

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-735 / S-052, S-053

Trade Name: Floxin

Generic Name: ofloxacin

Sponsor: Johnson & Johnson Pharmaceutical R & D, LLC

Approval Date: September 15, 2004

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APPROVAL LETTER



NDA 19-735/S-052, S-053

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Attention: Robyn S. Thomas
Regulatory Affairs
920 Route 202 South
P.O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Thomas:

Please refer to your supplemental new drug applications dated March 19, 2004, received March 23, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for FLOXIN[®] (ofloxacin tablets) Tablets, 200 mg, 300 mg, 400 mg.

We acknowledge receipt of your submissions dated April 9, 2004 and August 23, 2004.

These "Changes Being Effected" (CBE) supplemental new drug applications provide for the addition of quinolone class labeling in **WARNINGS** and **PRECAUTIONS, Information for Patients** as was requested in the supplement request letter dated November 26, 2003 and the facsimiles from the Division dated March 10, 2004 and July 12, 2004.

These CBE supplemental new drug applications provide for the following revisions to the package insert:

1. "FLOXIN[®] (ofloxacin) Tablets" was changed to "FLOXIN[®] (ofloxacin tablets) Tablets" throughout the label.
2. References to "Videx[®] (Didanosine) chewable/ buffered tablets or the pediatric powder for oral solution" have been changed to just "Videx[®] (didanosine)" throughout the label.
3. **WARNINGS**
 - A **Peripheral neuropathy** subsection was added to read:

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 ofloxacin. Ofloxacin should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness or other alterations of sensation including light touch, pain, temperature, position sense, and vibratory sensation in order to prevent the development of an irreversible condition.

- The **Tendon effects** subsection was revised to read:

Tendon effects: Ruptures of the shoulder, hand, and 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 increased in patients receiving corticosteroids, with ofloxacin and other quinolones especially the elderly. (see PRECAUTIONS). Ofloxacin 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 ofloxacin.

4. PRECAUTIONS

- A **Torsades de pointes** subsection was added to read:

Torsades de pointes: Some quinolones, including ofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. Rare cases of torsades de pointes have been spontaneously reported during post-marketing surveillance in patients receiving quinolones, including ofloxacin. Ofloxacin should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia, and patients receiving class IA (quinidine, procainamide), or class III (amiodarone, sotalol) antiarrhythmic agents.

- The following bullet concerning peripheral neuropathy was added under **Information for Patients:**

- that peripheral neuropathies have been associated with ofloxacin use. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness develop, they should discontinue treatment and contact their physicians;

- The following paragraph was added to the **Geriatric Use** subsection:

Elderly patients may be more sensitive to drug-associated effects on the QT interval. Therefore, precaution should be taken when using ofloxacin with concomitant drugs that can result in prolongation of the QT interval (e.g. class IA or class III antiarrhythmics) or in patients with risk factors for Torsade de pointes (e.g. known QT prolongation, uncorrected hypokalemia). (See PRECAUTIONS: GENERAL: Torsades de pointes)

5. HOW SUPPLIED

- The first two sentences in this section were revised to read:

FLOXIN® (ofloxacin tablets) Tablets are supplied as 200 mg light yellow, 300 mg white, and 400 mg pale gold oval, straight-edged, film coated tablets. Each tablet is distinguished by an imprint of "FLOXIN" and the appropriate strength.

We completed our review of these applications, as amended, and they are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling (text for the package insert submitted August 23, 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 is 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 supplement NDA 19-735/S-052, S-053.**" Approval of this submission by FDA is not required before the labeling is used.

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, HFD-410
FDA
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 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

Enclosure

**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
9/15/04 04:07:29 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-735 / S-052, S-053

LABELING

Text of Proposed Labeling

FLOXIN[®] TABLETS
(ofloxacin tablets)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of FLOXIN[®] (ofloxacin tablets) Tablets and other antibacterial drugs, FLOXIN (ofloxacin tablets) Tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

FLOXIN[®] (ofloxacin tablets) Tablets is a synthetic broad-spectrum antimicrobial agent for oral administration. Chemically, ofloxacin, a fluorinated carboxyquinolone, is the racemate, (±)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid. The chemical structure is:

<INSERT STRUCTURE>

Its empirical formula is C₁₈H₂₀FN₃O₄, and its molecular weight is 361.4. Ofloxacin is an off-white to pale yellow crystalline powder. The molecule exists as a zwitterion at the pH conditions in the small intestine. The relative solubility characteristics of ofloxacin at room temperature, as defined by USP nomenclature, indicate that ofloxacin is considered to be *soluble* in aqueous solutions with pH between 2 and 5. It is *sparingly* to *slightly soluble* in aqueous solutions with pH 7 (solubility falls to 4 mg/mL) and *freely soluble* in aqueous solutions with pH above 9. Ofloxacin has the potential to form stable coordination compounds with many metal ions. This *in vitro* chelation potential has the following formation order: Fe⁺³ > Al⁺³ > Cu⁺² > Ni⁺² > Pb⁺² > Zn⁺² > Mg⁺² > Ca⁺² > Ba⁺².

