



NDA 19-384/S-040, S-042, S-043

Merck & Co., Inc.  
Attention: Mary Beth Wigley  
Manager, Regulatory Affairs  
P.O. Box 4  
Sumneytown Pike, BLA-20  
West Point, PA 19486-0004

Dear Ms. Wigley:

Please refer to your following supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NOROXIN™ (norfloxacin) Tablets, 400 mg.

<u>Supplement</u>	<u>Date submitted</u>	<u>Date received</u>
040	November 27, 2002	November 29, 2002
042	January 26, 2004	January 27, 2004
043	January 29, 2004	January 30, 2004

We acknowledge receipt of your amendments for NDA 19-384/S-040 dated October 3, 2003, October 17, 2003, January 20, 2004, and for NDA 19-384/S-040, S-042, S-043 dated March 19, 2004, May 6, 2004 and July 19, 2004.

NDA 19-384/S-040 provides for the following revisions:

- **WARNINGS** to add information on peripheral neuropathy and include revisions to the tendon rupture statement
- **PRECAUTIONS, General** and **ADVERSE REACTIONS, Post Marketing, Cardiovascular** to include information on QTc prolongation and torsades de pointes
- **PRECAUTIONS, Drug Interactions**, to include an interaction with glyburide.
- **ADVERSE REACTIONS, Post Marketing** to include elevated creatine kinase.

Your submission of March 19, 2004 constitutes a complete response to our September 30, 2003 action letter.

NDA 19-384/S-042 provides for revisions to the package insert under **PRECAUTIONS, Drug Interactions** concerning warfarin, **ADVERSE REACTIONS, Post Marketing, Hematologic** adding agranulocytosis, and **ADVERSE REACTIONS, Post Marketing, Special Senses** adding hearing loss.

NDA 19-384/S-043 was submitted as Changes Being Effected (CBE) and provides for antibacterial drug resistance labeling revisions as specified in the Division's September 11, 2003 letter. This CBE request letter was sent per the Final Rule entitled "**Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use**" (68FR 6062, February 6, 2003).

These supplemental new drug applications provide for the following revisions to the package insert (additions are double underlined and deletions are ~~strike through~~):

**NDA 19-384/S-040**

1. The following revisions were made under the **WARNINGS** section:

**Safety in Children, Adolescents, Nursing Mothers, and during Pregnancy: THE SAFETY AND EFFICACY OF ORAL NORFLOXACIN IN PEDIATRIC PATIENTS, ADOLESCENTS (UNDER THE AGE OF 18), PREGNANT WOMEN, AND NURSING MOTHERS HAVE NOT BEEN ESTABLISHED.** (See **PRECAUTIONS, *Pediatric Use, Pregnancy, and Nursing Mothers*** subsections.) The oral administration of single doses of norfloxacin, 6 times\*\*\* the recommended human clinical dose (on a mg/kg basis), caused lameness in immature dogs. Histologic examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Other quinolones also produced erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species. (See **ANIMAL PHARMACOLOGY.**)

**Seizures:** Convulsions have been reported in patients receiving norfloxacin. Convulsions, increased intracranial pressure, and toxic psychoses have been reported in patients receiving drugs in this class. Quinolones may also cause central nervous system (CNS) stimulation which may lead to tremors, restlessness, lightheadedness, confusion, and hallucinations. If these reactions occur in patients receiving norfloxacin, the drug should be discontinued and appropriate measures instituted.

The effects of norfloxacin on brain function or on the electrical activity of the brain have not been tested. Therefore, until more information becomes available, norfloxacin, like all other quinolones, should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis, epilepsy, and other factors which predispose to seizures. (See **ADVERSE REACTIONS.**)

**Hypersensitivity/anaphylaxis:** Serious and occasionally fatal hypersensitivity (anaphylactoid or anaphylactic) reactions, some following the first dose, have been reported in patients receiving quinolone therapy. 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.

**Pseudomembranous colitis:** Pseudomembranous colitis has been reported with nearly all antibacterial agents, including norfloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management

---

\*\*\* Based on a patient weight of 50 kg.

with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

*Peripheral neuropathy:* Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones, including norfloxacin. Norfloxacin should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness, or is found to have deficits in light touch, pain, temperature, position sense, vibratory sensation, and/or motor strength in order to prevent the development of an irreversible condition.

*Tendon effects:* Ruptures of the shoulder, hand, and Achilles tendons or other tendons that required surgical repair or resulted in prolonged disability have been reported with in patients receiving quinolones, including norfloxacin. Post-marketing surveillance reports indicate that this risk may be increased in patients receiving concomitant corticosteroids, especially in the elderly. Norfloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been confidently excluded. Tendon rupture can occur at any time during or after therapy with quinolones, including norfloxacin.

