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

U.S. REPORTING

Drug Experience Report

Searle Research and Development

Approved by FDA on September 17, 1993

MW report # 000405-SK976

UF/Dist report #

FDA Use Only

000405-SK976

B. Adverse event or product problem (continued)

5. Describe event or problem

was uneventful. The infant's cephalhematoma had not resolved by day 12, but he was otherwise well."

APR 19 2000

DSS

APR 20 2000

INCLUDED IN
REFERENCE LIST

2 pages

PRINT DATE: 25-APR-2000 08:10:15

34S4592-7-00-01

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

U.S. REPORTING

E Drug Experience Report

Searle Research and Development

Approved by FDA on September 17, 1993

Mfr report # 000414-SK112

UF/Dist report #

FDA Use Only

000414-SK112

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 ____ (mo/day/yr)
☐ life-threatening
☐ hospitalization - initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☑ other: Medically Significant

3. Date of event (mo/day/yr)	4. Date of this report (mo/day/yr)
Unknown	APR 24 2000

5. Describe event or problem

MEDICALLY SIGNIFICANT

Bugalho, A., Bique, C., Machungo, F., Bergstroem, S. A Comparative Study Of Vaginal Misoprostol And Intravenous Oxytocin For Induction Of Labour. Gynecol Obstet Invest 1995; 39: 252 - 256.

"The study was carried out at the [hospital] in [city], Mozambique. The patients delivering in the Department of Obstetrics and Gynaecology, about a third of the city total of 48,000 deliveries per year, represent a concentrated obstetric high-risk population, often with clinical indication of pregnancy interruption due to severe maternal morbidity (pre-eclampsia or eclampsia, intrauterine infection, rupture of membranes, intrauterine growth retardation, etc.)...

...For the study, two groups of patients were recruited..... Women with oxytocin infusion/Women with vaginal misoprostol.....

...Since preliminary experiences had indicated that misoprostol applied vaginally in the posterior fornix could be an alternative to intravenous oxytocin, a series of 404 consecutive pregnant women with indication of induction were then recruited. Oxytocin use was

(continues...)

6. Relevant test/laboratory data, including dates

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

CONCOMITANT ILLNESSES: PREG STATE, INCIDENTAL

MAY 0 1 2000

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.

C. Suspect medication(s)

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

#1 CYTOTEC

#2

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1 50.000 MCG VAG	#1 1 DOSE
#2	#2

4. Diagnosis for use (indication)

#1 MEDICAL INDUCTION LABOR

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

G. All manufacturers

1. Contact office - name/address

Dennis P. Miley, M.D.
G.D. Searle and Co.
9855 Woods Drive
Skokie, Illinois 60077

2. Phone number: (847) 581-7874

3. Report source (check all that apply)

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

4. Date received by manufacturer (mo/day/yr): APR 13 2000

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
ABORTION
Fetal death
DRUG EXPOSURE DURING PREGNANCY

9. Mfr. report number: 000414-SK112

E. Initial reporter

1. Name, address & phone #

S- Bergstrom MD
Dept. of International Health
PO Box 1130, Blindern
Oslo, N-0318
NORWAY

Telephone Nr: Unknown

MAY 01 2000

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA
☑ yes ☐ no	MD	☐ yes ☐ no ☑ unk

3494592-7-00-02

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

U.S. REPORTING

Drug Experience Report

Searle Research and Development

Mfr report #
000414-SK112
UF/Dist report #
FDA Use Only

B. Adverse event or product problem (continued)

5. Describe event or problem

suspended completely during that period and misoprostol was used exclusively for induction. The drug was administered according to table 1. (364/404 women with dose 50 mcg x1). In 40/404 women a second dose of 50 mcg was given vaginally 18 h after the first dose, if labour had not started with the single dose normally utilized. In 7/404 of these women, a third dose of 50 mcg had to be given 18 h after the second dose. No other drug was used to stimulate labour or to soften the cervix...

...In the oxytocin infusion group there was 1 perinatal death (Case 1)...and in the misoprostol group, 6 perinatal deaths (Cases 2 through 7)...

Case 3 (misoprostol): 26-year-old woman in her third pregnancy with gestational age 40 weeks. After induction during 10 h and 50 min, a vaginal haemorrhage occurred with signs of uterine rupture. Laparotomy showed uterine rupture in the posterior uterine wall and placenta accreta with Couvelaire uterus. The baby had died and subtotal hysterectomy was performed."

This is the second of six cases reported. The other cases are fetal/newborn death (000414-SK099, 000414-SK117, 000414-SK118, 000414-SK120, 000414-SK122).

INCLUDED IN
REFERENCE LIST

5 PAGES

...ividual Safety Report

3521502-6-00-01

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

U.S. REPORTING

Drug Experience Report

Searle Research and Development

Approved by FDA on September 17, 1993

Mfr report # 000614-SK250

UF/Distr report #

FDA Use Only

000614-SK250

A. Patient information

1. Patient identifier: --- In confidence

2. Age at time of event: 39 Yrs or Date of birth:

3. Sex: ☑ female ☐ male

4. Weight: 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 1998 (mo/day/yr)
☐ life-threatening
☐ hospitalization - initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☑ other: Medically Significant

3. Date of event (mo/day/yr): JAN 1998

4. Date of this report (mo/day/yr): JUN 26 2000

5. Describe event or problem

Daisley, H., MB. Maternal Mortality Following The Use Of Misoprostol. Med. Sci. Law 2000; 40 (1): 78-82.

'A 39-year-old healthy female was admitted to the obstetrical ward in January 1998, for induction of labour, being five days post date. She was gravida three, para two, abortion none. Her blood pressure was 140/90 mm Hg, pulse 90/min. Her fundal height was assessed as 39/40 weeks. Vaginal examination on admission revealed a closed, uneffaced cervix and an engaged foetal head.

Blood was drawn for group- and cross-match, and three units of whole blood requested, together with a complete blood count, urea and electrolytes. She was prepared for delivery, and one half of a 100 microgram tablet of misoprostol inserted in her posterior vaginal fornix.

Within an hour of misoprostol administration, uterine contractions were regular, and at four hours the cervix was fully effaced. She delivered a healthy male six hours after induction. Vaginal bleeding post-delivery was minimal. However, 30 minutes post-delivery she began to complain of headaches and abdominal pains; this was followed by unconsciousness. Her pulse was 130/min, and her blood pressure unrecordable. Her abdomen was

(continues...)

6. Relevant test/laboratory data, including dates

Admission:
WBC 11.6 x 10*9/L
RBC 4.52 x 10*12/L
Hb 11.5 g/dl
Hct 0.37 L/L
MCV 81.2 fL
MCHC 31.4 g/dl
Platelets 158 x 10*9/L

DSS

JUN 2 9 2000

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

CONCOMITANT ILLNESSES: PREG STATE, INCIDENTAL
Gravida 3, para 2, abortion 0

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.

C. Suspect medication(s)

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

#1 CYTOTEC

#2

2. Dose, frequency & route used

#1 50.000 MCG VAG

#2

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

#1 1 DOSE

#2

4. Diagnosis for use (indication)

#1 MEDICAL INDUCTION LABOR

#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)

G. All manufacturers

1. Contact office - name/address

Dennis P. Miley, M.D.
G.D. Searle and Co.
9855 Woods Drive
Skokie, Illinois 60077

JUN 2 8 2000

2. Phone number: (847) 581-7874

3. Report source (check all that apply)

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

4. Date received by manufacturer (mo/day/yr): JUN 14 2000

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
DRUG EXPOSURE DURING PREGNANCY

9. Mfr. report number: 000614-SK250

E. Initial reporter

1. Name, address & phone #

H- Daisley, Jr. DM(Path)
Univ.of the West Indies
Faculty of Medical Science
St. Augustine,
TRINIDAD

Telephone Nr: Unknown

2. Health professional? ☑ yes ☐ no

3. Occupation: DM(Path)

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

Individual Safety Report

3521502-6-00-02

U.S. REPORTING

Drug Experience Report

Searle Research and Development

Approved by FDA on September 17, 1993

MIr report # 000614-SK250

UF/Diet report #

FDA Use Only

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

B. Adverse event or product problem (continued)

5. Describe event or problem

assessed as 24/40 weeks gestational size. Syntocinon infusion was commenced in 500 ml dextrose saline but there was little effect on uterine tone. Dopamine was added to the infusion. The patient had a cardio-respiratory arrest and died despite resuscitative measures. Her complete blood count on admission was WBC 11.6 x 10*9/L, RBC 4.52 x 10*12/L, Hb 11.5 g/dl, Hct 0.37 L/L, MCV 81.2 fL, MCHC 31.4 g/dl, platelets 158 x 10*9/L.

At autopsy the body was that of a young Indian female. Her mucous membranes were pale. There was pallor of the brain, and cerebral oedema. There was no cerebral haemorrhage. There was pallor of the myocardium. The endocardium had focal ecchymosis as evidence of recent cardiac massage. The heart valves were structurally unremarkable. There was pulmonary oedema and aspiration pneumonitis but no evidence of pulmonary embolism. The gastrointestinal tract was structurally unremarkable. The uterus was postpartum, measuring 30 x 20 x 18 cm. There was a 10 cm area of rupture in the right retroperitoneum, extending to involve the peri-renal tissue on the right side. The endometrial cavity contained 40 mg of clotted blood. The kidneys were pale and swollen. The spleen was soft with a wrinkled capsule. Histology of the lungs confirmed aspiration pneumonitis and oedema. There was no evidence of amniotic fluid embolism. Diagnoses of ruptured uterus with hypovolaemic shock were made."

This is the second of 3 cases reported. The other cases are septic abortion, death (000614-SK247) and septic abortion (000614-SK255).

JUN 2 8 2000

DSS

JUN 2 9 2000

000614-SK250

INCLUDED IN

REFERENCE LIST

5 PAGES

Individual Safety Report

3522918-4-00-01

PRINT DATE: 29-JUN-2000 13:49:53

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

U.S. REPORTING

'LE Drug Experience Report

Searle Research and Development

Page 1 of 1

Approved by FDA on September 17, 1993

Mfr report # 000619-SK110

UF/Dist report #

FDA Use Only

000619-SK110

A. Patient information

1. Patient identifier	2. Age at time of event: or Date of birth:	3. Sex	4. Weight
--- In confidence	36 Yrs	☑ 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 (mo/day/yr) ☐ life-threatening ☐ hospitalization - initial or prolonged ☐ disability ☐ congenital anomaly ☐ required intervention to prevent permanent impairment/damage ☑ other: Medically Significant

3. Date of event (mo/day/yr)	4. Date of this report (mo/day/yr)
MAR 31 1999	JUN 29 2000

5. Describe event or problem

MEDICALLY SIGNIFICANT

Jwarah E., Greenhalf J.O. Rupture of the uterus after 800 micrograms misoprostol given vaginally for termination of pregnancy. British Journal of Obstetrics and Gynaecology, June 2000, Vol 107, pp. 807.