FLOXIN Tablets contain the following inactive ingredients: anhydrous lactose, corn starch, hydroxypropyl cellulose, hypromellose, magnesium stearate, polyethylene glycol, polysorbate 80, sodium starch glycolate, titanium dioxide and may also contain synthetic yellow iron oxide.

CLINICAL PHARMACOLOGY

Following oral administration, the bioavailability of ofloxacin in the tablet formulation is approximately 98%. Maximum serum concentrations are achieved one to two hours after an oral dose. Absorption of ofloxacin after single or multiple doses of 200 to 400 mg is predictable, and the amount of drug absorbed increases proportionately with the dose. Ofloxacin has biphasic elimination. Following multiple oral doses at steady-state administration, the half-lives are approximately 4-5 hours

Text of Proposed Labeling

and 20-25 hours. However, the longer half-life represents less than 5% of the total AUC. Accumulation at steady-state can be estimated using a half-life of 9 hours. The total clearance and volume of distribution are approximately similar after single or multiple doses. Elimination is mainly by renal excretion. The following are mean peak serum concentrations in healthy 70-80 kg male volunteers after single oral doses of 200, 300, or 400 mg of ofloxacin or after multiple oral doses of 400 mg.

Oral Dose	Serum Concentration 2 Hours After Admin. ($\mu\text{g/mL}$)	Area Under the Curve ($\text{AUC}_{(0-\infty)}$) ($\mu\text{g}\cdot\text{h/mL}$)
200 mg single dose	1.5	14.1
300 mg single dose	2.4	21.2
400 mg single dose	2.9	31.4
400 mg steady-state	4.6	61.0

Steady-state concentrations were attained after four oral doses, and the area under the curve (AUC) was approximately 40% higher than the AUC after single doses. Therefore, after multiple-dose administration of 200 mg and 300 mg doses, peak serum levels of 2.2 $\mu\text{g/mL}$ and 3.6 $\mu\text{g/mL}$, respectively, are predicted at steady-state.

In vitro, approximately 32% of the drug in plasma is protein bound.

The single dose and steady-state plasma profiles of ofloxacin injection were comparable in extent of exposure (AUC) to those of ofloxacin tablets when the injectable and tablet formulations of ofloxacin were administered in equal doses (mg/mg) to the same group of subjects. The mean steady-state $\text{AUC}_{(0-12)}$ attained after the intravenous administration of 400 mg over 60 min was 43.5 $\mu\text{g}\cdot\text{h/mL}$; the mean steady-state $\text{AUC}_{(0-12)}$ attained after the oral administration of 400 mg was 41.2 $\mu\text{g}\cdot\text{h/mL}$ (two one-sided t-test, 90% confidence interval was 103-109). (See following chart.)

<INSERT CHART>

Between 0 and 6 h following the administration of a single 200 mg oral dose of ofloxacin to 12 healthy volunteers, the average urine ofloxacin concentration was approximately 220 $\mu\text{g/mL}$. Between 12 and 24 hours after administration, the average urine ofloxacin level was approximately 34 $\mu\text{g/mL}$.

Following oral administration of recommended therapeutic doses, ofloxacin has been detected in blister fluid, cervix, lung tissue, ovary, prostatic fluid, prostatic tissue, skin, and sputum. The mean concentration of ofloxacin in each of these various body fluids

Text of Proposed Labeling

and tissues after one or more doses was 0.8 to 1.5 times the concurrent plasma level. Inadequate data are presently available on the distribution or levels of ofloxacin in the cerebrospinal fluid or brain tissue.

Ofloxacin has a pyridobenzoxazine ring that appears to decrease the extent of parent compound metabolism. Between 65% and 80% of an administered oral dose of ofloxacin is excreted unchanged via the kidneys within 48 hours of dosing. Studies indicate that less than 5% of an administered dose is recovered in the urine as the desmethyl or N-oxide metabolites. Four to eight percent of an ofloxacin dose is excreted in the feces. This indicates a small degree of biliary excretion of ofloxacin.

