SEARLE

08/31/00

August 21, 2000

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

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 ——

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.

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

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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

Electronic Mail Message

Date: 4/14/00 4:00:52 PM
From: [redacted]
To: [redacted]
Cc: [redacted]
Cc: [redacted]
Subject: Cytotec "Dear Health Care Practitioner" letter

[redacted]

I tried to call you this afternoon, but were told you were out of the office. I am on leave, or I wouldn't be bugging you this late on Friday. I am trying to get out of here for vacation, but something ALWAYS comes up.

Searle has submitted (3/9/00)a draft Dear Health Care Practitioner letter that they would like to issue ASAP. What else is new, huh?? Anyway, we transferred a drug group from one PM [redacted], to another [redacted] and this sort of fell thru the cracks[redacted]... is on leave next week also. The letter is about the "unapproved use of intravaginal or oral misoprostol in pregnant women for induction of labor or abortion".

As you may know, misoprostol is used with mifepristone (??? spelling) to induce abortions, which I hear is back in the FDA for review with a FDAMA goal date of sometime in September. I would like DDMAC to look at this letter, but because it previously fell thru the cracks, we need someone to look at it ASAP.

I would like to consult it up to you, and if it needs to be turfed to someone else, that is fine. I will contact you when I return from leave on 4/24.

Sorry for the babbling.

[redacted]

Electronic Mail Message

Date: 10/17/00 9:14:42 AM
From: [redacted]
To: [redacted]
To: [redacted]
Cc: [redacted]
Subject: FWD: - no subject (01JVEW7I77ZE8Y52Z0) -

[redacted] had a few calls last month from the American College of OB GYN and they were saying the new cytotec letter was scaring some institutions about using this for Abortions, or at the least causing reevaluation of its use at institutions. The college was planning to hold a meeting on whether it should change its guidelines for use because of this letter.

[redacted], can you follow up with the OBGYN contact on their conference they had earlier this month and see if they are changing the college's recommendation for its use. Let us know. Thanks.

[redacted]

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF THE COMMISSIONER MEETING
EXECUTIVE SUMMARY

Date: July 14, 2000
Time: 11:30 – 12:00 PM
Location: Rm. 14-68, PKLN

Subject: Mifepristone

Attendees: Jane Henney

Meeting Purpose: To provide an update on the review of mifepristone.

Meeting Agenda: will lead the briefing.

Background: Mifepristone, also know as RU 486, is an abortifacient to be used with misoprostol for medical abortion. Mifepristone is being reviewed by CDER with a PDUFA date of September 30, 2000. The drug's sponsor, The Population Council (PC), has three areas to address from the last approvable action of February 18, 2000: chemistry/manufacturing, distribution system, and labeling.

Chemistry/manufacturing - In May 2000, FDA was informed that the manufacturing processes for the drug substance have been changed from how the NDA described the process. These changes are significant and require pre- and post-change comparative physical, analytical, and stability data to demonstrate that quality is maintained. The sponsor is responsible for supplying physical and analytical data by mid-July and stability data sometime in September.

The inspection of the Chinese drug substance maker is scheduled for July 27 and 28.

Distribution System - On July 5, 2000, the sponsor proposed that mifepristone be directly distributed to health care providers who self-attest to specific qualifications. PC proposes that the drug be provided by or under the supervision of a physician who has the ability to assess the duration of pregnancy accurately, to diagnose ectopic pregnancies, and to assure patient access to medical facilities equipped to provide emergency treatment of incomplete abortion, blood transfusions and emergency resuscitation. The sponsor does not believe it is necessary for prescribers to possess all the qualifications needed to perform every step in the patient's care. PC believes the prescriber can be advised to plan for care such as handling of incomplete abortions and the need for surgery and to give patient information about how to obtain these types of care. The sponsor does not propose health care providers who are distributing this drug be trained in the use of this drug, but the sponsor is making available educational programs. The sponsor also objects to approving this drug under Subpart H's provision for restricted distribution

Labeling - The sponsor

Executive Secretariat Contact

APPEARS THIS WAY
ON ORIGINAL