"A 36 year-old woman attended the family planning clinic on 18 March 1999 requesting termination of pregnancy. According to the ultrasound report she was eight weeks and 2 days pregnant. She had two children: one had been delivered by caesarean section, the other by normal vaginal delivery. She was admitted to the hospital on 31 March 1999 and received 800 micrograms of misoprostol in the vagina at 11:25 hours in order to prepare the cervix for surgical termination of pregnancy. At 14:00 hours she experienced vaginal bleeding and severe lower abdominal pain. At examination under anaesthesia, bleeding was profuse, consistent with rupture of the uterus. Laparotomy was performed when it was found that the scar in the uterus had ruptured with division of both uterine arteries. Subtotal hysterectomy was performed, and she received a blood transfusion of two units of blood. Her post-operative recovery was uneventful."

6. Relevant test/laboratory data, including dates

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

CONCOMITANT ILLNESSES: CESAREAN DEL-NO INDICATE; NORMAL DELIVERY; DELIVERY-SINGLE LIVEBORN; PREG STATE, INCIDENTAL

She had two children: one had been delivered by caesarean section, the other by normal vaginal delivery.

C. Suspect medication(s)

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

#1 CYTOTEC

#2

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1 800.000 MCG VAG	#1 MAR 31 1999 - MAR 31 1999
#2	#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)	7. Exp. date (if known)
#1 UNK	#1 UNK
#2	#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)

G. All manufacturers

1. Contact office - name/address

Dennis P. Miley, M.D.
G.D. Searle and Co.
9855 Woods Drive
Skokie, Illinois 60077

2. Phone number: (847) 581-7874

3. Report source (check all that apply)

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

4. Date received by manufacturer (mo/day/yr): JUN 19 2000

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
DRUG EXPOSURE DURING PREGNANCY

9. Mfr. report number: 000619-SK110

E. Initial reporter

1. Name, address & phone #

E- Jwarah MD
Dept. of Obstetrics & Gynaecology
Wycombe General Hospital
High Wycombe, HP11 2IT
UNITED KINGDOM

Telephone Nr: Unknown

Local Code: AD/000619/522

DSS

JUL 03 2000

JUN 30 2000

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA
☑ yes ☐ no	MD	☐ 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.

REPRINT INCLUDED
IN REFERENCE LIST

1 PAGE

Individual Safety

3535666-1-00-01

PRINT DATE: 24-JUL-2000 14:28:33

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

U.S. REPORTING

SEARLE Drug Experience Report

Searle Research and Development

Approved by FDA on September 17, 1993

Mfr report #: 000713-SK605

UF/Dist report #:

FDA Use Only

000713-SK605

CYTOTEC

A. Patient information

1. Patient identifier: — In confidence

2. Age at time of event: 38 Yrs or Date of birth:

3. Sex: ☑ female ☐ male

4. Weight: 140 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: Medically Significant

3. Date of event (mo/day/yr): MAR 6 2000

4. Date of this report (mo/day/yr): JUL 24 2000

5. Describe event or problem

On Jul-11-00 this consumer called to inquire about using Cytotec for labor induction. This 38 year old female patient received 2 doses of Cytotec (misoprostol) 100mcg intravaginally (patient is unsure of actual dose) for the induction of labor on Mar-06-00. The first Cytotec dose was ineffective. Approximately 1.5 hours later, a second Cytotec injection was administered accompanied by intravenous Pitocin. After the last injection, she experienced "having a very mushy feeling inside" and began having heavy, lengthy contractions although the caregivers said that the patient was "not ready". The patient felt a big pressure inside and she "exploded" with the baby still inside of her. The infant was delivered by suction. She was hemorrhaging and her blood pressure dropped dramatically requiring resuscitation with medication. Some hours later, on Mar-06-00, exploratory surgery was done after an X-ray demonstrated a ruptured artery and uterus. Two and a half liters of blood was found in the patient's abdomen. The uterus could not be reconstructed. The uterus and the right ovary and fallopian tube were removed. The patient received 15 units of blood and spent 5 additional days in the intensive care unit. The patient was transferred to the regular unit for 5 more days and then discharged in Mar-00.

(continues...)

6. Relevant test/laboratory data, including dates

Mar-06-00 - X-ray demonstrated ruptured artery and uterus

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

CONCOMITANT ILLNESSES: PREG STATE, INCIDENTAL

Three previous childbirths

Patient has received Pitocin with no problems in past and has also had to have a casearean section performed in the past.

C. Suspect medication(s)

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

#1 CYTOTEC

#2

2. Dose, frequency & route used

#1 200.000 MCG QD VAG

#2

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

#1 MAR 6 2000 - MAR 6 2000

#2

4. Diagnosis for use (indication)

#1 MEDICAL INDUCTION LABOR

#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)

OXYTOCIN MAR 6 2000 - MAR 6 2000

G. All manufacturers

1. Contact office - name/address

Dennis P. Miley, M.D.
G.D. Searle and Co.
9855 Woods Drive
Skokie, Illinois 60077

JUL 26 2000

2. Phone number: (847) 581-7874

3. Report source (check all that apply)

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

4. Date received by manufacturer (mo/day/yr): JUL 11 2000

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
FETAL DISTRESS
DYSPNEA
DRUG EXPOSURE DURING PREGNANCY

9. Mfr. report number: 000713-SK605

E. Initial reporter

1. Name, address & phone #

-- Patient

UNITED STATES

Telephone Nr: Unknown

Local Code:

DSS JUL 27 2000

2. Health professional? ☐ yes ☑ no

3. Occupation

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.

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

SEARLE

U.S. REPORTING

Drug Experience Report

Searle Research and Development

Approved by FDA on September 17, 1993

Mfr report #: 000713-SK605

UF/Dist report #:

FDA Use Only

B. Adverse event or product problem (continued)

5. Describe event or problem

On Jul-11-00 the consumer also reported that two intravaginal injections of Cytotec (misoprostol), dose unknown, were used to induce labor on Mar-06-00. Intravenous Pitocin was administered with the second Cytotec injection. The infant's "heart rate died" for about 1 minute and the infant had to be "suctioned out" which resulted in a cephalohematoma on the infant's head. A baby boy was delivered with the placenta and was resuscitated. Following delivery, the infant boy was placed on oxygen for 1.5 days and has had nasal congestion for the first 2 months of his life. As of Jul-11-00 the infant boy is experiencing a lot of allergies and it is unknown if the child will have any problems due to the difficult delivery.

Additional information has been requested.

000713-SK605

Individual Safety Report

3471220-8-00-01

CDER

VOLUNTARY reporting by health professionals of adverse events and product problems

CDER

Form Approved: OMB No. 0910-0291 Expires: 12/31/00
See OMB statement on reverse.

FDA Use Only (MAPP)

Triage unit sequence #: 118456

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Page 1 of ___

CDER

A. Patient information

1. Patient identifier: ~ In confidence
2. Age at time of event: 29 or Date of birth:
3. Sex: ☑ female ☐ male
4. Weight: ___ lbs or 75.75 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: Emergency c-section + hysterectomy
3. Date of event (mm/dd/yy)
4. Date of this report (mm/dd/yy)
5. Describe event or problem

(See attached)

6. Relevant tests/laboratory data, including dates

NA

DSS

MAR - 8 2000

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

(See attached)

C. Suspect medication(s)

1. Name (give labeled strength & manufacturer, if known)
   - #1 Cytotec (misoprostil)
   - #2 Oxytocin (Pitocin)
2. Dose, frequency & route used
   - #1 50mcg x 2 doses Intravaginal
   - #2 up to 20mu/min Intravenous max
3. Therapy dates (if unknown, give duration)
   - #1 12/29/99 @ 9pm, 12/30 @ 2:30 am
   - #2 12/29/99 12/30/99
4. Diagnosis for use (indication)
   - #1 Labor induction/Cervical ripening
   - #2 Labor induction
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) NA
10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name: NA
2. Type of device: NA
3. Manufacturer name & address: NA
4. Operator of device
   - ☐ health professional
   - ☐ lay user/patient
   - ☐ other: NA
5. Expiration date (mm/dd/yy): NA
6. model # NA
   catalog #
   serial #
   lot # MEDWATCH CTU
   other #
7. If implanted, give date (mm/dd/yy): NA
8. If explanted, give date (mm/dd/yy): NA

RECEIVED
MAR 08 2000

9. Device available for evaluation? NA (Do not send to FDA)
   ☐ yes ☐ no ☐ returned to manufacturer on ___ (mm/dd/yy)
10. Concomitant medical products and therapy dates (exclude treatment of event)

NA

E. Reporter (see confidentiality section on back)

1. Name, address & phone #

[redacted]

2. Health professional? ☑ yes ☐ no
3. Occupation: Pharmacist
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. ☒

FDA

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

FDA Form 3500 (9/98)

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

CTU 118456

118456

Summary of Medications
Individual Safety Report
3471220-8-00-02

Age/Sex: 29 F
DIS -

All Medications

All Other Medication

Timeline of Results

Dates of Administration for the mother

All Medications	
ACETAMINOPHEN	1/2 - 1/7/00
ALBUMIN HUMAN 5%	12/30 (one 500mL vial, one 250mL vial) 12/31 (one 100mL vial)
AMINO ACIDS 10%	TPN on 1/2/00
AMOXICILL/K CLAVULAN	1/6 - 1/7/00
AMPICILLIN/SULBACTAM	12/30/99
CALCIUM GLUCONATE 10	In TPN 1/2/00 and alone on 12/30 - 12/31/99
CEFAZOLIN SODIUM	12/30/99 - 1/1/00
CITRIC ACID/SODIUM C	12/31/99
NEUREPIN/DEXTROSE 5%-WATER DRIP	12/30/99 - 1/7/00
DEXTROSE 70%-WATER	In TPN 1/2/00
DOPAMINE HCL	12/30 - 1/1/00
DROPERIDOL PRN	1/3 - 1/6/00
FAMOTIDINE	12/30 - 1/7/00
~~FAT EMULSIONS 20% NOA~~	
FENTANYL CITRATE	1/3/00
~~WATER FOR INJECTION,~~	
HYDROCODONE BITARTRA	1/6 - 1/7/00
HEPARIN SODIUM	1/1 - 1/2/00
HETASTARCH 6 % in NS	12/30 - 12/30/99
~~IV SOLUTION~~	
~~LANOLIN/MINERAL OIL~~	
~~LIDOCAINE HCL 2%~~	
LORAZEPAM	12/30 - 1/4/00
~~MAGNESIUM SULFATE 50~~	
~~MASSAGE~~	
METOCLOPRAMIDE HCL	1/3 - 1/5/00
METRONIDAZOLE	12/30 - 1/4/00
MIDAZOLAM HCL	12/30/99 - 1/1/00
MORPHINE SULFATE	12/30 - 1/5/00
~~MULTIVITAMINS~~	
~~MULTIVITAMINS, THER W~~	
~~SODIUM CHLORIDE 0.9%~~	
~~NALOXONE HCL~~	
~~NOREPINEPHRINE BITAR~~	
PHENYLEPHRINE HCL	12/30/99 - 1/3/00
PIPERACILLIN/TAZOBAC	1/1/00 - 1/6/00
POTASSIUM CHLORIDE	In TPN
POTASSIUM PHOSPHATE	In TPN
PROPOFOL	12/30 - 1/4/00
ROCURONIUM BROMIDE	12/30/99 (one dose)
~~SODIUM CHLORIDE~~	
~~SENNA/DOCUSATE SODIU~~	
~~SODIUM ACETATE~~	
~~SODIUM CHLORIDE BACT~~	
~~SUCCINYLCHOLINE CHLO~~	
~~THIOPENTAL SODIUM~~	

D5S
MAR - 8 2000

CTU 118456

Summary of Medications

Individual Safety Report

3471220-8-00-03

Age/Sex: 29 F
DIS -

All Medications

Medication | Sig - Feb 23, 00 | Timeline of Results

All Medications (Con	Ending SIG	Feb 16, 2000 16	17	18	8 Days 19	20	21	Feb 23, 2000 22	23
TRACE METALS	In TPN 1/2/00								
VANCOMYCIN HCL	1/1/00 - 1/7/00								
PHYTONADIONE	In TPN 1/2/00								

DSS
MAR - 8 2000

CTU 118456

118459

The patient was admitted for labor induction. History: gravida 4, para 4, expected due date 12/21/99. Baby delivered 12/31/99. Nothing significant in prenatal history. Patient induced with Pitocin the first day (12/29/99), receiving up to 20 milliunits (mu)/minute with minimal contractions. Pitocin stopped at 1800 first day. First dose of Cytotec (50mcg) given intravaginally at 2100. Minimal response to the Cytotec. A second dose of Cytotec 50mcg was given on 12/30/99 at 2:30 a.m.. No change in the cervix and minor contractions. Pitocin restarted on 12/30/99 at 6:30 a.m. at 1mu/min and increased to 2mu/min at 7:10 a.m. Pitocin off at 8:00 a.m. Physician ruptured membranes at 8:30 a.m. At 9:15 a.m. patient had severe abdominal pain and a tonic-clonic seizure episode. Emergency c-section performed and found a ruptured uterus, vertically, on the right side.