The administration of FLOXIN[®] with food does not affect the C_{max} and AUC_{∞} of the drug, but T_{max} is prolonged.

Clearance of ofloxacin is reduced in patients with impaired renal function (creatinine clearance rate ≤ 50 mL/min), and dosage adjustment is necessary. (See **PRECAUTIONS: General and DOSAGE AND ADMINISTRATION.**)

Following oral administration to healthy elderly subjects (65-81 years of age), maximum plasma concentrations are usually achieved one to two hours after single and multiple twice-daily doses, indicating that the rate of oral absorption is unaffected by age or gender. Mean peak plasma concentrations in elderly subjects were 9-21% higher than those observed in younger subjects. Gender differences in the pharmacokinetic properties of elderly subjects have been observed. Peak plasma concentrations were 114% and 54% higher in elderly females compared to elderly males following single and multiple twice-daily doses. [This interpretation was based on study results collected from two separate studies.] Plasma concentrations increase dose-dependently with the increase in doses after single oral dose and at steady state. No differences were observed in the volume of distribution values between elderly and younger subjects. As in younger subjects, elimination is mainly by renal excretion as unchanged drug in elderly subjects, although less drug is recovered from renal excretion in elderly subjects. Consistent with younger subjects, less than 5% of an administered dose was recovered in the urine as the desmethyl and N-oxide metabolites in the elderly. A longer plasma half-life of approximately 6.4 to 7.4 hours was observed in elderly subjects, compared with 4 to 5 hours for young subjects. Slower elimination of ofloxacin is observed in elderly subjects as compared with younger subjects which may be attributable to the reduced renal function and renal clearance observed in the elderly subjects. Because ofloxacin is known to be

Text of Proposed Labeling

substantially excreted by the kidney, and elderly patients are more likely to have decreased renal function, dosage adjustment is necessary for elderly patients with impaired renal function as recommended for all patients. (See **PRECAUTIONS: General and DOSAGE AND ADMINISTRATION**)

MICROBIOLOGY

Ofloxacin is a quinolone antimicrobial agent. The mechanism of action of ofloxacin and other fluoroquinolone antimicrobials involves inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair and recombination.

Ofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. Ofloxacin is often bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

Fluoroquinolones, including ofloxacin, differ in chemical structure and mode of action from aminoglycosides, macrolides and β -lactam antibiotics, including penicillins. Fluoroquinolones may, therefore, be active against bacteria resistant to these antimicrobials.

Resistance to ofloxacin due to spontaneous mutation *in vitro* is a rare occurrence (range: 10^{-9} to 10^{-11}). Although cross-resistance has been observed between ofloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to ofloxacin.

Ofloxacin has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section:

Aerobic gram-positive microorganisms

Staphylococcus aureus (methicillin-susceptible strains)

Streptococcus pneumoniae (penicillin-susceptible strains)

Streptococcus pyogenes

Aerobic gram-negative microorganisms

Citrobacter (diversus) koseri

Enterobacter aerogenes

Escherichia coli

Haemophilus influenzae

Text of Proposed Labeling

Klebsiella pneumoniae

Neisseria gonorrhoeae

Proteus mirabilis

Pseudomonas aeruginosa

As with other drugs in this class, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with ofloxacin.

Other microorganisms

Chlamydia trachomatis

The following *in vitro* data are available, **but their clinical significance is unknown.**

Ofloxacin exhibits *in vitro* minimum inhibitory concentrations (MIC values) of 2 µg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of ofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic gram-positive microorganisms

Staphylococcus epidermidis (methicillin-susceptible strains)

Staphylococcus saprophyticus

Streptococcus pneumoniae (penicillin-resistant strains)

Aerobic gram-negative microorganisms

Acinetobacter calcoaceticus

Bordetella pertussis

Citrobacter freundii

Enterobacter cloacae

Haemophilus ducreyi

Klebsiella oxytoca

Moraxella catarrhalis

Morganella morganii

Proteus vulgaris

Providencia rettgeri

Providencia stuartii

Serratia marcescens

Text of Proposed Labeling

Anaerobic microorganisms

Clostridium perfringes

Other microorganisms

Chlamydia pneumoniae

Gardnerella vaginalis

Legionella pneumophila

Mycoplasma hominis

Mycoplasma pneumoniae

Ureaplasma urealyticum

Ofloxacin is not active against *Treponema pallidum* (See **WARNINGS**.)

