



NDA 19-384/S-049

Merck & Co., Inc.
Attention: Peter Kusma
Manager, Worldwide Regulatory Affairs
UG2CD-48
P.O. Box 1000
North Wales, PA 19454-1099

Dear Mr. Kusma:

Please refer to your supplemental new drug application dated and received May 2, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NOROXIN[®] (norfloxacin), Tablets, 400mg.

We also acknowledge receipt of your submission dated June 6, 2008 containing final printed label.

This "Changes Being Effected" Supplemental New Drug Application (sNDA), provides for the following revisions to the package insert for NOROXIN[®] to ensure consistency in the communication of the risks of acute liver failure and acute severe live injury, QTc prolongation/torsades de pointes, tendon rupture, toxic epidermal necrolysis (TEN), and phototoxicity submitted in response to the Supplement Request letter issued by the Division on March 19, 2008. The submission also provides for a Patient Package Insert.

The supplemental application provides for revisions as follows (deletions are ~~struck through~~ and additions are underlined):

1. In the **WARNINGS** section, the title of the *Hypersensitivity Reaction* subsection is revised as follows:

Hypersensitivity Reactions/~~anaphylaxis~~.

2. The **WARNINGS**/*Hypersensitivity Reactions* subsection is modified as follows:

Serious and occasionally fatal hypersensitivity (~~anaphylactoid or anaphylactic~~) reactions, some following the first dose, have been reported in patients receiving quinolone therapy, including NOROXIN. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria and itching. Only a few patients had a history of hypersensitivity reactions. If an allergic reaction to norfloxacin occurs, discontinue the drug. Serious acute hypersensitivity reactions ~~may~~ require immediate emergency treatment with epinephrine. Oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, including intubation, should be administered as indicated.

Other serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with quinolones, including NOROXIN. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following:

- fever, rash or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome);
- vasculitis; arthralgia; myalgia; serum sickness;
- allergic pneumonitis
- interstitial nephritis; acute renal insufficiency or failure;
- hepatitis; jaundice; acute hepatic necrosis or failure;
- anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hemotologic abnormalities.

The drug should be discontinued immediately at the first appearance of a skin rash, jaundice, or any other signs of hypersensitivity and supportive measures instituted (See **PRECAUTIONS/ Information for Patients** and **ADVERSE REACTIONS**).

3. In the **PRECAUTIONS/General** subsection, the third paragraph is modified as follows:

Moderate to severe photosensitivity/phototoxicity reactions have been observed in patients who are exposed to the latter of which may manifest as exaggerated sunburn reactions (e.g., burning, erythema, exudation, vesicles, blistering, edema) involving areas exposed to light (typically the face, “V” area of the neck, extensor surfaces of the forearms, dorsa of the hands), can be associated with the use of quinolone antibiotics after sun or UV light exposure. Therefore, excessive sunlight while receiving some members of this drug class. Excessive sun exposure to these sources of light should be avoided. Therapy Drug therapy should be discontinued if phototoxicity occurs (see **ADVERSE REACTIONS, Post-marketing**).

4. In the **PRECAUTIONS/Information for Patients** subsection, the last three bullets are modified as follows:

- To discontinue treatment and inform their physician if they experience pain, inflammation, or rupture of a tendon, and to rest and refrain from exercise ~~until the diagnosis of tendinitis or tendon rupture has been confidently excluded.~~ The risk of serious tendon disorders with quinolones is higher in those over 65 years of age and those on corticosteroids.
- ~~To avoid undue exposure to excessive sunlight while receiving norfloxacin and to discontinue therapy if phototoxicity occurs.~~
- That photosensitivity/phototoxicity has been reported in patients receiving quinolones. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while taking quinolones. If patients need to be outdoors while using quinolones, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. If a sunburn-like reaction or skin eruption occurs, patients should contact their physician.

5. In the **PRECAUTIONS/Geriatric Use** subsection, the following two paragraphs are added at the end of the subsection:

In general, elderly patients may be more susceptible to drug-associated effects on the QTc interval. Therefore, precaution should be taken when using NOROXIN concomitantly with drugs that can result in prolongation of the QTc interval (e.g., class IA or class III antiarrhythmics) or in patients with risk factors for torsades de pointes (e.g., known QTc prolongation, uncorrected hypokalemia).

Patients over 65 years of age are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as NOROXIN. This risk is further

increased in patients receiving concomitant corticosteroid therapy. Tendon rupture usually involves the Achilles, hand, or shoulder tendons and can occur during therapy or up to a few months post completion of therapy. Caution should be used when prescribing NOROXIN to elderly patients, especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue therapy and inform their physicians if any tendon symptoms occur.