PRINT DATE: 09-AUG-1994 10:22:09

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

SEARLE

U.S. REPORTING

Drug Experience Report

Searle Research and Development

Approved by FDA on September 17, 1993

MfR report # 940804-SK733

1493280

Page 1 of 1

A. Patient information

1. Patient identifier	2. Age at time of event: / or Date of birth:	3. Sex	4. Weight
--- In confidence	Unk	☑ 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) ☐ disability
☐ life-threatening ☐ congenital anomaly
☑ hospitalization - initial or prolonged ☐ required intervention to prevent permanent impairment/damage
☐ other: ____

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

4. Date of this report (mm/dd/yy): AUG 09 1994

5. Describe event or problem

Contraception 1994:49, February, 101-110

Literature report entitled, "Misoprostol: The experience of women in Fortaleza, Brazil" received on Aug. 4, 1994 reports three cases of uterine perforation. The other 2 are 940804-SK735 and 940804-SK736. This (940804-SK733) is the first of the three.

(MISSING)

uter rupt

6. Relevant test/laboratory data, including dates

LITERATURE

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

JTB (8/23/94)

C. Suspect medication(s)

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

#1 MISOPROSTOL (MISOPROSTOL)

#2

2. Dose, frequency & route used

#1 UNKNOWN UNK

#2

3. Therapy dates (if unknown, give duration)

#1 UNKNOWN

#2

4. Diagnosis for use (indication)

#1 ABORTION NOS UNCOMPLICAT

#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)

N

G. All manufacturers

1. Contact office - name/address

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

2. Phone number: (7081 982-8714

3. Report source (check all that apply)

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

DIVISION OF EPIDEMIOLOGY

4. Date received by manufacturer (mm/dd/yy): AUG 04 1994

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

940804-SK733

E. Initial reporter

1. Name, address & phone #

HL Coelho MD
Dept. of Pharmacy, Fed. Univ. of
Ceara, P O Box 3212
Fortalezace, 60431-327
BRAZIL

CONFIDENTIAL

Telephone Nr: Unknown

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.

940804-SK736, 940804-SK735

940804-SK733

REPRINT INCLUDED IN
THE REFERENCE LISTING

10 PAGES

E:490152

PRINT DATE 09-AUG-1994 10.22 59

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

SEARLE

U S REPORTING

Drug Experience Report

Searle Research and Development

Page 1 of 1

Approved by FDA on September 17, 1993

Mfr report # 940804-SK735

UF/Log report # 1792707

940804-SK735

A. Patient information

1. Patient identifier	2. Age at time of event / or Date of birth	3. Sex	4. Weight
--- In confidence	Unk	☑ 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 ____ (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)	4 Date of this report (mo/day/yr)
Unknown	AUG 09 1994

5 Describe event or problem

Contraception 1994:49, February, 101-110

Literature report entitled, "Misoprostol The experience of women in Fortaleza, Brazil" received on Aug 4, 1994 reports three cases of uterine perforation The other 2 are 940804-SK733 and 940804-SK736 This (940804-SK735) is the second of the three

uter rupt

6 Relevant test/laboratory data including dates

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

LITERATURE

JTB 08/23/94

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

C. Suspect medication(s)

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

#1 A MISOPROSTOL (MISOPROSTOL)

#2

2 Dose, frequency & route used	3 Therapy dates (if unknown, give duration)
#1 UNKNOWN UNK	#1
#2	#2

4 Diagnoses for use (indication)	5 Event abated after use stopped or dose reduced
#1 ABORTION NOS UNCOMPLICAT	#1 ☐ yes ☐ no ☑ doesn't apply
#2	#2 ☐ yes ☐ no ☐ doesn't apply

6 Lot # (if known)	7 Exp date (if known)	8 Event reappeared after reintroduction
#1 UNK	#1 UNK	#1 ☐ yes ☐ no ☑ doesn't apply
#2	#2	#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)

N

G. All manufacturers

1. Contact office - name/address

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

2 Phone number (708) 982-8714

3 Report source (check all that apply)

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

DIVISION OF EPIDEMIOLOGY AND SURVEILLANCE

4 Date received by manufacturer (mo/day/yr) AUG 04 1994

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 01)

8 Adverse event term(s)
UTERINE PERFORATION

9. Mfr report number
940804-SK735

E. Initial reporter

1 Name, address & phone #

HL Coelho MD
Dept. of Pharmacy, Fed Univ of
Ceara, P O Box 3212
Fortalezace, 60431-327
BRAZIL

Telephone Nr Unknown

CONFIDENTIAL

2. Health professional?	3. Occupation	4 Initial reporter also sent report to FDA
☑ yes ☐ no	MD	☐ yes ☐ no ☑ unk

RELATED DER'S: 940804-SK736, 940804-SK733

940804-SK735

C4P PRINT DATE: 11-NOV-1996 07:10:52

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

SEARLE

U.S. REPORTING

Drug Experience Report

Searle Research and Development

Page 1 of 2

Approved by FDA on September 17, 1995

Mfr report # 961023-SK024

UF/Distr 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 ____ (mo/da/yr)
☐ life-threatening
☑ hospitalization - initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other: ____

3. Date of event (mo/da/yr): Unknown

4. Date of this report (mo/da/yr): 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	3. Therapy dates (if unknown, give duration) (mo/da/yr or best estimate)
#1 600.000 MCG Q6H VAG	#1 2 DOSES
#2	#2

4. Diagnosis for use (indication)	5. Event abated after use stopped or dose reduced
#1 UNSPECIFIED ABORTION	#1 ☐ yes ☐ no ☑ doesn't apply
#2	#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)	7. Exp. date (if known)	8. Event reappeared after reintroduction
#1 UNK	#1 UNK	#1 ☐ yes ☐ no ☑ doesn't apply
#2	#2	#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 (mo/da/yr): 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 #

K- Phillips MD
Dept. of Gynaecology, Glasgow
Royal Infirmary, Castle Street
Scotland, SC G31 40H
UNITED KINGDOM

Telephone Nr: Unknown

CONFIDENTIAL

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA
☑ yes ☐ no	MD	☐ 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.

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

SEARLE

U.S. REPORTING
Drug Experience Report
Searle Research and Development

Approved by FDA on September 17, 1993

MW report #
961023-SK024

USPDist report #

FDA Use Only

961023-SK024

B. Adverse event or product problem (continued)

5. Describe event or problem

this case 6 h after her first dose of misoprostol, in the absence of uterine contractions and with the cervical os closed, further misoprostol (600 mcg) was administered vaginally. Four hours later painful uterine contractions had established and slow intravenous diamorphine, totalling 10 mg, was given for analgesia. Vaginal bleeding developed, estimated at 100 ml, the cervical os was open with fetal head palpable. Vaginal haemorrhage persisted and the fetus was delivered with manual assistance 30 min later, but with the placenta retained. Severe abdominal pain then occurred and necessitated further intravenous diamorphine (10 mg) to obtain adequate analgesia. At this stage she appeared pale and peripherally shut down. Her pulse was 88/min, blood pressure 100/60 mmHg. Her haemoglobin had fallen from 12.2 g/dl on admission to 7.9 g/dl. Other blood parameters were white cell count 14.2 x 10 to the ninth/l, platelets 152 x 10 to the ninth/l, hydrogen ion concentration 46.9 mmol/l, coagulation screen; activated partial thromboplastin time 50 s, prothrombin time 18 s and thrombin clotting time 11 s.

Emergency manual removal of the placenta was performed under general anaesthesia. The placenta had separated and was partially through a dilated cervial os. Once removed the uterine cavity was checked digitally and it was evident that there was a large defect in the uterine wall, the right ovary being palpable within the uterine cavity. Laparotomy was performed and the findings of a 8-cm right uterine side wall rupture, with substantial haemorrhage into the broad ligament and abdominal cavity confirmed. Hysterectomy and right salpingo-oophorectomy were required to control the haemorrhage. Overall blood loss was estimated at 4000 ml: resuscitation required seven units of packed red cells, 1500 ml of gelofusine, 2 l of crystalloid and two units of fresh frozen plasma. Peri-operative antibiotic cover of 1.2 g augmentin and 120 mg gentamicin was administered. She made an uneventful post-operative recovery. Pathological analysis of the specimen revealed an 80-mm rupture along the right side of the uterus. Endometrial decidualisation and myometrial hypertrophy were normal, with no obvious underlying weakness to account for the uterine rupture.

6. Relevant test/laboratory data, including dates

Overall blood loss: estimated 4000 ml

Pathological analysis of specimen: revealed an 80-mm rupture along the right side of the uterus.

REPRINT INCLUDED IN
REFERENCE LISTING

2 PAGES

1844960 VV

PRINT DATE: 29-JAN-1997 09:53:12 000-00052

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

U.S. REPORTING

SEARLE Drug Experience Report

Searle Research and Development

Page 1 of 1

Approved by FDA on September 17, 1993

MFR report # 961022-SK848

LP/Date T422147

FDA Use Only

961022-SK848

A. Patient information

1. Patient Identifier	2. Age at time of event: UNK 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): JAN 8 1997

5. Describe event or problem

A physician called on Oct-17-96 to report that he had two patients who experienced a ruptured uterus with the use of Cytotec vaginally. In this case, Cytotec was used following Prostin to induce an abortion. This is the first report, the other is DER #961022-SK850.