Many strains of other streptococcal species, *Enterococcus* species, and anaerobes are resistant to ofloxacin.

Susceptibility Tests

Dilution techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MIC values). These MIC values provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC values should be determined using a standardized procedure. Standardized procedures are based on a dilution method¹ (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ofloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing aerobic microorganisms other than *Haemophilus influenzae*, *Neisseria gonorrhoeae*, and *Streptococcus pneumoniae*:

MIC (µg/mL)	Interpretation
≤ 2	Susceptible (S)
4	Intermediate (I)
≥ 8	Resistant (R)

For testing *Haemophilus influenzae*:^a

Text of Proposed Labeling

MIC ($\mu\text{g/mL}$)	Interpretation
≤ 2	Susceptible (S)

^a This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* using *Haemophilus* Test Medium¹

The current absence of data on resistant strains precludes defining any results other than “Susceptible”. Strains yielding MIC results suggestive of a “nonsusceptible” category should be submitted to a reference laboratory for further testing.

Text of Proposed Labeling

For testing *Neisseria gonorrhoeae*.^b

MIC (µg/mL)	Interpretation
≤ 0.25	Susceptible (S)
0.5-1	Intermediate (I)
≥ 2	Resistant (R)

^b These interpretive standards are applicable only to agar dilution tests using GC agar base and 1% defined growth supplement incubated in 5% CO₂.

For testing *Streptococcus* species including *Streptococcus pneumoniae*.^c

MIC (µg/mL)	Interpretation
≤ 2	Susceptible (S)
4	Intermediate (I)
≥ 8	Resistant (R)

^c These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard ofloxacin powder should provide the following MIC values:

Text of Proposed Labeling

Microorganism		MIC Range (µg/mL)
<i>Escherichia coli</i>	ATCC 25922	0.015-0.12
<i>Haemophilus influenzae</i>	ATCC 49247 ^d	0.016-0.06
<i>Neisseria gonorrhoeae</i>	ATCC 49226 ^e	0.004-0.016
<i>Pseudomonas aeruginosa</i>	ATCC 27853	1-8
<i>Staphylococcus aureus</i>	ATCC 29213	0.12-1
<i>Streptococcus pneumoniae</i>	ATCC 49619 ^f	1-4

^d This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a microdilution procedure using *Haemophilus* Test Medium (HTM)¹.

^e This quality control range is applicable only to *N. gonorrhoeae* ATCC 49226 tested by an agar dilution procedure using GC agar base with 1% defined growth supplement incubated in 5% CO₂.

^f This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

Diffusion techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure² requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-µg ofloxacin to test the susceptibility of microorganisms to ofloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-µg ofloxacin disk should be interpreted according to the following criteria:

For testing aerobic microorganisms other than *Haemophilus influenzae*, *Neisseria gonorrhoeae*, and *Streptococcus pneumoniae*:

Zone Diameter (mm)	Interpretation
≥16	Susceptible (S)
13-16	Intermediate (I)
≤12	Resistant (R)

For testing *Haemophilus influenzae*:^b

Zone Diameter (mm)	Interpretation
≥ 16	Susceptible (S)

^b This zone diameter standard is applicable only to disk diffusion tests with *Haemophilus influenzae* using *Haemophilus* Test Medium (HTM)² incubated in 5% CO₂.

The current absence of data on resistant strains precludes defining any results other than “Susceptible”. Strains yielding zone diameter results suggestive of a “nonsusceptible” category should be submitted to a reference laboratory for further testing.

Text of Proposed Labeling

For testing *Neisseria gonorrhoeae*.^h

Zone Diameter (mm)	Interpretation
≥ 31	Susceptible (S)
25-30	Intermediate (I)
≤ 24	Resistant (R)

^h These zone diameter standards are applicable only to disk diffusion tests using GC agar base and 1% defined growth supplement incubated in 5% CO₂

For testing *Streptococcus* species including *Streptococcus pneumoniae*.ⁱ

Zone Diameter (mm)	Interpretation
≥ 16	Susceptible (S)
13-15	Intermediate (I)
≤ 12	Resistant (R)

ⁱ These zone diameter standards are applicable only to disk diffusion tests performed using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood and incubated in 5% CO₂.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for ofloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5-μg ofloxacin disk should provide the following zone diameters in these laboratory quality control strains:

Text of Proposed Labeling

Microorganism		Zone Diameter (mm)
<i>Escherichia coli</i>	ATCC 25922	29-33
<i>Haemophilus influenzae</i>	ATCC 49247 ^j	31-40
<i>Neisseria gonorrhoeae</i>	ATCC 49226 ^k	43-51
<i>Pseudomonas aeruginosa</i>	ATCC 27853	17-21
<i>Staphylococcus aureus</i>	ATCC 25923	24-28
<i>Streptococcus pneumoniae</i>	ATCC 49619 ^l	16-21

^j This quality control range is applicable only to *H. influenzae* ATCC 49247 tested by a disk diffusion procedure using *Haemophilus* Test Medium (HTM)² incubated in 5% CO₂.