*Syphilis treatment:* Norfloxacin has **not** been shown to be effective in the treatment of syphilis. Antimicrobial agents used in high doses for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis. Patients treated with norfloxacin should have a follow-up serologic test for syphilis after three months.

2. The following text was added as the first five bullets in the **PRECAUTIONS**, *Information for Patients* subsection:

—that norfloxacin may cause changes in the electrocardiogram (QTc interval prolongation).  
—that norfloxacin should be avoided in patients receiving class IA (e.g., quinidine, procainamide) or class III (e.g., amiodarone, sotalol) antiarrhythmic agents.  
— that norfloxacin should be used with caution in subjects receiving drugs that affect the QTc interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants.  
— to inform their physicians of any personal or family history of QTc prolongation or proarrhythmic conditions such as hypokalemia, bradycardia or recent myocardial ischemia.  
—that peripheral neuropathies have been associated with norfloxacin use. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness develop, they should discontinue treatment and contact their physicians.

3. The following text was added in the **PRECAUTIONS**, *Drug Interactions* subsection:

The concomitant administration of quinolones including norfloxacin with glyburide (a sulfonylurea agent) has, on rare occasions, resulted in severe hypoglycemia. Therefore, monitoring of blood glucose is recommended when these agents are co-administered.

4. The following text was revised in the **PRECAUTIONS**, *Geriatric Use* subsection:

Of the 340 subjects in one large clinical study of NOROXIN for treatment of urinary tract infections, 103 patients were 65 and older, 77 of whom were 70 and older; no overall differences in safety and effectiveness were evident between these subjects and younger subjects. In clinical

practice, no difference in the type of reported adverse experiences have been observed between the elderly and younger ~~patients; however, patients~~ except for a possible increased risk of tendon rupture in elderly patients receiving concomitant corticosteroids (see WARNINGS). In addition, increased risk for other adverse experiences in some older individuals cannot be ruled out (see **ADVERSE REACTIONS**).

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see **DOSAGE AND ADMINISTRATION**).

A pharmacokinetic study of NOROXIN in elderly volunteers (65 to 75 years of age with normal renal function for their age) was carried out (see **CLINICAL PHARMACOLOGY**).

5. The following text was added under the **ADVERSE REACTIONS, Post Marketing** subsection:

*Cardiovascular*

On rare occasions, prolonged QTc interval and ventricular arrhythmia including torsades de pointes.

*Musculoskeletal*

Tendonitis, tendon rupture; exacerbation of myasthenia gravis (see PRECAUTIONS) ; elevated creatine kinase (CK).

**NDA 19-384/S-042**

1. The following revisions were made under the **PRECAUTIONS, Drug Interactions** subsection:

Quinolones, including norfloxacin, may enhance the effects of ~~the oral anticoagulant oral~~ anticoagulants, including warfarin or its derivatives or similar agents. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

2. The following revisions were made under the **ADVERSE REACTIONS, Post Marketing** subsection:

*Hematologic*

Neutropenia; leukopenia; agranulocytosis; hemolytic anemia, sometimes associated with glucose-6-phosphate dehydrogenase deficiency; thrombocytopenia.

*Special Senses*

~~Transient hearing loss (rare)~~, Hearing loss, tinnitus, diplopia, dysgeusia.

Other adverse events reported with quinolones include: agranulocytosis, albuminuria, candiduria, crystalluria, cylindruria, dysphagia, elevation of blood glucose, elevation of serum cholesterol, elevation of serum potassium, elevation of serum triglycerides, hematuria, hepatic necrosis, symptomatic hypoglycemia, nystagmus, postural hypotension, prolongation of prothrombin time, and vaginal candidiasis.

**NDA 19-384/S-043**

1. The following sentence was added at the beginning of the label under the Product Name:

To reduce the development of drug-resistant bacteria and maintain the effectiveness of NOROXIN and other antibacterial drugs, NOROXIN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

2. The following was added as the last paragraph in the **INDICATIONS AND USAGE** section:

To reduce the development of drug-resistant bacteria and maintain the effectiveness of NOROXIN and other antibacterial drugs, NOROXIN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

3. The following was added as the last paragraph in the **PRECAUTIONS, General** subsection:

Prescribing NOROXIN in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

4. The following was added as the last paragraph in the **PRECAUTIONS, Information for Patients** subsection:

Patients should be counseled that antibacterial drugs including NOROXIN should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When NOROXIN is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by NOROXIN or other antibacterial drugs in the future.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text (enclosed). Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted July 19, 2004).

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999) and *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004). The guidances specify that labeling to be submitted in pdf format. To assist in our review, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper. For administrative purposes, these submissions should be designated "**FPL for approved supplements**

**NDA 19-384/S-040, S-042, S-043.**" Approval of these submissions by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Robin Anderson, R.N., M.B.A., Labeling Reviewer, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.  
Director  
Division of Special Pathogen and Immunologic  
Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

-----  
**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  
7/23/04 01:58:54 PM