UTER RUPT
PREGN UNINTEND

5:32

6. Relevant tests/laboratory data, including dates

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

CONCOMITANT ILLNESSES: PREG STATE, INCIDENTAL

C. Suspect medication(s)

1. Name (give labeled strength & manufacturer, if known)
- #1 CYTOTEC
- #2

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration)
#1 UNKNOWN VAG	#1 UNKNOWN
#2	#2

4. Diagnosis for use (indication)	5. Event abated after use stopped or dose reduced
#1 ABORTION NOS UNCOMPLICAT	#1 ☐ yes ☐ no ☑ doesn't apply
#2	#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)	7. Exp. date (if known)	8. Event reappeared after reintroduction
#1 UNK	#1 UNK	#1 ☐ yes ☐ no ☑ doesn't apply
#2	#2	#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)

PROSTIN E2 Unknown - Unknown

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 17 1996

5. (A) NDA # 19-268
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. # 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 DISORDER NOS
Ruptured uterus
DRUG EXPOSURE DURING PREGNANCY

9. Mfr. report number: 961022-SK848

E. Initial reporter

1. Name, address & phone #

CONFIDENTIAL

Telephone Nr: ____

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA
☑ yes ☐ no	MD	☐ 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.

RELATED DER'S: 961022-SK850

961022-SK848

PRINT DATE: 29-JAN-1997 09:33:13 000-00053

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

SEARLE

U.S. REPORTING

Drug Experience Report

Searle Research and Development

Page 1 of 1

Approved by FDA on September 17, 1993

FDA report # 961022-SK850

MFR report # 1922133

961022-SK850

A. Patient information

1. Patient identifier: --- In confidence
2. Age at time of event: UNK or Date of birth:
3. Sex: ☑ female ☐ male
4. Weight: 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): JAN 8 1997
5. Describe event or problem

A physician called on Oct-17-96 to report that he had two patients who experienced a ruptured uterus with the use of Cytotec vaginally. In this case, Cytotec was used to induce labor. This is the second report, the other is DER #961022-SK848.

UTER RUPT
PREGN UNINTEND

6. Relevant test/laboratory data, including dates

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

CONCOMITANT ILLNESSES: PREG STATE, INCIDENTAL

C. Suspect medication(s)

1. Name (give labeled strength & manufacturer, if known)
   - #1 CYTOTEC
   - #2
2. Dose, frequency & route used
   - #1 UNKNOWN VAG
   - #2
3. Therapy dates (if unknown, give duration) (mm/dd/yy or best estimate)
   - #1 UNKNOWN
   - #2
4. Diagnosis for use (indication)
   - #1 EARLY ONSET OF DELIVERY
   - #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)

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 17 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. 01)
8. Adverse event term(s)

UTERINE DISORDER NOS
Ruptured uterus
DRUG EXPOSURE DURING PREGNANCY

9. Mfr. report number: 961022-SK850

E. Initial reporter

1. Name, address & phone #

[redacted]

CONFIDENTIAL

Telephone Nr: ____

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.

RELATED DER'S: 961022-SK848

961022-SK850

CAP N 192427

PRINT DATE: 05-JUN-1997 14:27:06

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

U.S. REPORTING

SEARLE **Drug Experience Report**

Searle Research and Development

Approved by FDA on September 17, 1993

Page 1 of 1

MFR report # 970529-SK651

FDA/Dist report # 1960766

970529-SK651

A. Patient information

1. Patient Identifier	2. Age at time of event: 27 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 ____ (mo/da/yr)
☑ life-threatening
☑ hospitalization - initial or prolonged
☑ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other: ____

3. Date of event (mo/da/yr)	4. Date of this report (mo/da/yr)
APR 27 1997	JUN 5 1997

5. Describe event or problem

"Misoprostol was used for abortion in a patient who was twenty weeks pregnant. Six hours later, this lead to a ruptured uterus. Patient had an abdominal hysterectomy and required 4 units of blood." The patient recovered. [Per C. Muirhead, Searle, South Africa]

RECEIVED
DIVISION OF EPIDEMIOLOGY
AND SURVEILLANCE
97 JUN -9 AM 8:34

UTER RUPT

6. Relevant test/laboratory data, including dates

Hb 4 g/dl

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

CONCOMITANT ILLNESSES: HYPERTENSION NOS
"Third pregnancy. First was caesarian delivery 1987, second was a miscarriage in 1993."

C. Suspect medication(s)

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

#1 MISOPROSTOL (MISOPROSTOL)

#2

2. Dose, frequency & route used

#1 400.000 MCG VAG

#2

3. Therapy dates (if unknown, give duration)

#1 APR 27 1997 - APR 27 1997

#2

4. Diagnosis for use (indication)

#1 LEGAL ABORT UNCOMPLICAT

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

NONE

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 (mo/da/yr): MAY 29 1997

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

970529-SK651

E. Initial reporter

1. Name, address & phone #

CONFIDENTIAL

Telephone Nr: Unknown

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA
☑ yes ☐ no	MD	☐ 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.

970529-SK651

CP 6/17/97

CAP 1960303

PRINT DATE: 28-JUL-1997 09:11:47

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

SEARLE

U.S. REPORTING

Drug Experience Report
Searle Research and Development

Page 1 of 2

MFR report # 970714-SK994

MFR/Dist report # 2005810

970714-SK994

MISOPROSTOL

A. Patient information

1. Patient Identifier	2. Age at time of event: or Date of birth:	3. Sex	4. Weight
--- In confidence	34 Yrs	☑ 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): JUL 24 1997

5. Describe event or problem

Uterine Rupture During Induction of Labor at Term with Intravaginal Misoprostol, B.B. Bennett, Obstetrics and Gynecology, Vol 89, Page 832-833, (1997)

"A healthy 34-year-old woman was admitted to the hospital for labor induction at 39 weeks gestation because of a low amniotic fluid index (5 cm) and poor fetal growth. The obstetric history included three term vaginal deliveries followed by a D&C for spontaneous first-trimester abortion. Vaginal examination on admission revealed a closed, uneffaced cervix and an unengaged fetal head. Our protocol for induction in the presence of an unfavorable cervix call for misoprostol 25 mcg (one-quarter of a 100 mcg tablet) placed in the posterior vaginal fornix every 3 hours until onset of active labor or until a consistent pattern of a least three contractions in 10 minutes is established.

The first dose of misoprostol stimulated only mild, irregular contractions. After the second dose, the contractions remained irregular overall, and infrequent episodes of tachysystole were noted. The cervix was 1 cm dilated and 40% effaced, and the vertex was at -2 station. Three hours after the second dose, the patient was reevaluated, and misoprostol was withheld because of the intermittent tachysystole. Her cervix had not (continues...)

6. Relevant tests/laboratory data, including dates

FETAL D/S
UTER RUPT

DIVISION OF EPIDEMIOLOGY AND HEALTH SYSTEMS RESEARCH
97 JUL 30 AM 7:20

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

CONCOMITANT ILLNESSES: SPON ABORTION UNCOMPLIC; D & C NEC
Three term vaginal deliveries
One first-trimester spontaneous abortion followed by D&C

LITERATURE

C. Suspect medication(s)

1. Name (give labeled strength & manufacturer, if known)
- #1 MISOPROSTOL
- #2

2. Dose, frequency & route used
- #1 25.000 MCG BID VAG
- #2

3. Therapy dates (if unknown, give duration)
- #1 1 DAY
- #2

4. Diagnosis for use (indication)
- #1 MEDICAL INDUCTION LABOR
- #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)

TERBUTALINE Unknown - Unknown

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): JUL 7 1997

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
FETAL DISTRESS

9. Mfr. report number: 970714-SK994

E. Initial reporter

1. Name, address & phone #

BB Bennett MD
U. of Florida College of Medicine
P.O. Box 100294, Dept. of OB/GYN
Gainesville, FL 32610
UNITED STATES

Telephone Nr: Unknown
Local Code:

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.

cj 8/14/97

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

SEARLE

U.S. REPORTING
Drug Experience Report
Searle Research and Development

MFR report #: 970714-SK994
FDA/Other report #: 200581/0 Only

B. Adverse event or product problem (continued)

5. Describe event or problem

changed, and a continuous tracing of the fetal heart rate displayed small accelerations and occasional mild variable decelerations. Tachysystole persisted over the following 2 hours, and the fetal tracing remained stable. The patient did not report excessive pain, but she did complain of an urge to push.

Five hours after the second misoprostol dose, the fetus developed bradycardia unresponsive to change in maternal position and oxygen administration. The uterine hyperstimulation was refractory to terbutaline administration. Digital examination revealed blood in the vagina, a floating fetal head, and cervical dilation of 2 cm. Placental abruption or uterine rupture was suspected, and the patient was immediately transported to the operating room. There, the fetal heart rate could not be detected by Doppler, and ultrasound examination demonstrated a rate of 20 beats per minute.

Eighteen minutes after the onset of bradycardia, a 2427-g female infant was delivered by emergency cesarean. Approximately 500 ml of blood was encountered upon entry into the abdominal cavity, but the uterus appeared intact. The infant was delivered from a cephalic presentation through a vertical uterine incision. She was resuscitated vigorously and her Apgar scores were 1, 8, and 9 at 1, 5, and 10 minutes respectively. The arterial cord blood pH was 6.83.

After delivery of the anterior placenta, uterine inspection revealed a 15-cm linear rupture of the left posterior uterine wall, which was bleeding profusely. The defect extended from the level of the internal os to the left cornu and included the left utero-ovarian and broad ligaments (Figure 1). Hysterectomy and left salpingo-oophorectomy were considered necessary to control the hemorrhage. Blood loss was estimated to be 2000 mL and the patient's postoperative hematocrit stabilized at 14.5%. No blood transfusion was given. Vaginal cuff cellulitis and ileus complicated the patient's postoperative course, but both problems responded to standard management. The infant's hematocrit at birth was 42.5%. She was initially observed under a 50% oxygen hood and received intravenous fluids, but no further intervention was required. Both the mother and infant were discharged home on the eight postoperative day in good condition."

REPRINT INCLUDED
IN THE REFERENCE LIST

2 PAGES

RECEIVED AT DRUG SAFETY SURVEILLANCE
09-MAR-1998-0094

SEARLE

Individual Safety Report
3051561-9-00

7.1995

FDA Use Only

980114-SK161

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Page

A. Patient information

1. Patient identifier	2. Age at time of event: 34 Yrs or Date of birth:	3. Sex	4. Weight
UNK 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 (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)	4. Date of this report (mo/day/yr)
SEP 24 1997	MAR 6 1998

5. Describe event or problem

On Jan-12-98 a pediatrician called to report that a hospital's OB-GYN department has been using Cytotec for cervical ripening. There have been two fetal deaths. This is the first case; the second is 980114-SK162.

A 3500 form received on Feb-24-98 from a nurse reads: "Patient was administered IV oxytocin beginning at 4:20 p.m. according to protocol. Patient had Cesarean section at approximately 10:45 p.m. At the time of abdominal incision, a uterine rupture was noted with delivery of stillborn infant. We do not know if Misoprostol was a contributing factor or not..."
The patient received 50 mcg doses of Cytotec at 07:23 AM, 10:20 AM and 1:50 PM for cervical ripening. "Death of infant" was specified as the outcome of the adverse event in Block B2.

6. Relevant test/laboratory data, including dates

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

CONCOMITANT ILLNESSES: HYPERTENSION NOS; MANUAL ASSIST DELIV NEC; ASPIRAT CURET-PREG TERMI; D & C NEC
"Chronic hypertension - on: Aldomet 250 mg t.i.d.

