DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 12-623/S-061
NDA 20-334/S-004
NDA 20-868/S-008

SUPPLEMENTS APPROVAL

Pfizer, Inc.
Attention: Ms. Beatrice Curran
Associate Director
Worldwide Regulatory Strategy
235 East 42nd Street
New York, NY 10017-5755

Dear Ms. Curran:

Please refer to your supplemental new drug applications (sNDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA Number Name of Drug Product and Formulation Strengths	Supplement Number	Letter and Receipt Date of Supplement
12-623 FLAGYL® (metronidazole) Tablets	061	January 15, 2010
20-334 FLAGYL® (metronidazole) Capsules	004	January 15, 2010
20-868 FLAGYL® ER (metronidazole) Tablets	008	January 15, 2010

We acknowledge receipt of your amendment to each of these three supplemental NDAs dated June 25, 2010.

SUMMARY OF LABELING SUPPLEMENTS

These "Changes Being Effected" supplemental new drug applications provide for changes to strengthen the **WARNINGS** and **ADVERSE REACTIONS** sections of the package insert. Additionally, you also identified a need to make a change to strengthen the Hypersensitivity subsection under the **ADVERSE REACTIONS** section. This change is also included in the updated package insert.

REVISIONS TO THE PACKAGE INSERT

The revisions to the package insert (PI) that were agreed upon for the above three supplements are as follow (additions are noted with underline and deletions with ~~strikethrough~~):

a. Under the **WARNINGS** section, the subheading is revised and new information is added:

~~Convulsive Seizures and Peripheral Neuropathy~~Central and Peripheral Nervous System Effects: Convulsive seizures, encephalopathy, aseptic meningitis, optic and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity, have been reported in patients treated with metronidazole. The appearance of abnormal neurologic signs demands the prompt discontinuation of Flagyl (metronidazole) therapy. Flagyl should be administered with caution to patients with central nervous system diseases.

b. Under the **ADVERSE REACTIONS** section, the first word is revised and new information is added in first paragraph, and the "Central Nervous System" and "Hypersensitivity" subsections:

~~Two~~The most serious adverse reactions reported in patients treated with Flagyl (metronidazole) have been convulsive seizures, encephalopathy, aseptic meningitis, optic and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity. Since persistent peripheral neuropathy has been reported in some patients receiving prolonged administration of Flagyl, patients should be specifically warned about these reactions and should be told to stop the drug and report immediately to their physicians if any neurologic symptoms occur.

The most common adverse reactions reported have been referable to the gastrointestinal tract, particularly nausea reported by about 12% of patients, sometimes accompanied by headache, anorexia, and occasionally vomiting; diarrhea; epigastric distress; and abdominal cramping. Constipation has also been reported.

The following reactions have also been reported during treatment with Flagyl (metronidazole):

Mouth: A sharp, unpleasant metallic taste is not unusual. Furry tongue, glossitis, and stomatitis have occurred; these may be associated with a sudden overgrowth of *Candida* which may occur during therapy.

Hematopoietic: Reversible neutropenia (leukopenia); rarely, reversible thrombocytopenia.

Cardiovascular: Flattening of the T-wave may be seen in electrocardiographic tracings.

Central Nervous System: Encephalopathy, aseptic meningitis, ~~C~~convulsive seizures, optic neuropathy, peripheral neuropathy, dizziness, vertigo, incoordination, ataxia, confusion, dysarthria, irritability, depression, weakness, and insomnia.

Hypersensitivity: Urticaria, erythematous rash, Stevens-Johnson Syndrome, toxic epidermal necrolysis, flushing, nasal congestion, dryness of the mouth (or vagina or vulva), and fever.

Renal: Dysuria, cystitis, polyuria, incontinence, and a sense of pelvic pressure. Instances of darkened urine have been reported by approximately one patient in 100,000. Although the pigment which is probably responsible for this phenomenon has not been positively identified, it is almost certainly a metabolite of metronidazole and seems to have no clinical significance.

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text, including minor editorial revisions.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package inserts) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. 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 these NDAs, including pending "Changes Being Effected" (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.

LABELING

Submit final printed labeling as soon as they are available, but no more than 30 days after they are printed. The final printed labeling (FPL) must be identical to the package insert for each of the three NDAs.

The final printed labeling for each of the three NDAs should be submitted electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material for each NDA. For administrative purposes, designate these submissions "**Final Printed Labeling for approved**

NDA 21-623/S-061; Final Printed Labeling for approved NDA 20-334/S-004; Final Printed Labeling for approved NDA 20-868/S-008." Approval of these submissions by FDA is not required before the labeling is used.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about these drug products (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to these NDAs, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

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 Jacquelyn Smith, M.A., Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Ozlem Belen, M.D.
Deputy Director of Safety
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Package Insert (PI) for
NDA 12-623, FLAGYL® (metronidazole) Tablets
NDA 20-868, FLAGYL® (metronidazole) Capsules
NDA 20-334, FLAGYL® ER (metronidazole) Tablets

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20868	SUPPL-8	GD SEARLE LLC	FLAGYL-ER
NDA-20334	SUPPL-4	GD SEARLE LLC	FLAGYL
NDA-12623	SUPPL-61	GD SEARLE LLC	FLAGYL

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/s/

OZLEM A BELEN
08/19/2010