^k This quality control range is applicable only to *N. gonorrhoeae* ATCC 49226 tested by a disk diffusion procedure using GC agar base with 1% defined growth supplement incubated in 5% CO₂.

^l This quality control range is applicable only to *S. pneumoniae* ATCC 49619 tested by a disk diffusion procedure using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood and incubated in 5% CO₂.

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of FLOXIN® (ofloxacin tablets) Tablets and other antibacterial drugs, FLOXIN (ofloxacin tablets) Tablets 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.

FLOXIN (ofloxacin tablets) Tablets are indicated for the treatment of adults with mild to moderate infections (unless otherwise indicated) caused by susceptible strains of the designated microorganisms in the infections listed below. Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

Acute bacterial exacerbations of chronic bronchitis due to *Haemophilus influenzae* or *Streptococcus pneumoniae*.

Community-acquired Pneumonia due to *Haemophilus influenzae* or *Streptococcus pneumoniae*.

Uncomplicated skin and skin structure infections due to *Staphylococcus aureus*, *Streptococcus pyogenes*, or *Proteus mirabilis*.

Acute, uncomplicated urethral and cervical gonorrhea due to *Neisseria gonorrhoeae*. (See **WARNINGS**.)

Nongonococcal urethritis and cervicitis due to *Chlamydia trachomatis*. (See **WARNINGS**.)

Mixed Infections of the urethra and cervix due to *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. (See **WARNINGS**.)

Acute pelvic inflammatory disease (including severe infection) due to *Chlamydia trachomatis* and/or *Neisseria gonorrhoeae*. (See **WARNINGS**.)

NOTE: If anaerobic microorganisms are suspected of contributing to the infection, appropriate therapy for anaerobic pathogens should be administered.

Text of Proposed Labeling

Uncomplicated cystitis due to *Citrobacter diversus*, *Enterobacter aerogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, or *Pseudomonas aeruginosa*.

Complicated urinary tract infections due to *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Citrobacter diversus**, or *Pseudomonas aeruginosa**

Prostatitis due to *Escherichia coli*.

* = Although treatment of infections due to this organism in this organ system demonstrated a clinically significant outcome, efficacy was studied in fewer than 10 patients.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing the infection and to determine their susceptibility to ofloxacin. Therapy with ofloxacin may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

As with other drugs in this class, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with ofloxacin. Culture and susceptibility testing performed periodically during therapy will provide information not only on the therapeutic effect of the antimicrobial agent but also on the possible emergence of bacterial resistance.

CONTRAINDICATIONS

FLOXIN[®] (ofloxacin tablets) Tablets is contraindicated in persons with a history of hypersensitivity associated with the use of ofloxacin or any member of the quinolone group of antimicrobial agents.

WARNINGS

THE SAFETY AND EFFICACY OF OFLOXACIN IN PEDIATRIC PATIENTS AND ADOLESCENTS (UNDER THE AGE OF 18 YEARS), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See PRECAUTIONS: Pediatric Use, Pregnancy, and Nursing Mothers subsections.)

In the immature rat, the oral administration of ofloxacin at 5 to 16 times the recommended maximum human dose based on mg/kg or 1-3 times based on mg/m² increased the incidence and severity of osteochondrosis. The lesions did not regress after 13 weeks of drug withdrawal. Other quinolones also produce similar erosions in the weight-bearing joints and other signs of arthropathy in immature animals of various species. (See *ANIMAL PHARMACOLOGY*.)