1982- Spontaneous vaginal delivery
1992- 16 week spontaneous abortion with D&C&E"

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.

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 CYTOTEC
#2

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1 150.000 MCG VAG	#1 SEP 24 1997 - SEP 24 1997
#2	#2

4. Diagnosis for use (indication)	5. Event abated after use stopped or dose reduced
#1 MEDICAL INDUCTION LABOR	#1 ☐ yes ☐ no ☑ doesn't apply
#2	#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)	7. Exp. date (if known)	8. Event reappeared after reintroduction
#1 UNK	#1 UNK	#1 ☐ yes ☐ no ☑ doesn't apply
#2	#2	#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)
OXYTOCIN SEP 24 1997 - SEP 24 1997

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 (mo/day/yr): JAN 12 1998

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. 1)

8. Adverse event term(s)
UTERINE PERFORATION
ABORTION
DRUG EXPOSURE DURING PREGNANCY

9. Mfr. report number: 980114-SK161

E. Initial reporter

1. Name, address & phone #

Telephone Nr: Unknown

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA
☑ yes ☐ no	RN	☐ yes ☐ no ☑ unk

CYTOTEC

PRINT DATE: 20-AUG-1998 15:23:11

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

SEARLE

Approved by FDA on September 17, 1998

3121134-8-00-01

FDA Use Only

980114-SK162

A. Patient information

1. Patient Identifier	2. Age at time of event: or Date of birth:	3. Sex	4. Weight
UNK In confidence	29 Yrs	☑ 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 (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)	4. Date of this report (mo/day/yr)
NOV 10 1997	AUG 20 1998

5. Describe event or problem

On Jan-12-98 a pediatrician called to report that a hospital's OB-GYN department has been using Cytotec for cervical ripening. There have been two fetal deaths. This is the second case; the first is 980114-SK161.

A 3500 form received on Feb-24-98 from a nurse reads: "Discharged the patient after 3.5 hours (12 noon). Patient returned to hospital @ 6:52 p.m. in severe discomfort, abdomen tender. Stated contractions became more regular and firm at 5:30 p.m. On admission to Labor Room, after exam, determined a Cesarean section was necessary. Upon peritoneal entry, the infant's head was encountered with an immediate diagnosis of uterine rupture. Infant was delivered and resuscitated. Infant was transferred to a tertiary center and expired in 3-4 days. We do not know if Misoprostol was a contributing factor or not...."
Cytotec had been given at 8:35 AM. "Death of infant" was specified as the outcome of the adverse event in Block B2.

(Follow-Up) AUG 18 1998
Hospital history and physical received on Aug-18-98:

"HISTORY:
This is a 29 year-old, G-4, now P-3, black female, blood
(continues...)

6. Relevant test/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)
CONCOMITANT ILLNESSES: TRANS HYPERTENSION PREG; MILD/NOS PRE-ECLAMPSIA; CD & REMOVAL FETUS; MANUAL ASSISTED DEL NEC; SICKLE-CELL ANEMIA NOS
"History of labile HTN with this pregnancy.
History of toxemia with first pregnancy.
1989 Cesarean Section - low transverse incision
1993 Normal vaginal delivery
1996 Normal vaginal delivery"

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 CYTOTEC
#2

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1 50.000 MCG VAG	#1 1 DOSE
#2	#2

4. Diagnosis for use (indication)
#1 MEDICAL INDUCTION LABOR
#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)	7. Exp. date (if known)
#1 UNK	#1 UNK
#2	#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)

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 (mo/day/yr): AUG 18 1998

5. (A) NDA # 19-268
IND #
PLA #
pre-1938 ☐ yes
OTC product ☐ yes

6. # IND, protocol #

7. Type of report (check all that apply)
- ☐ 5-day ☑ 15-day
- ☐ 10-day ☐ periodic
- ☐ initial ☑ follow-up # 1 (Rev No. 3)

8. Adverse event term(s)
UTERINE PERFORATION
ABORTION
DRUG EXPOSURE DURING PREGNANCY

9. Mfr. report number: 980114-SK162

E. Initial reporter

1. Name, address & phone #

Telephone Nr: Unknown

AUG 25 1998

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA
☑ yes ☐ no	RN	☐ 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.

CYTOTEC

980114-SK162

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

SEARLE D

U.S. REPORTING ... 1993

3121134-B-00-02

FDA Use Only

Page

980114-SK162

B. Adverse event or product problem (continued)

5. Describe event or problem

type O positive, antibody screen negative, rubella immune with Sickle Cell trait.

The patient delivered yesterday PM at 39 2/7 weeks by last menstrual period confirmed by first trimester ultrasound (emergent midline cesarean section for fetal decelerations in the 50s). The patient arrived to the emergency room with complaints of abdominal pain and uterine contraction. She was immediately transferred to the labor and delivery ward where external fetal dopplers were unable to pick-up fetal heart tones. A realtime ultrasound was rapidly performed and it was noted that the infant's heart tones were in the low 50s. Upon that time, OB back-up was called and the patient was transferred to the operating room for a STAT C-section.

The patient had previously, earlier that day, undergone cervical ripening with Cytotec due to labile and significantly elevated blood pressures. NST at that time had been performed and found to be a normal reactive strip. Upon arrival to the labor and delivery ward, pelvic exam revealed a 2-3 cm dilated cervix approximately 30% effacement at a -1 to -2 station. No ballotable fetal parts were appreciated at that time or any membranes. Clear liquid was revealed on my glove at that time.

Upon peritoneal entry during the C-section it was discovered that a uterine rupture at a previous C-section site had occurred and the infant was rapidly delivered at that point and given to the pediatrician. The infant was soon life-flighted to [hospital] for respiratory distress. Uterine repair on the mother was then performed without complication and transfer to the maternity floor after recovery from anesthesia. During the pre-operative course, she had received one gram of Cefotan at that time.

The patient's post-operative course was without complication. The patient's vitals were stable. She was afebrile. This morning, she was tolerating a clear liquid diet and still on IV fluids of 125 cc of D5 lactated ringers. Flatus had been noted by the patient and she had good bowel sounds upon examination and she was starting to ambulate the halls.

The patient this morning received the bad news that her infant was not doing very well and at that time both she and her family requested a transfer to [hospital] so she could be near her daughter.

PAST MEDICAL HISTORY: Non-contributory. The patient has no past medical history of heart disease, diabetes mellitus, kidney or lung disease.

PAST SURGICAL HISTORY: Cesarean section. Please see below.

OB-GYNE HISTORY:
(A)
1. in 1989, preeclampsia. The patient had a C-section performed at that time, delivered a 7 lb 0 oz male.
2. In 1993, the patient had a twelve-hour labor for a normal vaginal delivery of a 7 lb 8 1/4 oz female.
3. In 1996, five hour labor, delivered 37 weeks via normal vaginal delivery, a 6 lb female infant.

(B)
The patient reports having an abnormal Pap exam at her

(continues...)

B. Adverse event or product problem (continued)

5. Describe event or problem

previous primary care physicians discovery. A repeat Pap was performed at the [clinic], unfortunately no endocervical cells were noted. She was scheduled for a repeat Pap in the postpartum period.

CURRENT MEDICATIONS AT THIS TIME CONSIST OF:
1. Buprenx 0.3 to 0.5 mg IV q4-6h PRN, pain.
2. Phenergan 25 mg IV q6h prn, nausea.
3. IV fluids of D5 lactated ringers at 125 cc an hour
4. The patient had previously been on prenatal vitamins, one tablet po q day in the perinatal period.

ALLERGIES: No known drug allergies.

PHYSICAL EXAMINATION:
Vitals: Current temperature 97.7 degrees Fahrenheit. Heart rate 88, respiratory rate 20, blood pressure 134/98.
HEENT: Normocephalic, atraumatic. Pupils are equally reactive to light and accommodation. Extraocular movements intact. Normal tympanic membranes. External auditory canals, nares, patent and oropharynx within normal limits.
NECK: Supple with full range of motion. No lymphadenopathy or JVD noted. 2+ carotid upstrokes bilaterally.
LUNGS: Clear to auscultation bilaterally without any rhonchi, wheezes or rales.
HEART: Regular rhythm without murmur. No S3 or S4 heart sounds.
ABDOMEN: Normal bowel sounds in all four quadrants. Mild tenderness over the uterus. Clean uterine incision without any erythema or other signs of infection. The uterus is firm and at the level of the umbilicus. Lochia bright-red, two pads so far today.
BREASTS: Mildly tender.
NEUROLOGIC EXAM: Without any focal deficits, generally intact.

LABS: WBC 12.1 with a hemoglobin of 13.2, hematocrit 38,6 and platelets 192 on 11/10/97. After delivery this morning on 11/11/97, WBCs were 14.7, hemoglobin 10.1, hematocrit 30.8, platelets 128.

ASSESSMENT & PLAN:
This is post-op day #1 for status post emergent midline cesarean section for fetal distress and discovered uterine rupture. Post-operative course so far uncomplicated. The patient is ambulating and tolerating a clear liquid diet while still on IV fluids. We are considering stopping the IV fluids when the po intake is believed to be adequate.

Pain control is currently well controlled with Buprenex 0.3 to 0.4 mg IV q4-6h prn, pain. Again, change to po narcotics with good po intake was being considered prior to delivery. At this time, she's to be transferred to [hospital] under the care of [doctor] for her emotional state and for basic well being, to be near her infant at this time particularly important since the infant's status is worsening as per the pediatricians at [hospital]."

AUG 25 1998

DATE: 11/11/97.

TIME: 9:00 AM.

HISTORY: This is a 29 year-old, G-4, now P-3, black female, blood type O positive, antibody screen negative, rubella immune with Sickle Cell trait.

The patient delivered yesterday PM at 39 2/7 weeks by last menstrual period confirmed by first trimester ultrasound (emergent midline cesarean section for fetal decelerations in the 50s). The patient arrived to The Medical Center emergency room with complaints of abdominal pain and uterine contraction. She was immediately transferred to the labor and delivery ward where external fetal dopplers were unable to pick-up fetal heart tones. A realtime ultrasound was rapidly performed and it was noted that the infants heart tones were in the low 50s. Upon that time, OB back-up was called and the patient was transferred to the operating room for a STAT C-section.

The patient had previously, earlier that day, undergone cervical ripening with Cytotec due to labile and significantly elevated blood pressures. NST at that time had been performed and found to be a normal reactive strip. Upon arrival to the labor and delivery ward, pelvic exam revealed a 2-3 cm dilated cervix approximately 30% effacement at a -1 to -2 station. No ballotable fetal parts were appreciated at that time or any membranes. Clear liquid was revealed on my glove at that time.

Upon peritoneal entry during the C-section it was discovered that a uterine rupture at a previous C-section site had occurred and the infant was rapidly delivered at that point and given to the pediatrician. The infant was soon life-flighted to West Penn Hospital for respiratory distress.

980114-SK162

Uterine repair on the mother was then performed without complication and transfer to the maternity floor after recovery from anesthesia. During the pre-operative course, she had received one gram of Cefotan at that time.

The patient's post-operative course was without complication. The patient's vitals were stable. She was afebrile. This morning, she was tolerating a clear liquid diet and still on IV fluids of 125 cc of D5 lactated ringers. Flatus had been noted by the patient and she had good bowel sounds upon examination and she was starting to ambulate the halls.

