



NDA 19-735/S-057

Ortho McNeil Pharmaceutical, Inc.  
c/o Johnson & Johnson Pharmaceutical Research & Development, L.L.C.  
Attention: Ms. Cynthia Chianese  
Director, Regulatory Affairs  
1000 U.S. Highway 202 South, P.O. Box 300  
Raritan, NJ 08869-0602

Dear Ms. Chianese:

Please refer to your supplemental new drug application dated April 30, 2007, received April 30, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Floxin<sup>®</sup> (ofloxacin) Tablets, 200 mg, 300 mg, and 400 mg.

This "Special Supplement - Changes Being Effected" supplemental new drug application provides for revisions to the package insert for Floxin<sup>®</sup> to ensure consistency in the communication of the risks of acute liver failure and acute severe liver injury, QTc prolongation/torsades de pointes, tendon rupture, and toxic epidermal necrolysis (TEN), submitted in response to the Supplement Request letter issued by the Division on May 19, 2006.

The supplemental application provides for revisions (~~strike through~~ = deleted and underlined = added) as follows:

1. The fifth paragraph in the **WARNINGS** section (the second paragraph regarding hypersensitivity) was replaced with the double underlined text below to provide greater clarity in the grouping of hypersensitivity findings, and a section heading of **Hypersensitivity Reactions** was added before the fourth paragraph. The subsection reads as follows:

**Hypersensitivity Reactions**

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with quinolones, including ofloxacin. These reactions often occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat, or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath, and acute respiratory distress), dyspnea, urticaria, itching, and other serious skin reactions. This drug should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated (See **PRECAUTIONS** and **ADVERSE REACTIONS**).

~~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 ofloxacin. 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 hematologic abnormalities. The drug should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity and supportive measures instituted. (See **PRECAUTIONS: Information for Patients** and **ADVERSE REACTIONS**.)~~

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 ofloxacin. 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 hematologic abnormalities.

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

2. The **WARNINGS/Tendon effects** subsection was modified to read:

Ruptures of the shoulder, hand, Achilles tendon or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including ofloxacin. Post-marketing surveillance reports indicate that the risk ~~may be~~ is increased in patients receiving corticosteroids, especially the elderly (see **PRECAUTIONS**).

3. The text in the **PRECAUTIONS/Information for Patients** subsection was modified to read:

- to discontinue FLOXIN 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 excluded. The risk of serious tendon disorders is higher in those over 65 years of age, especially those on steroids.

4. The following text was added to the **PRECAUTIONS/Information for Patients** subsection following the last bulleted point:

- to inform their physician of any personal or family history of QTc prolongation or proarrhythmic conditions such as hypokalemia, bradycardia, or recent myocardial ischemia; if they are taking any class IA (quinidine, procainamide), or class III (amiodarone, sotalol) antiarrhythmic agents. Patients should notify their physicians if they have any symptoms of prolongation of the QTc interval, including prolonged heart palpitations or a loss of consciousness.

5. Under the **PRECAUTIONS/Geriatric Use** subsection, the following text was included after the current second paragraph in the labeling:

Patients over 65 are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as FLOXIN. This risk is further increased with concomitant steroid 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 FLOXIN 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. Under the **ADVERSE REACTIONS/Post-Marketing Adverse Reactions** subsection, the following events were added:

- hepatic failure (including fatal cases)
- torsades de pointes
- toxic epidermal necrolysis

7. A new “Patient Information About: FLOXIN<sup>®</sup>” section in the package insert was added as follows, consistent with the LEVAQUIN<sup>®</sup> patient package insert.

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**Patient Information About:**  
**FLOXIN<sup>®</sup>**  
**(ofloxacin)Tablets**

**200 mg Tablets, 300 mg Tablets and 400 mg Tablets**

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

**What is FLOXIN<sup>®</sup>?**

FLOXIN<sup>®</sup> is a quinolone antibiotic used to treat lung, skin, and urinary tract infections caused by certain germs called bacteria. FLOXIN<sup>®</sup> kills many of the types of bacteria that can infect the lungs, skin, and urinary tract and has been shown in a large number of clinical trials to be safe and effective for the treatment of bacterial infections.

Sometimes viruses rather than bacteria may infect the lungs. FLOXIN<sup>®</sup>, like other antibiotics, does not kill viruses.

You should contact your health care professional if you think that your condition is not improving while taking FLOXIN<sup>®</sup>. FLOXIN<sup>®</sup> Tablets are light yellow for the 200 mg tablet, white colored for the 300 mg tablet, or pale gold for the 400 mg tablet.

### **How and when should I take FLOXIN<sup>®</sup>?**

FLOXIN<sup>®</sup> should be taken once as a single dose, or twice a day for 3 days to 6 weeks depending on the prescription. FLOXIN<sup>®</sup> Tablets should be swallowed and may be taken with or without food. Try to take the tablets at the same times each day and drink fluids liberally.