6. The **ADVERSE REACTIONS/Post-marketing/skin** subsection is modified as follows:

Skin

Toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme, exfoliative dermatitis, photosensitivity/phototoxicity reactions (see PRECAUTIONS)

7. In the **ADVERSE REACTIONS/Post-Marketing** subsection, a new subsection titled *Hepatic* is created as follows:

Hepatic

Hepatic failure, including fatal cases

PATIENT PACKAGE INSERT

8. A new Patient Package Insert is created as follows:

Patient Information

NOROXIN[®]
(norfloxacin)

400 mg Tablets

This section contains important information about NOROXIN (norfloxacin), and should be read completely before you begin treatment. This section does not take the place of discussions with your doctor or health care professional about your medical condition or your treatment. This section does not list all benefits and risks of NOROXIN. The medicine described here can be prescribed only by a licensed health care professional. If you have any questions about NOROXIN, talk with your health care professional. Only your health care professional can determine if NOROXIN is right for you.

What is NOROXIN?

NOROXIN is an antimicrobial used to treat urinary tract infections, kidney infections, prostatitis and some forms of sexually transmitted diseases (specifically gonorrhea), caused by certain germs called bacteria. NOROXIN kills many of the types of bacteria that can infect the bladder, kidneys, prostate gland and urethra and has been shown in clinical trials to be safe and effective for the treatment of these bacterial infections. NOROXIN is not effective in the treatment of syphilis.

You should contact your doctor if you think your condition is not improving while taking NOROXIN.

NOROXIN Tablets contain 400 mg of active drug.

How and when should I take NOROXIN?

NOROXIN is usually taken twice a day for 3 to 28 days depending on the condition for which you are being treated. For gonorrhea it is given as a single dose of 2 pills taken at one time. It should be swallowed whole and taken with a large glass of water at least 1 hour before or 2 hours after a meal. Try to take the tablet at the same time each day.

You may begin to feel better quickly; however, in order to make sure that all bacteria are killed, you should complete the full course of medication. Do not take more than the prescribed dose of NOROXIN even if you missed a dose by mistake. You should not take a double dose.

Who should not take NOROXIN?

You should not take NOROXIN if you have ever had a severe allergic reaction to any of the group of antimicrobials known as "quinolones" such as ciprofloxacin or levofloxacin. If you develop hives, difficulty breathing, or other symptoms of a severe allergic reaction, seek emergency treatment right away. If you develop a skin rash, you should stop taking NOROXIN and call your health care professional.

You should avoid NOROXIN if you have a rare condition known as congenital prolongation of the QTc interval. If you or any of your family members have this condition you should inform your health care professional. You should avoid NOROXIN if you are being treated for heart rhythm disturbances with certain medicines such as quinidine, procainamide, amiodarone or sotalol. Inform your health care professional if you are taking a heart rhythm drug or if you have any problems with your heart rhythm.

You should also avoid NOROXIN if the amount of potassium in your blood is low. Low potassium can sometimes be caused by medicines called diuretics such as furosemide and hydrochlorothiazide. If you are taking a diuretic medicine you should speak with your health care professional.

If you are pregnant or planning to become pregnant while taking NOROXIN, talk to your doctor before taking this medication. NOROXIN is not recommended for use during pregnancy or nursing, as the effects on the unborn child or nursing infant are unknown.

NOROXIN is not recommended for children.

What are the possible side effects of NOROXIN?

NOROXIN is generally well tolerated. The most common side effects caused by NOROXIN, which are usually mild, include dizziness, nausea, heartburn, headache, and rash. If a rash occurs stop taking NOROXIN and call your health care provider. Less common side effects may include changes in hearing and pain, burning, tingling, numbness, and/or weakness in arms or legs.

If you should develop hives, trouble breathing, wheezing, or other signs of an allergic reaction seek help immediately.

You should be careful about driving or operating machinery until you are sure NOROXIN is not causing dizziness.

Pain, swelling, and tears of the Achilles, shoulder, or hand tendons have been reported in patients receiving fluoroquinolones, including NOROXIN. The risk for tendon effects is higher if you are over 65 years of age, or if you are taking corticosteroids. If you develop pain, swelling, or tear of a tendon you should stop taking NOROXIN, avoid exercise and strenuous use of the affected area, and contact your health care provider.

Convulsions have been reported in patients receiving quinolone antibiotics. Be sure to let your physician know if you have a history of convulsions. Quinolones, including NOROXIN, have been rarely associated with other central nervous system events including confusion, tremors, hallucinations, anxiety, and depression.