The patient this morning received the bad news that her infant was not doing very well and at that time both she and her family requested a transfer to West Penn Hospital so she could be near her daughter.

PAST MEDICAL HISTORY: Non-contributory. The patient has no past medical history of heart disease, diabetes mellitus, kidney or lung disease.

PAST SURGICAL HISTORY: Cesarean section. Please see below.

OB-GYNE HISTORY:

(A)

1. In 1989, pre-eclampsia. The patient had a C-section performed at that time, delivered a 7 lb 0 oz male.
2. In 1993, the patient had a twelve-hour labor for a normal vaginal delivery of a 7 lb 8 1/4 oz female.
3. In 1996, five-hour labor, delivered 37 weeks via normal vaginal delivery, a 6 lb female infant.

980114-SK162

(B)

The patient reports having an abnormal Pap exam at her previous primary care physicians discovery. A repeat Pap was performed at the Prenatal Clinic, unfortunately no endocervical cells were noted. She was scheduled for a repeat Pap in the postpartum period.

CURRENT MEDICATIONS AT THIS TIME CONSIST OF:

1. Buprenex 0.3 to 0.5mg IV q4-6h p.r.n., pain.
2. Phenergan 25mg IV q6h p.r.n., nausea.
3. IV fluids of D5 lactated ringers at 125 cc an hour.
4. The patient had previously been on prenatal vitamins, one tablet p.o. q day in the perinatal period.

ALLERGIES: No known drug allergies.

PHYSICAL EXAMINATION:

VITALS: Current temperature 97.7 degrees Fahrenheit. Heart rate 88, respiratory rate 20, blood pressure 134/98.

HEENT: Normocephalic, atraumatic. Pupils are equally reactive to light and accommodation. Extraocular movements intact. Normal tympanic membranes. External auditory canals, nares, patent and oropharynx within normal limits.

NECK: Supple with full range of motion. No lymphadenopathy or JVD noted. 2+ carotid upstrokes bilaterally.

LUNGS: Clear to auscultation bilaterally without any rhonchi, wheezes or rales.

980114-SK162

At this time, she's to be transferred to [redacted] under the care of [redacted] for her emotional state and for basic well being, to be near her infant at this time particularly important since the infants status is worsening as per the pediatricians at [redacted]

D: 11/11/97 - 9:52 AM
T: 11/10/97 - 10:30 AM

8
cc: CMA

-5-

980114-SK162

HEART: Regular rhythm without murmur. No S3 or S4 heart sounds.

ABDOMEN: Normal bowel sounds in all four quadrants. Mild tenderness over the uterus. Clean uterine incision without any erythema or other signs of infection. The uterus is firm and at the level of the umbilicus. Lochia bright-red, two pads so far today.

BREASTS: Mildly tender.

NEUROLOGIC EXAM: Without any focal deficits, generally intact.

LABS: WBC 12.1 with a hemoglobin of 13.2, hematocrit 38.6 and platelets 192 on 11/10/97. After delivery this morning on 11/11/97, WBCs were 14.7, hemoglobin 10.1, hematocrit 30.8, platelets 128.

ASSESSMENT & PLAN:

This is post-op day #1 for status post emergent midline cesarean section for fetal distress and discovered uterine rupture. Post-operative course so far uncomplicated. The patient is ambulating and tolerating a clear liquid diet while still on IV fluids. We are considering stopping the IV fluids when the p.o. intake is believed to be adequate.

Pain control is currently well controlled with Buprenex 0.3 to 0.4mg IV q4-6h p.r.n., pain. Again, change to p.o. narcotics with good p.o. intake was being considered prior to delivery.

980114-SK162

PRINT DATE: 16 APR 1998 00:00:00

RECEIVED AT DRUG SAFETY SURVEILLANCE
20-APR-1998-0643

U.S. REPORTI
Drug E
Searle Researc

Individual Safety Report
3065272-7-00

THE MEDICAL PRODUCTS REPORTING PROGRAM

80407-SK060

CYTOTEC

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 ____ (mo/day/yr)
- ☐ life-threatening
- ☑ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☑ other: Medically Significant

3. Date of event (mo/day/yr)	4. Date of this report (mo/day/yr)
Unknown	APR 16 1998

5. Describe event or problem

Uterine Rupture During Preinduction Cervical Ripening with Misoprostol in a Patient with a Previous Caesarean Delivery; A.C. Sciscione, DO, et al; Austrialian New Zealand Journal of Obstetrics and Gynecology; Vol. 38 (1) pages 96-97 (1998)

A 26-year-old gravida 4, para 2-0-1-2 at 40 2/7 weeks' gestation was undergoing biophysical testing for an elevated second trimester maternal serum alpha fetoprotein value. Oligohydramnios was noted and delivery planned. The patient had had 2 previous low transverse Caesarean deliveries, the first for 'fetal distress', and a subsequent elective repeat Caesarean delivery. Following counselling early in her pregnancy she decided on a trial of labour. After reviewing the risks, the patient elected to enter the study and was randomized to the misoprostol treatment arm. According to protocol, misoprostol was given at a dose of 50 mcg every 4 hours to a maximum of 3 doses, providing the fetal heart rate was reassuring, there was no evidence of uterine hyperstimulation, and Bishop score was equal to or less than 5.

The patient received the first dose without incident. The fetal heart rate was reassuring and contractions occurred consistently every 4 to 5 minutes for 30 to 45

(continues...)

6. Relevant test/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)
CONCOMITANT ILLNESSES: LOW CERVICAL C-SECTION

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 CYTOTEC
#2

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration) (mo/day/yr or best estimate)
#1 50.000 MCG Q4H VAG	#1 2 DOSES
#2	#2

4. Diagnosis for use (indication)	5. Event abated after use stopped or dose reduced
#1 MEDICAL INDUCTION LABOR	#1 ☑ yes ☐ no ☐ doesn't apply
#2	#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)	7. Exp. date (if known)	8. Event reappeared after reintroduction
#1 UNK	#1 UNK	#1 ☐ yes ☐ no ☐ doesn't apply
#2	#2	#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)

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) 982-8716

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☑ literature
- ☐ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer (mo/day/yr): APR 7 1998

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 PERFORMATION

9. Mfr. report number
980407-SK060

E. Initial reporter

1. Name, address & phone #
A- Sciscione DO
Christiana Care Health System
4755 Ogletown-Stanton Road
Newark, DE 19718
UNITED STATES

Telephone Nr: Unknown

APR 21 1998

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA
☑ yes ☐ no	DO	☐ 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.

RECEIVED AT DRUG SAFETY SURVEILLANCE
20-APR-1998-0644

U.S. REPORTING

RLE **Drug Experience Report**

Searle Research and Development

Approved by FDA on September 17, 1993

MIR report # 980407-SK060

UF/Diist report #

FDA Use Only

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

B. Adverse event or product problem (continued)

5. Describe event or problem

seconds duration, as assessed by external monitoring. Four hours after the initial dose, the contraction frequency decreased to 4-6 per hour and a second dose of misoprostol was given. The Bishop score had increased from 3 to 4. Within 1 hour of the second dose, uterine hyperstimulation (6 or more contractions in 10 minutes) was noted. The fetal heart rate was reassuring throughout the period of hyperstimulation. No intervention was performed. The uterine hyperstimulation resolved over 20 to 30 minutes. Eight hours after the second dose, the fetus was noted to have a prolonged heart rate deceleration lasting 4 minutes with good recovery after resuscitative manoeuvres. There was no evidence of uterine hyperstimulation. The patient had no abdominal pain, but had mild vaginal bleeding (less than 100 mL). The fetal heart rate pattern again became reassuring. Approximately 1 hour later, the fetal heart rate pattern revealed occasional, moderate variable decelerations, with good variability in between. An intrauterine pressure catheter was placed and revealed a baseline tone of 15 mmHg rising to 60 mmHg, with contractions occurring every 3-4 minutes. Approximately an hour later, the patient became fully dilated, and the fetal head was at +2 station. As preparation was made for vaginal delivery, the delivery attendant noted a dramatic loss of station and fetal bradycardia. Because the fetal head was no longer in the pelvis, the patient was taken to Caesarean delivery. At the time of the delivery, the fetus was noted to have been extruded through a large uterine perforation at the site of the previous Caesarean delivery scar.

Active bleeding without haematoma formation was noted at the site of the uterine rupture. The fetus, birth-weight 3,220 g, had Apgar scores of 0, 5, and 7 at 1, 5, and 10 minutes, respectively. The umbilical vein pH was 6.81 and the base excess was -22.8. The uterus was repaired primarily with good haemostasis. No other induction or augmentation agent was used except the 2 doses of intravaginal misoprostol. The fetus was taken to the Neonatal Intensive Care Unit for hypovolaemia, where he was observed and received hydration. The infant was discharged from the hospital 8 days after delivery and at the time of this writing, 8 months after the event. remains well.

Individual Safety Report

3065272-7-00

980407-SK060

CYTOTEC

APR 21 1998

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.

PRINT DATE: 26-JAN-1999 15:06:41

Individual Safety Report

3189268-X-00-01

SEARLE

U.S. REPORTING

Drug Experience Report

Searle Research and Development

Approved by FDA on September 17, 1985

MFR report # 990125-SK821

UF/Distr report #

FDA Use Only

990125-SK821

MISOPROSTOL

1. Patient identifier	2. Age at time of event: 39 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 ____ (mo/day/yr)
☐ life-threatening
☑ hospitalization - initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☑ other: Medically Significant

3. Date of event (mo/day/yr): Unknown

4. Date of this report (mo/day/yr): JAN 26 1999

5. Describe event or problem

MEDICALLY SIGNIFICANT

Wing, D.A., MD, Lovett, K., MD, Paul, R.H., MD. Disruption of Prior Uterine Incision Following Misoprostol For Labor Induction In Women With Previous Cesarean Delivery. Obstetrics & Gynecology 1998; 91/5: 828-830.

"A 39-year-old woman, gravida 2, was admitted for labor induction for fetal growth restriction and oligohydramnios at 35.5 weeks' gestation. Her first infant was delivered by cesarean for arrest of dilation; again, we were unable to document the type of uterine incision. She received an initial dose of misoprostol 25 microgr intravaginally following an initial cervical examination that revealed no effacement or dilation. This dose initiated regular uterine activity for almost 8 hours. When she had fewer than two contractions in 10 minutes and her cervical examination had not changed, the second dose of misoprostol 25 microg was given. This resulted in regular uterine activity for almost 13 hours. Approximately 21 hours after the first dose of medication, her cervix became soft and slightly dilated. With minimal uterine activity, she was given a third dose of misoprostol 25 microg. Over the next 6 hours, her cervix progressed to 4 cm dilation. No uterine activity

(continues...)