Text of Proposed Labeling

Convulsions, increased intracranial pressure, and toxic psychosis have been reported in patients receiving quinolones, including ofloxacin. Quinolones, including ofloxacin, may also cause central nervous system stimulation which may lead to: tremors, restlessness/agitation, nervousness/anxiety, lightheadedness, confusion, hallucinations, paranoia and depression, nightmares, insomnia, and rarely suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving ofloxacin, the drug should be discontinued and appropriate measures instituted. Insomnia may be more common with ofloxacin than some other products in the quinolone class. As with all quinolones, ofloxacin should be used with caution in patients with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction). (See **PRECAUTIONS: General, Information for Patients, Drug Interactions and ADVERSE REACTIONS.**)

Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid) reactions have been reported in patients receiving therapy with quinolones, including ofloxacin. These reactions often occur following the first dose. Some reactions were 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/hives, itching, and other serious skin reactions. A few patients had a history of hypersensitivity reactions. The 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 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/failure; hepatitis; jaundice; acute hepatic necrosis/failure; anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia;

Text of Proposed Labeling

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.**)

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 ofloxacin. Ofloxacin should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness or other alterations of sensation including light touch, pain, temperature, position sense, and vibratory sensation in order to prevent the development of an irreversible condition.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ofloxacin, 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 any antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate 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 with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis. (See **ADVERSE REACTIONS.**)

Tendon effects: 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 increased in patients receiving corticosteroids, especially the elderly. (see **PRECAUTIONS**) Ofloxacin 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 during or after therapy with quinolones, including ofloxacin.

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Ofloxacin 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 ofloxacin for gonorrhea should have a follow-up serologic test for syphilis after three months and, if positive, treatment with an appropriate antimicrobial should be instituted .

PRECAUTIONS

General:

Prescribing FLOXIN[®] (ofloxacin tablets) Tablets 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.

Adequate hydration of patients receiving ofloxacin should be maintained to prevent the formation of a highly concentrated urine.

Administer ofloxacin with caution in the presence of renal or hepatic insufficiency/impairment. In patients with known or suspected renal or hepatic insufficiency/impairment, careful clinical observation and appropriate laboratory studies should be performed prior to and during therapy since elimination of ofloxacin may be reduced. In patients with impaired renal function (creatinine clearance ≤ 50 mg/mL), alteration of the dosage regimen is necessary. (See **CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.**)

Moderate to severe phototoxicity reactions have been observed in patients exposed to direct sunlight while receiving some drugs in this class, including ofloxacin. Excessive sunlight should be avoided. Therapy should be discontinued if phototoxicity (e.g., a skin eruption) occurs.

As with other quinolones, ofloxacin should be used with caution in any patient with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction). (See **WARNINGS and Drug Interactions.**)

A possible interaction between oral hypoglycemic drugs (e.g., glyburide/glibenclamide) or with insulin and fluoroquinolone antimicrobial agents have been reported resulting

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in a potentiation of the hypoglycemic action of these drugs. The mechanism for this interaction is not known. If a hypoglycemic reaction occurs in a patient being treated with ofloxacin, discontinue ofloxacin immediately and consult a physician. (See ***Drug Interactions and ADVERSE REACTIONS.***)

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy. (See ***WARNINGS and ADVERSE REACTIONS.***)

Torsades de pointes: Some quinolones, including ofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. Rare cases of torsades de pointes have been spontaneously reported during post-marketing surveillance in patients receiving quinolones, including ofloxacin. Ofloxacin should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia, and patients receiving class IA (quinidine, procainamide), or class III (amiodarone, sotalol) antiarrhythmic agents.

Information for Patients:

Patients should be advised:

- Patients should be counseled that antibacterial drugs including FLOXIN[®] (ofloxacin tablets) Tablets should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When FLOXIN (ofloxacin tablets) Tablets are 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 FLOXIN (ofloxacin tablets) Tablets or other antibacterial drugs in the future.
- that peripheral neuropathies have been associated with ofloxacin use. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness develop, they should discontinue treatment and contact their physicians;
- to drink fluids liberally;
- that mineral supplements, vitamins with iron or minerals, calcium- , aluminum- or magnesium-based antacids, sucralfate or Videx[®] (didanosine) should not be taken within the two-hour period before or within the two-hour period after taking ofloxacin (See ***Drug Interactions***);
- that ofloxacin can be taken without regard to meals;

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- that ofloxacin may cause neurologic adverse effects (e.g., dizziness, lightheadedness) and that patients should know how they react to ofloxacin before they operate an automobile or machinery or engage in activities requiring mental alertness and coordination (See **WARNINGS and ADVERSE REACTIONS**);
- 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;
- that ofloxacin may be associated with hypersensitivity reactions, even following the first dose, to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema (e.g., swelling of the lips, tongue, face; tightness of the throat, hoarseness), or any other symptom of an allergic reaction (See **WARNINGS and ADVERSE REACTIONS**);
- to avoid excessive sunlight or artificial ultraviolet light while receiving ofloxacin and to discontinue therapy if phototoxicity (e.g., skin eruption) occurs;
- that if they are diabetic and are being treated with insulin or an oral hypoglycemic drug, to discontinue ofloxacin immediately if a hypoglycemic reaction occurs and consult a physician (See **PRECAUTIONS: General and Drug Interactions**);
- that convulsions have been reported in patients taking quinolones, including ofloxacin, and to notify their physician before taking this drug if there is a history of this condition.

