DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19384/S-056

SUPPLEMENT APPROVAL

Merck Sharp & Dohme Corp.
Attention: Daniel Larkins
Manager, Regulatory Affairs
P.O. Box 1000, UG2CD-50
North Wales, PA 19454-2505

Dear Mr. Larkins:

Please refer to your Supplemental New Drug Application (sNDA) dated and received December 14, 2010 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for NOROXIN® (norfloxacin) Tablets.

We acknowledge receipt of your amendments dated January 14, 2011.

(b) (4)

We also refer to our letter dated November 15, 2010, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for all fluoroquinolone products. This information pertains to the risk of fluoroquinolone-associated myasthenia gravis exacerbation, which is a potentially life-threatening event and may require ventilatory support.

This supplemental new drug application provides for revisions to the labeling for NOROXIN® (norfloxacin). The agreed upon changes to the language included in our November 15, 2010, letter are as follows (additions are noted by underline and deletion are noted by ~~strikethrough~~).

I. BOXED WARNING

WARNING:
Fluoroquinolones, including NOROXIN®, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (See WARNINGS).

Fluoroquinolones, including NOROXIN®, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid NOROXIN® in patients with known history of myasthenia gravis (See Warnings).

II. The following sub-section has been added after the **WARNINGS/Tendinopathy and Tendon Rupture** sub-section:

Exacerbation of myasthenia gravis
Fluoroquinolones, including NOROXIN, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Postmarketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid NOROXIN in patients with known history of myasthenia gravis. [See **PRECAUTIONS/Information for Patients and ADVERSE REACTIONS/Post-Marketing/*Musculoskeletal*]**

III. **PRECAUTIONS/General** has been revised as follows:
General

Needle-shaped crystals were found in the urine of some volunteers who received either placebo, 800 mg norfloxacin, or 1600 mg norfloxacin (at or twice the recommended daily dose, respectively) while participating in a double-blind, crossover study comparing single doses of norfloxacin with placebo. While crystalluria is not expected to occur under usual conditions with a dosage regimen of 400 mg b.i.d., as a precaution, the daily recommended dosage should not be exceeded and the patient should drink sufficient fluids to ensure a proper state of hydration and adequate urinary output.

Alteration in dosage regimen is necessary for patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Moderate to severe phototoxicity reactions have been observed in patients who are exposed to excessive sunlight while receiving some members of this drug class. Excessive sunlight should be avoided. Therapy should be discontinued if phototoxicity occurs.

Rarely, hemolytic reactions have been reported in patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity who take quinolone antibacterial agents, including norfloxacin. (See ADVERSE REACTIONS.)

~~Quinolones, including norfloxacin, may exacerbate the signs of myasthenia gravis and lead to life-threatening weakness of the respiratory muscles. Caution should be exercised when using quinolones, including NOROXIN, in patients with myasthenia gravis (see ADVERSE REACTIONS).~~

IV. **PRECAUTIONS/Information for Patients** has been revised as follows:

Information for Patients:
Patients should be advised:

- to contact their healthcare provider if they experience pain, swelling, or inflammation of a tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and discontinue NOROXIN treatment. The risk of

severe tendon disorder with fluoroquinolones is higher in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.

- that fluoroquinolones like NOROXIN may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Patients should call their healthcare provider right away if you have any worsening muscle weakness or breathing problems.

V. **ADVERSE REACTIONS/Post-Marketing/*Musculoskeletal*** section has been revised as follows:

Musculoskeletal

Tendinitis, tendon rupture; exacerbation of myasthenia gravis (see ~~PRECAUTIONS~~**WARNINGS/Exacerbation of myasthenia gravis**); elevated creatine kinase (CK).

VI. Medication guide:

a. In the section "**What is the most important information I should know about NOROXIN**? The following has been added as the last bulleted paragraph:

- **Worsening of myasthenia gravis (a disease which causes muscle weakness).** Fluoroquinolones like NOROXIN may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Call your healthcare provider right away if you have any worsening muscle weakness or breathing problems.

See the section **"What are the possible side effects of NOROXIN?"** for more information about side effects

b. The section **"What should I tell my healthcare provider before taking NOROXIN?"** has been revised as follows:

What should I tell my healthcare provider before taking NOROXIN?

See **"What is the most important information I should know about NOROXIN?"**

Tell your healthcare provider about all your medical conditions, including if you:

- have tendon problems
- have a disease that causes muscle weakness (myasthenia gravis)
- have central nervous system problems (such as epilepsy)
- have nerve problems
- ~~have myasthenia gravis~~
- have or anyone in your family has an irregular heartbeat, especially a condition called "QT prolongation."
- have low potassium (hypokalemia)

- have history of seizures
- have kidney problems. You may need a lower dose of NOROXIN if your kidneys do not work well.
- have rheumatoid arthritis (RA) or other history of joint problems
- are pregnant or planning to become pregnant. It is not known if NOROXIN will harm your unborn child.
- are breast-feeding or planning to breast-feed. It is not known if NOROXIN passes into breast milk. You and your healthcare provider should decide whether you will take NOROXIN or breast-feed.

- The section **"What are the possible side effects of NOROXIN?"** has been revised as follows:

  - ~~**Worsening of myasthenia gravis symptoms.** Fluoroquinolones, including NOROXIN, may worsen the signs of myasthenia gravis. This may cause trouble breathing which may be life-threatening. Tell your healthcare provider right away if you get this symptom.~~

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 (text for the package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (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).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

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
Division of Drug Marketing, Advertising, and Communications
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 Division of Drug Marketing, Advertising, and Communications (DDMAC), 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.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (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 this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

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 Hyun Son, Pharm.D., Safety Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Content of Labeling

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

/s/

OZLEM A BELEN
02/25/2011