6. Relevant test/laboratory data, including dates

DSS

FEB 0 1 1999

ADVERSE EVENT REPORTING SYSTEM

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

CONCOMITANT ILLNESSES: PREV CD NOS-UNSPEC; POOR FETAL GROWTH-NOS; OLIGOHYDRAMNIOS-UNSPEC

RECEIVED
FEB 0 1 1999
BY:

C. Suspect medication(s)

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

#1 MISOPROSTOL

#2

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration)
#1 25.000 MCG PRN VAG	#1 3 DOSES
#2	#2

4. Diagnosis for use (indication)

#1 MEDICAL INDUCTION LABOR

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

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 (mo/day/yr): JAN 21 1999

5. (A) NDA # 19-268
IND #
PLA #
pre-1938 ☐ yes
OTC product ☐ yes

6. # 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

990125-SK821

E. Initial reporter

1. Name, address & phone #

DA Wing MD
Women's and Children's Hospital
Room 5K40 1240 N. Mission Rd.
Los Angeles, CA 90033
UNITED STATES

Telephone Nr: Unknown

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA
☑ yes ☐ no	MD	☐ 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.

RECEIVED
JAN 2 9 1999
BY:

3189268-X-00-02

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

U.S. REPORTING

Drug Experience Report

Searle Research and Development

Approved by FDA on September 17, 1993

FDA report # 990125-SK821

MFR/Dist report #

FDA Use Only

990125-SK821

MISOPROSTOL

B. Adverse event or product problem (continued)

5. Describe event or problem

abnormalities were detected. Amniotomy was performed at 4 cm dilation, and a prophylactic amnioinfusion was begun. While at epidural catheter was being placed, loss of fetal heart tones occurred and a change in contour of the subject's abdomen was noted. Ultrasonography confirmed fetal bradycardia. The patient underwent an emergency cesarean for fetal distress and suspected uterine rupture, and a viable 2395-g male infant with Apgar score of 5 and 8 and 1 and 5 minutes, respectively, was delivered 10 minutes later. The arterial cord blood pH was 7.01, and the analysis was consistent with respiratory acidosis. The transverse uterine defect measured 8 cm, through which no fetal parts had been extruded. There was also a 3-cm vertical extension at the right lateral margin. The uterus was repaired without incident, and no blood products were required. Both the mother and her infant did well postoperatively, and were discharged from the hospital in good condition." This is the second of two cases reported. The first case is found in 990125-SK820.

DSS

FEB 0 1 1999

ADVERSE EVENT REPORTING SYSTEM

RECEIVED
JAN 2 9 1999
BY:

RECEIVED
FEB 0 1 1999
BY:

REPRINT INCLUDED

IN THE REFERENCE LIST

3 PAGES

Individual Safety Report

3189258-7-00-01

U.S. REPORTING

Drug Experience Report

Searle Research and Development

Approved by FDA on September 17, 1993

990126-SK155

FDA Use Only

990126-SK155

MISOPROSTOL

A. Patient information

1. Patient identifier: --- (In confidence)
2. Age at time of event: 22 Yrs or Date of birth:
3. Sex: ☑ female ☐ male
4. Weight: 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 Unknown (mo/day/yr)
- ☐ life-threatening
- ☐ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☑ other: Medically Significant

3. Date of event (mo/day/yr): Unknown

4. Date of this report (mo/day/yr): JAN 27 1999

5. Describe event or problem

MEDICALLY SIGNIFICANT

Fletcher, H. MD, McCaw-Binns, A.. Rupture Of The Uterus With Misoprostol (Prostaglandin EI) Used For Induction Of Labour. Journal of Obstetrics & Gynaecology 1998; 18/2 184-185.

"A 22-year-old (gravida 2, para 1) unbooked patient with one previous uncomplicated delivery presented to a rural referral hospital having had an eclamptic fit at home. Her gestational age was unknown and she was conscious but drowsy and not responding to commands. Her pulse rate was 120/min, blood pressure 200/100 and respiratory rate 20/min. Her abdomen bore no scars and the fundal height was 20 weeks. Vaginal examination revealed a cervix that was minimally effaced with the os admitting one finger. Laboratory findings were, urine albumen 3+, Hb 12.6 g/d, white cell count 19 x 10*6/l, platelets 125 x 10*6/l, sickle test positive. Urea normal, glucose 264 mg/dl. She was stabilized with parenteral apresoline and magnesium sulphate and induced with 200 microg misoprostol. She remained stable and conscious, had no further seizures and also started to have uterine contractions. She was monitored through to the following day. After 22 hours and 20 minutes a repeat vaginal examination revealed that the cervix was now fully

(continues...)

6. Relevant test/laboratory data, including dates

DSS

FEB 01 1999

ADVERSE EVENT REPORTING SYSTEM

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

CONCOMITANT ILLNESSES: ECLAMPSIA; SICKLE-CELL ANEMIA NOS

RECEIVED
JAN 29 1999
BY:

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.

C. Suspect medication(s)

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

#1 MISOPROSTOL

#2

2. Dose, frequency & route used

#1 300.000 MCG VAG

#2

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

#1 UNKNOWN

#2

4. Diagnosis for use (indication)

#1 MEDICAL INDUCTION LABOR

#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)

HYDRALAZINE HYDROCHLORIDE	Unknown - Unknown
MAGNESIUM SULFATE	Unknown - Unknown
OXYTOCIN	Unknown - Unknown
ERGOMETRINE	Unknown - Unknown

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 (mo/day/yr): JAN 26 1999

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
CARDIAC ARREST

9. Mfr. report number: 990126-SK155

E. Initial reporter

1. Name, address & phone #

H- Fletcher MD
Dept. of Obstetrics & Gynecology
University of the West Indies
Mona, Kingston,
JAMAICA

Telephone Nr: Unknown

RECEIVED
FEB 01 1999
BY:

2. Health professional? ☑ yes ☐ no

3. Occupation: MD

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

Individual Safety Report

3189258-7-00-02

U.S. REPORTING

LE **Drug Experience Report**

Searle Research and Development

Approved by FDA on September 17, 1993

990126-SK155

FDA Use Only

B. Adverse event or product problem (continued)

5. Describe event or problem

effaced and 2 cm dilated. Although she was contracting, a further 100 microg misoprostol was inserted. One-and-a-half hours later she had a spontaneous delivery of a previable fetus with the placenta and membranes all expelled as one sac. Blood loss was estimated at 350 ml. She was then given 5 units of oxytocin intramuscularly. Fifteen minutes later she was found to be restless and the uterus was noted to be flabby and syntometrine (1 ampoule) given intravenously. Fifteen minutes later she had a cardiorespiratory arrest and could not be resuscitated. Post mortem findings revealed pleural and pericardial effusions, intracerebral haemorrhage and uterine rupture with 200 ml blood in the broad ligament with a tear along the right lateral border of the uterus starting 5 cm inferior to the cornu of the uterus and extending downward to the cervix." This is the first of two cases. The second case is found in 990126-SK156.

990126-SK155

MISOPROSTOL

DSS

FEB 0 1 1999

ADVERSE EVENT REPORTING SYSTEM

RECEIVED
JAN 2 9 1999
BY:

RECEIVED
FEB 0 1 1999
BY:

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.

REPRINT INCLUDED IN THE REFERENCE LIST

2 PAGES

Individual Safety Report
3188502-X-00-01

U.S. REPORTING

LE Drug Experience Report

Searle Research and Development

Approved by FDA on September 17, 1998

MFR report # 990126-SK156

UF/Diet report #

FDA Use Only

990126-SK156

MISOPROSTOL

A. Patient information

1. Patient Identifier	2. Age at time of event: 27 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 Unknown (mo/day/yr)
- ☐ life-threatening
- ☐ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☑ other: Medically Significant

3. Date of event (mo/day/yr): Unknown

4. Date of this report (mo/day/yr): JAN 27 1999

5. Describe event or problem

MEDICALLY SIGNIFICANT

Fletcher, H. MD, McCaw-Binns, A.. Rupture Of The Uterus With Misoprostol (Prostaglandin EI) Used For Induction Of Labour. Journal of Obstetrics & Gynaecology 1998; 18/2 184-185.

"A 27-year-old (gravida 4, para 2 plus one) with two previous uncomplicated spontaneous vaginal deliveries and one spontaneous abortion treated with dilatation and curettage. She was booked in a rural hospital and her gestational age at presentation was 35 weeks. She was transferred to the obstetric unit, of a rural referral hospital, with a diagnosis of severe preeclampsia with hyperreflexia, headache and a blood pressure of 170/120 mmHg urine albumen 3+. Haemoglobin level 9.6 g/dl, sickle positive, prothrombin time and partial thromboplastin times were normal. Urea and electrolytes were normal. She was stabilized and treated with apresoline and magnesium sulphate. The fetus was assessed as normal. She was induced with 100 microg misoprostol and monitored to the following day. She did not make any progress and continued to be treated with apresoline and magnesium sulphate. After more than 30 hours she started to complain of lower abdominal pain.

(continues...)

6. Relevant test/laboratory data, including dates

DSS

FEB 0 1 1999

ADVERSE EVENT REPORTING SYSTEM

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

CONCOMITANT ILLNESSES: SEVERE PRE-ECLAM NOS; PREG W HX OF ABORTION; D&C NEC; SICKLE-CELL ANEMIA NOS

RECEIVED
FEB 0 1 1999
BY:

C. Suspect medication(s)

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

#1 MISOPROSTOL

#2

2. Dose, frequency & route used

#1 150.000 MCG VAG

#2

3. Therapy dates (if unknown, give duration)

#1 UNKNOWN

#2

4. Diagnosis for use (indication)

#1 MEDICAL INDUCTION LABOR

#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)

HYDRALAZINE HYDROCHLORIDE	Unknown - Unknown
MAGNESIUM SULFATE	Unknown - Unknown
OXYTOCIN	Unknown - Unknown
ERGOMETRINE	Unknown - Unknown

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 (mo/day/yr): JAN 26 1999

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
ABORTION
Fetal death

9. Mfr. report number: 990126-SK156

RECEIVED
JAN 2 9 1999
BY:

E. Initial reporter

1. Name, address & phone #

H- Fletcher MD
Dept. of Obstetrics & Gynecology
University of the West Indies
Mona, Kingston,
JAMAICA

Telephone Nr: Unknown

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.

Individual Safety Report

3188502-X-00-02

U.S. REPORTING

Drug Experience Report

Searle Research and Development

Approved by FDA on September 17, 1985

MFR report # 990126-SK156

IND/Dist report #

FDA Use Only

B. Adverse event or product problem (continued)

5. Describe event or problem

Her vital signs remained as before with no worsening. A further 50 microg of misoprostol was inserted intravaginally. About 5 hours later 2.5 units of oxytocin was started as an intravenous drip titrated in 500 mg Ringer's lactate solution. About 3 hours later and 38 hours after she was first given misoprostol, she delivered a fresh stillbirth. Blood loss at delivery was estimated at 250 ml, but a record was made that the lochia was heavy and the uterus was high and bulky. Fifteen minutes after delivery oxytocin 10 units intravenously was given and syntometrine 1 ampoule intramuscularly was also given. Two hours and 15 minutes later the patient was noted to be in hypovolaemic shock. The consultant was summoned and a laparotomy and total abdominal hysterectomy performed. At laparotomy a uterine rupture was noted into the left broad ligament involving the uterine artery. The tear extended down into the vagina. Blood loss was estimated at 4 litres and the patient remained in shock despite 11 units of blood, 1980 ml fresh frozen plasma and 5 units of cryoprecipitate. She developed a disseminated intravascular coagulopathy and died. Post mortem revealed 300 mg blood in the pleural cavity, 1800 ml blood in the peritoneal cavity." This is the second of two cases. The first case is found in 990126-SK155.