Drug Interactions:

Antacids, Sucralfate, Metal Cations, Multivitamins:

Quinolones form chelates with alkaline earth and transition metal cations. Administration of quinolones with antacids containing calcium, magnesium, or aluminum, with sucralfate, with divalent or trivalent cations such as iron, or with multivitamins containing zinc or with Videx[®] (didanosine) may substantially interfere with the absorption of quinolones resulting in systemic levels considerably lower than desired. These agents should not be taken within the two-hour period before or within the two-hour period after ofloxacin administration. (See **DOSAGE AND ADMINISTRATION**.)

Caffeine:

Interactions between ofloxacin and caffeine have not been detected.

Cimetidine:

Cimetidine has demonstrated interference with the elimination of some quinolones. This interference has resulted in significant increases in half-life and AUC of some

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quinolones. The potential for interaction between ofloxacin and cimetidine has not been studied.

Cyclosporine:

Elevated serum levels of cyclosporine have been reported with concomitant use of cyclosporine with some other quinolones. The potential for interaction between ofloxacin and cyclosporine has not been studied.

Drugs metabolized by Cytochrome P450 enzymes:

Most quinolone antimicrobial drugs inhibit cytochrome P450 enzyme activity. This may result in a prolonged half-life for some drugs that are also metabolized by this system (e.g., cyclosporine, theophylline/methylxanthines, warfarin) when co-administered with quinolones. The extent of this inhibition varies among different quinolones. (See other *Drug Interactions*.)

Non-steroidal anti-inflammatory drugs:

The concomitant administration of a non-steroidal anti-inflammatory drug with a quinolone, including ofloxacin, may increase the risk of CNS stimulation and convulsive seizures. (See *WARNINGS* and *PRECAUTIONS: General*.)

Probenecid:

The concomitant use of probenecid with certain other quinolones has been reported to affect renal tubular secretion. The effect of probenecid on the elimination of ofloxacin has not been studied.

Theophylline:

Steady-state theophylline levels may increase when ofloxacin and theophylline are administered concurrently. As with other quinolones, concomitant administration of ofloxacin may prolong the half-life of theophylline, elevate serum theophylline levels, and increase the risk of theophylline-related adverse reactions. Theophylline levels should be closely monitored and theophylline dosage adjustments made, if appropriate, when ofloxacin is co-administered. Adverse reactions (including seizures) may occur with or without an elevation in the serum theophylline level. (See *WARNINGS* and *PRECAUTIONS: General*.)

Warfarin:

Some quinolones have been reported to enhance the effects of the oral anticoagulant warfarin or its derivatives. Therefore, if a quinolone antimicrobial is administered

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concomitantly with warfarin or its derivatives, the prothrombin time or other suitable coagulation test should be closely monitored.

Antidiabetic agents (e.g., insulin, glyburide/glibenclamide):

Since disturbances of blood glucose, including hyperglycemia and hypoglycemia, have been reported in patients treated concurrently with quinolones and an antidiabetic agent, careful monitoring of blood glucose is recommended when these agents are used concomitantly. (See **PRECAUTIONS: General and Information for Patients.**)

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Long-term studies to determine the carcinogenic potential of ofloxacin have not been conducted.

Ofloxacin was not mutagenic in the Ames bacterial test, *in vitro* and *in vivo* cytogenetic assay, sister chromatid exchange (Chinese Hamster and Human Cell Lines), unscheduled DNA Repair (UDS) using human fibroblasts, dominant lethal assays, or mouse micronucleus assay. Ofloxacin was positive in the UDS test using rat hepatocytes and Mouse Lymphoma Assay.

Pregnancy:

Teratogenic Effects. Pregnancy Category C.

