



NDA 019268/S-047

SUPPLEMENT APPROVAL

Worldwide Regulatory Strategy
Pfizer Inc.
Attention: Jonathan G. Carrier
Senior Director
235 East 42nd Street
New York, NY 10017-5755

Dear Mr. Carrier:

Please refer to your Supplemental New Drug Application (sNDA) dated and received August 10, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Cytotec (misoprostol) Tablets, 100 mcg and 200 mcg and your misoprostol authorized generic.

We acknowledge receipt of your amendment dated September 10, 2012.

We also refer to our letter dated July 11, 2012, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for misoprostol. This information pertains to risk information and guidance to improve the safety of misoprostol if it is used for the unapproved use of cervical ripening or labor induction in pregnant women at or near term. The information has been added to the Warnings section of labeling as follows:

WARNINGS

For hospital use only if misoprostol were to be used for cervical ripening, induction of labor, or for the treatment of serious post partum hemorrhage, which are outside of the approved indication.

Additionally, the agreed upon changes to the language included in your amendment submitted on September 10, 2012, that differ from our July 11, 2012, letter are as follows (additions are noted by underline and deletion are noted by ~~strike through~~).

PRECAUTIONS

Drug interactions:

Prostaglandins such as Cytotec may augment the activity of oxytocic agents, especially when given less than 4 hours prior to initiating oxytocin treatment. ^{(b) (4)}

(b) (4)

Labor and delivery: Cytotec can induce or augment uterine contractions. Vaginal administration of Cytotec, outside of its approved indication, has been used as a cervical ripening agent, for the induction of labor and for treatment of serious postpartum hemorrhage in the presence of uterine atony. (b) (4)

(b) (4)

A major adverse effect of the obstetrical use of Cytotec is uterine tachysystole which may progress to uterine tetany with marked impairment of uteroplacental blood flow, and uterine rupture (requiring surgical repair, hysterectomy, and/or salpingo-oophorectomy), (b) (4) or amniotic fluid embolism and lead to adverse fetal heart changes. Uterine activity and fetal status should be monitored by trained obstetrical personnel in a hospital setting (b) (4)

(b) (4)

The risk of uterine rupture (b) (4) increases with advancing gestational ages and prior uterine surgery, including Cesarean delivery. Grand multiparity also appears to be a risk factor for uterine rupture.

The use of Cytotec outside of its approved indication may also be associated with meconium passage, meconium staining of amniotic fluid, and Cesarean delivery. Maternal shock, maternal death, fetal bradycardia, and fetal death have also been reported with the use of misoprostol.

Cytotec should not be used in the third trimester in women with a history of Cesarean section or major uterine surgery because of an increased risk of uterine rupture. (b) (4) Cytotec should not be used (b) (4) in cases where uterotonic drugs are generally contraindicated or where hyperstimulation of the uterus is considered inappropriate, such as cephalopelvic disproportion, grand multiparity, hypertonic or hyperactive uterine patterns, or fetal distress where delivery is not imminent, or when (b) (4) surgical intervention is more appropriate.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (package insert), with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jagjit Grewal, Regulatory Project Manager, at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Director for Safety
Division of Gastroenterology and Inborn Error
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Label

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOYCE A KORVICK
11/19/2012