990126-SK156

MISOPROSTOL

3198076-5-00-01

SEARLE

U.S. REPORTING

Drug Experience Report

Searle Research and Development

Approved by FDA on September 17, 1993

MFR report # 990209-SK266

MFR/Dist report #

FDA Use Only

THE FDA

Page 1 of 1

A. Patient information

1. Patient identifier	2. Age at time of event: UNK 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 ____ (mo/day/yr)
- ☐ life-threatening
- ☐ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☑ other: Medically Significant

3. Date of event (mo/day/yr)	4. Date of this report (mo/day/yr)
Unknown	FEB 11 1999

5. Describe event or problem

MEDICALLY SIGNIFICANT

Aguero, O. MD. Use Of Misoprostol In Obstetrica. Rev. Obstet. Ginecol. Venez 1996; 56 (2): 67-74.

"Quadrigesta, elective induction in week 38 with 200 micrograms of misoprostol. Normal birth in 2 hours, 53 minutes. When examining the uterus postpartum, left anterolateral uterine rupture was found. Hysterorrhaphy. Good development." This is the second of two cases. The first case is found in 990209-SK262.

DSS

FEB 16 1999

ADVERSE EVENT REPORTING SYSTEM

6. Relevant test/laboratory data, including dates

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

RECEIVED

FEB 12 1999

BY:

C. Suspect medication(s)

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

#1 MISOPROSTOL

#2

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration)
#1 200.000 MCG UNK	#1 UNKNOWN
#2	#2

4. Diagnosis for use (indication)

#1 MEDICAL INDUCTION LABOR

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

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 (mo/day/yr): FEB 8 1999

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

990209-SK266

E. Initial reporter

1. Name, address & phone #

O- Aguero MD
Hosp. Privado Centro Medico

Caracas,
VENEZUELA

Telephone Nr: Unknown

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA
☑ yes ☐ no	MD	☐ 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.

990209-SK266

MISOPROSTOL

REPRINT
INCLUDED IN REFERENCE LIST

26 PAGES

Individual Safety Report

3454176-3-00-01

PRINT DATE: 03-FEB-2000 16:30:37

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

...PORTING

...g Experience Report

Searle Research and Development

Approved by FDA on September 17, 1993

Mfr report # 991217-SK980

UF/Diet report #

FDA Use Only

991217-SK980

A. Patient information

1. Patient identifier	2. Age at time of event: 38 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 ____ (mo/day/yr)
- ☑ life-threatening
- ☑ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☑ other: Medically Significant

3. Date of event (mo/day/yr)	4. Date of this report (mo/day/yr)
NOV 19 1999	FEB 3 2000

5. Describe event or problem

32 year-old female patient took by herself, the morning, one tablet of Cytotec, when she was pregnant (38 weeks of amenorrhea). She presented uterine contractions and bleeding and she was hospitalized. The patient gave birth at 8:15 pm to a baby who did not present any problem. An uterine rupture was found (lower segment and cervix) which was treated by suture and embolization of the uterine artery.

(Follow-Up) JAN 25 2000
38 year-old female patient took by herself, on Nov-19-99 at 9:00 am, one tablet of CYTOTEC, by vaginal route. The labor started about 10:00 - 11:00 am. the patient was admitted to the maternity unit at 14:00 pm. An epidural block was performed at 17:00 pm. a pain of the left side and minor metrorrhagia persisted. The normal childbirth occurred at 10:20 pm, with abundant bleeding. A suture was done due to a bleeding of the vaginal wall and the left fornix of vagina. Due to the persistence of the hemorrhagia, the patient had a new suture under general anesthesia in operating room. An uterine bleeding persisted, leading to suspect an uterine tears. The patient was transfused (12 globular units) and she received hydroxyethylamidon (1500 ml), calcium/potassium/sodium chloride (2000 ml) and albumin (5000 ml). An embolization of the right and left uterine

(continues...)

6. Relevant test/laboratory data, including dates

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

CONCOMITANT ILLNESSES: LEGAL AB W COMP NEC
Legal abortion with uterine perforation

(Follow-Up) JAN 25 2000
2 legal abortions with one uterine perforation (fundus) in 1992 and 2 pregnancies with normal deliveries

C. Suspect medication(s)

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

#1 CYTOTEC (MISOPROSTOL)

#2

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1 200.000 MCG QD VAG	#1 NOV 19 1999 - NOV 19 1999
#2	#2

4. Diagnosis for use (indication)	5. Event abated after use stopped or dose reduced
#1 UNKN CAUSE MORB/MORT NEC	#1 ☐ yes ☐ no ☑ doesn't apply
#2	#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)	7. Exp. date (if known)	8. Event reappeared after reintroduction
#1 UNK	#1 UNK	#1 ☐ yes ☐ no ☑ doesn't apply
#2	#2	#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)

G. All manufacturers

1. Contact office - name/address

Dennis P. Miley, M.D.
G.D. Searle and Co.
9855 Woods Drive
Skokie, Illinois 60077

2. Phone number: (847) 581-7874

3. Report source (check all that apply)

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

4. Date received by manufacturer (mo/day/yr): JAN 25 2000

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 # 1 (Rev No. 1)

8. Adverse event term(s)
UTERINE PERFORATION
BIRTH PREMATURE

9. Mfr. report number: 991217-SK980

FEB 07 2000

E. Initial reporter

1. Name, address & phone #
-- Unidentified Physician MD

FRANCE

Telephone Nr: Unknown
Local Code:

DSS

FEB 08 2000

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA
☑ yes ☐ no	MD	☐ 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.

3454176-3-00-02

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

REPORTING

ug Experience Report

Searle Research and Development

Approved by FDA on September 17, 1998

Mfr report #: 991217-SK980

UF/Dist report #:

FDA Use Only

991217-SK980

B. Adverse event or product problem (continued)

5. Describe event or problem

arteries was done and the bleeding rapidly subsided. The patient was transferred to the surgical resuscitate unit.

The patient recovered with sequela.

Patient's age now indicated as 38 years.

FEB 07 2000

DSS

FEB 08 2000

FOLLOW-UP

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.

Individual Safety Report

3383627-8-00-01

o Wellcome

(Page 1 of 1)

Approved by the FDA (HF-2) on 3 Nov 93

Mfr report # B0072245A

UF/Dist report #

FDA Use Only

A. Patient information

1. Patient identifier	2. Age at time of event: 39Y or Date of birth UNK	3. Sex	4. Weight (lb)
In confidence		☒ female ☐ male ☐ unknown	UNK

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

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

- ☐ death
- ☐ life-threatening
- ☒ hospitalization - initial or prolonged
- ☒ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: UNK

4. Date of this report: 25Oct1999

5. Describe event or problem

A physician reported that a 39 year old pregnant lady received chlorambucil (Leukeran) 4mg orally throughout her pregancy, until 19 weeks, for an unspecified indication. The patient took misoprostol during her pregnancy, without medical prescription and for the purposes of producing abortion, and this resulted in uterine rupture at 19 weeks. The event required a caesarian section and hysterectomy to be performed. Examination revealed a 19 week dead fetus, weight 480 grams and length 19cm, which was without microscopic evidence of defects. A histopathologic examination was not performed.

6. Relevant tests/laboratory data, including dates

UNK

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

UNK

DSS

OCT 2 8 1999

ADVERSE EVENT REPORTING SYSTEM

C. Suspect medication(s)

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

#1 Leukeran Tablet (Chlorambucil)

#2 Misoprostol (formulation unknown) (Misoprostol)

2. Dose / frequency / route used

#1 2 mg / Twice per day / Oral

#2 UNK / UNK / Unknown

3. Therapy dates

#1 UNK

#2 UNK

4. Diagnosis for use (indication)

#1 UNK

#2 Elective abortion

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 None

#2 None

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 (if known)

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

UNK

G. All manufacturers

1. Contact office - name/address

Glaxo Wellcome
North American Product Surveillance
PO Box 13398
Research Triangle Park
NC 27709

2. Phone number 1-888-825-5249 ext. 37070

3. Report source

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

4. Date received by manufacturer 15Oct1999

5. (A)NDA # 10-669

IND #

PLA #

pre-1938 ☐ yes

OTC product ☐ yes

6. If IND, protocol #

7. Type of report

☐ 5-day ☒ 15-day

☐ 10-day ☐ periodic

☒ initial ☐ follow-up #

8. Adverse event term(s)

Uterine rupture
Cesarean delivery
Hysterectomy
Intrauterine death

9. Mfr. report number B0072245A

E. Initial Reporter

1. Name, address & phone #

[redacted]

2. Health professional? ☒ yes ☐ no

3. Occupation: Physician

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

FDA Form 3500A Facsimile

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

CYTOTEC ARTICLE AND JOURNAL REFERENCES

List of References

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

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

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

Clinical Management Guidelines for Obstetrician-Gynecologists. 1999. ACOG Practice Bulletin. 10: 1-9.

Coelho HL, Teixeira AC, Cruz M et al. 1994. Misoprostol: The experience of women in Fortaleza, Brazil. Contraception. 49: 101-109.

Daisley H. 2000. Case Reports. Medical Science Law. 40: 79-82.

Fletcher H, McCaw-Binns A. 1998. Rupture of the uterus with misoprostol (prostaglandin E1) used for induction of labour. Journal of Obsterics and Gyneocology. 18: 184-185.

Goldberg A, Greenberg, M, Darney. 2001. Misoprostol and Pregnancy. New England Journal of Medicine. 344: 38-61.

Gonzalez CH, Marques-Dias MJ, Kim CA, et.al. 1998. Congenital abnormalities in Brazilian children associated with misoprostol misuse in first trimester of pregnancy. Lancet. 351: 1624-1627.

Induction of Labor with Misoprostol. 1999. The American College of Obstetricians and Gynecologists. Number 228.

Jwarah E, Greenhalf JO. 2000.Rupture of the uterus after 800 micrograms misoprostol given vaginally for termination of pregnancy. British Journal of Obsetrics and Gynocology. 107: 807.

Mathews JE, Mathai M, George A. 2000. Uterine rupture in a multiparous

woman during labor induction with oral misoprostol. International Journal of Gynocology & Obstetrics. 68: 43-44.

Phillips K, Berry C, Mathers AM. 1996. Uterine rupture during second trimester termination of pregnanacy using mifepristone and a prostaglandin. European Journal of Obstetrics & Gynecology and Reproductive Biology. 65: 175-176.

Plaut MM, Schwartz ML, Lubarsky SL. 1999. Uterine rupture associated with the use of misoprostol in the gravid patient with a previous cesarean section. American Journal Obstetrics and Gynecology. 180: 1535-1542.

Schaff E, Fielding S, Westhoff C, Ellertson C, Eisinger S, Stadalius L, Fuller L. 2000. Vaginal Misoprostol Administered 1,2, or 3 Days After Mifepristone for Early Medical Abortion, A Randomized Trial. JAMA. 284: 1948-1953.

Spitz IM, Bardin CW, Benton L, Robbins A. 1998. Early Pregnancy Termination with Mifepristone and Misoprostol in the United States. The New England Journal of Medicine. 338: 1241-1247.

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

Zimmerman R. 2000. FDA-Pharmacia Clash May Curb The Widespread Use of RU-486. The Wall Street Journal. October 18, 2000.

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.