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 FLOXIN<sup>®</sup> even if you missed a dose by mistake. You should not take a double dose.

### **Who should not take FLOXIN<sup>®</sup>?**

You should not take FLOXIN<sup>®</sup> if you have ever had a severe allergic reaction to any of the group of antibiotics known as “quinolones” such as ciprofloxacin. Serious and occasionally fatal allergic reactions have been reported in patients receiving therapy with quinolones, including FLOXIN<sup>®</sup>.

If you are pregnant or are planning to become pregnant while taking FLOXIN<sup>®</sup>, talk to your health care professional before taking this medication. FLOXIN<sup>®</sup> is not recommended for use during pregnancy or nursing, as the effects on the unborn child or nursing infant are unknown. FLOXIN<sup>®</sup> is not recommended for children.

### **What are the possible side effects of FLOXIN<sup>®</sup>?**

FLOXIN<sup>®</sup> is generally well tolerated. The most common side effects caused by FLOXIN<sup>®</sup>, which are usually mild, include nausea, sleeplessness, headache, dizziness, diarrhea, vomiting, rash, itching, external genital itching in women, vaginitis, and impaired taste.

You should be careful about driving or operating machinery until you are sure FLOXIN<sup>®</sup> is not causing dizziness.

Allergic reactions have been reported in patients receiving quinolones including FLOXIN<sup>®</sup>, even after just one dose. If you develop hives, skin rash or other symptoms of an allergic reaction, you should stop taking this medication and call your health care professional.

Pain, swelling, and tears of Achilles, shoulder, or hand tendons have been reported in patients receiving fluoroquinolones, including FLOXIN<sup>®</sup>. The risk for tendon effects is higher if you are over 65 years old, and especially if you are taking corticosteroids. If you develop pain,

swelling, or rupture of a tendon you should stop taking FLOXIN<sup>®</sup>, avoid exercise and strenuous use of the affected area, and contact your health care provider.

Some quinolone antibiotics have been associated with the development of phototoxicity (“sunburns” and “blistering sunburns”) following exposure to sunlight or other sources of ultraviolet light such as artificial ultraviolet light used in tanning salons. FLOXIN<sup>®</sup> has been infrequently associated with phototoxicity. You should avoid excessive exposure to sunlight or artificial ultraviolet light while you are taking FLOXIN<sup>®</sup>.

If you have diabetes and you develop a hypoglycemic reaction while on FLOXIN<sup>®</sup>, you should stop taking FLOXIN<sup>®</sup> and call your health care professional.

Convulsions have been reported in patients receiving quinolone antibiotics including FLOXIN<sup>®</sup>. If you have experienced convulsions in the past, be sure to let your physician know that you have a history of convulsions.

Quinolones, including FLOXIN<sup>®</sup>, may also cause central nervous system stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia, and rarely, suicidal thoughts or acts.

Diarrhea that usually ends after treatment is a common problem caused by antibiotics. 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 antibiotics including with FLOXIN<sup>®</sup>. If you develop a watery and bloody stool with or without stomach cramps and fever, contact your physician as soon as possible.

In a few people, FLOXIN<sup>®</sup>, like some other antibiotics, may produce a small effect on the heart that is seen on an electrocardiogram test. The rare heart problem is called QT prolongation and 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 QT interval, low potassium (hypokalemia), and 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 any prolonged heart palpitations (a change in the way your heart beats) or a loss of consciousness (fainting spells).

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

For more complete information regarding ofloxacin, please refer to the full prescribing information, which may be obtained from your health care professional, pharmacist, or the Physicians Desk Reference (PDR).

### **What about other medicines I am taking?**

Taking warfarin (Coumadin<sup>®</sup>) and FLOXIN<sup>®</sup> together can further predispose you to the development of bleeding problems. If you take warfarin, be sure to tell your health care professional.

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

It is important to let your health care professional know all of the medicines you are using.

**Other information**

Take your dose of FLOXIN<sup>®</sup> twice a day or once as a single dose depending on the prescription.

Complete the course of medication even if you are feeling better.

Keep this medication out of the reach of children.

Some quinolones, including ofloxacin, may produce false-positive urine screening results for opiates using commercially available immunoassay kits. Confirmation of positive opiate screens by more specific methods may be necessary.

This information does not take the place of discussions with your doctor or health care professional about your medical condition or your treatment.

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.

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  
5515 Security Lane  
HFD-001, Suite 5100  
Rockville, MD 20852

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, please call Kristen Miller, Pharm.D., Regulatory Project Manager, at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure

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**This is a representation of an electronic record that was signed electronically and  
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Renata Albrecht  
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