Quinolones, including NOROXIN, may worsen the signs of myasthenia gravis leading to difficulty breathing which may be life-threatening. If you develop this symptom contact your health care provider right away.

NOROXIN may cause a rare heart problem known as prolongation of the QTc interval. This condition can cause an abnormal heartbeat and can be very dangerous. The chances of this event are increased in those with a family history of prolonged QTc interval, low potassium (hypokalemia), and those who are taking drugs to control heart rhythm called class IA (quinidine, procainamide), or class III (amiodarone, sotalol) antiarrhythmic agents. You should call your healthcare provider right away if you have symptoms of prolongation of the QTc interval including prolonged heart palpitation (a change in the way your heart beats) or a loss of consciousness (fainting spells).

Diarrhea that usually ends after treatment is a common problem caused by antimicrobials. A more serious form of diarrhea can occur during or up to 2 months after the use of antibiotics. This has been reported with all antimicrobials, including NOROXIN. If you develop a watery or bloody stool, with or without stomach cramps and fever, contact your physician as soon as possible.

Sun sensitivity (photosensitivity), which can appear as skin eruption or severe sunburn, can occur in some patients taking quinolone antimicrobials after exposure to sunlight or artificial ultraviolet light (UV) (e.g., tanning beds). NOROXIN has been infrequently associated with photosensitivity. Avoid excessive exposure to sunlight or artificial UV light while taking NOROXIN. Use a sunscreen and wear protective clothing if you are exposed to the sun. If photosensitivity develops, contact your physician.

NOROXIN can cause crystals to form in the urine of patients taking it if they are dehydrated. Make sure you drink plenty of water while taking NOROXIN.

If you notice any side effects not mentioned in this section or you have any concerns about the side effects you are experiencing, please inform your health care professional.

What about other medicines I am taking?

Tell your doctor about all other prescription and non-prescription medicines, dietary supplements and herbals you are taking. You should avoid taking NOROXIN with certain medicines used to treat an abnormal heartbeat. These include quinidine, procainamide, amiodarone, and sotalol.

Some medicines also produce an effect on the electrocardiogram test, including cisapride, erythromycin, some antidepressants, and some antipsychotic drugs. These may increase the risk of heart beat problems when taken with NOROXIN.

Many antacids and multivitamins may interfere with the absorption of NOROXIN and may prevent it from working properly. You should take NOROXIN either 2 hours before or 2 hours after taking these products.

Remember

- Take your dose of NOROXIN every day.
- Complete the course of medication even if you are feeling better.
- Keep this medication out of the reach of children.

- This information does not take the place of discussions with your doctor or health care professional about your medical condition or your treatment.
- For more complete information about NOROXIN request full prescribing information from your health care professional, pharmacist, or visit our website at www.merck.com.

In addition, the following changes not described in our Supplement Request Letter dated March 19, 2009, are incorporated to the Patient Package Insert, for consistency with the Package Insert.

9. In the **“Patient Package Insert”/ “What are the possible side effects of NOROXIN?”** subsection, the following text was added:

NOROXIN is generally well tolerated. The most common side effects caused by NOROXIN which are usually mild, include dizziness, nausea, heartburn, headache, and rash. If a rash occurs stop taking NOROXIN and call your health care provider. Less common side effects may include changes in hearing and pain, burning, tingling, numbness, and/or weakness in arms or legs.

10. The third paragraph of the **“Patient Package Insert”/ “What are the possible side effects of NOROXIN?”** subsection, the last sentence was moved to the end of this sub-section.

You should be careful about driving or operating machinery until you are sure NOROXIN is not causing dizziness. ~~If you notice any side effects not mentioned in this section or you have any concern about the side effects you are experiencing, please inform your health care professional.~~

11. In the **“Patient Package Insert”/ “What are the possible side effects of NOROXIN”** subsection, the following text was added:

Quinolones, including NOROXIN, may worsen the signs of myasthenia gravis leading to difficulty breathing which may be life threatening. If you develop this symptom contact your health care provider right away.

12. In the **“Patient Package Insert”/ “What about other medicines I am taking?”** subsection was revised as follows:

You should take NOROXIN either ~~4~~2 hours before or 8 2 hours after taking these products.

13. Minor editorial changes throughout the label.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text for the Package Insert and Patient Package Insert submitted on June 6, 2008.

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

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., Senior Regulatory Project Manager, at (301) 796-1939.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, MD
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Package Insert
Patient Package Insert

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

/s/

Renata Albrecht
9/23/2008 04:36:39 PM