Ofloxacin has not been shown to have any teratogenic effects at oral doses as high as 810 mg/kg/day (11 times the recommended maximum human dose based on mg/m² or 50 times based on mg/kg) and 160 mg/kg/day (4 times the recommended maximum human dose based on mg/m² or 10 times based on mg/kg) when administered to pregnant rats and rabbits, respectively. Additional studies in rats with oral doses up to 360 mg/kg/day (5 times the recommended maximum human dose based on mg/m² or 23 times based on mg/kg) demonstrated no adverse effect on late fetal development, labor, delivery, lactation, neonatal viability, or growth of the newborn. Doses equivalent to 50 and 10 times the recommended maximum human dose of ofloxacin (based on mg/kg) were fetotoxic (i.e., decreased fetal body weight and increased fetal mortality) in rats and rabbits, respectively. Minor skeletal variations were reported in rats receiving doses of 810 mg/kg/day, which is more than 10 times higher than the recommended maximum human dose based on mg/m².

There are, however, no adequate and well-controlled studies in pregnant women. Ofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See **WARNINGS.**)

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Nursing Mothers:

In lactating females, a single oral 200-mg dose of ofloxacin resulted in concentrations of ofloxacin in milk that were similar to those found in plasma. Because of the potential for serious adverse reactions from ofloxacin in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. (See *WARNINGS* and *ADVERSE REACTIONS*.)

Pediatric Use:

Safety and effectiveness in pediatric patients and adolescents below the age of 18 years have not been established. Ofloxacin causes arthropathy (arthrosis) and osteochondrosis in juvenile animals of several species. (See *WARNINGS*.)

Geriatric Use:

In phase 2/3 clinical trials with ofloxacin, 688 patients (14.2%) were \geq 65 years of age. Of these, 436 patients (9.0%) were between the ages of 65 and 74 and 252 patients (5.2%) were 75 years or older. There was no apparent difference in the frequency or severity of adverse reactions in elderly adults compared with younger adults. The pharmacokinetic properties of ofloxacin in elderly subjects are similar to those in younger subjects. Drug absorption appears to be unaffected by age. Dosage adjustment is necessary for elderly patients with impaired renal function (creatinine clearance rate \leq 50 mL/min) due to reduced clearance of ofloxacin. In comparative studies, the frequency and severity of most drug-related nervous system events in patients \geq 65 years of age were comparable for ofloxacin and control drugs. The only differences identified were an increase in reports of insomnia (3.9% vs 1.5%) and headache (4.7% vs 1.8%) with ofloxacin. It is important to note that these geriatric safety data are extracted from 44 comparative studies where the adverse reaction information from 20 different controls (other antibiotics or placebo) were pooled for comparison with ofloxacin. The clinical significance of such a comparison is not clear. (See *CLINICAL PHARMACOLOGY* and *DOSAGE AND ADMINISTRATION*.)

Elderly patients may be more sensitive to drug-associated effects on the QT interval. Therefore, precaution should be taken when using ofloxacin with concomitant drugs that can result in prolongation of the QT interval (e.g. class IA or class III antiarrhythmics) or in patients with risk factors for Torsade de pointes (e.g. known QT prolongation, uncorrected hypokalemia). (See *PRECAUTIONS: GENERAL: Torsades de pointes*)

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ADVERSE REACTIONS

The following is a compilation of the data for ofloxacin based on clinical experience with both the oral and intravenous formulations. The incidence of drug-related adverse reactions in patients during Phase 2 and 3 clinical trials was 11%. Among patients receiving multiple-dose therapy, 4% discontinued ofloxacin due to adverse experiences.

In clinical trials, the following events were considered likely to be drug-related in patients receiving multiple doses of ofloxacin:

nausea 3%, insomnia 3%, headache 1%, dizziness 1%, diarrhea 1%, vomiting 1%, rash 1%, pruritus 1%, external genital pruritus in women 1%, vaginitis 1%, dysgeusia 1%.

In clinical trials, the most frequently reported adverse events, regardless of relationship to drug, were:

nausea 10%, headache 9%, insomnia 7%, external genital pruritus in women 6%, dizziness 5%, vaginitis 5%, diarrhea 4%, vomiting 4%.

In clinical trials, the following events, regardless of relationship to drug, occurred in 1 to 3% of patients:

Abdominal pain and cramps, chest pain, decreased appetite, dry mouth, dysgeusia, fatigue, flatulence, gastrointestinal distress, nervousness, pharyngitis, pruritus, fever, rash, sleep disorders, somnolence, trunk pain, vaginal discharge, visual disturbances, and constipation.

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Additional events, occurring in clinical trials at a rate of less than 1%, regardless of relationship to drug, were:

Body as a whole:	asthenia, chills, malaise, extremity pain, pain, epistaxis
Cardiovascular System:	cardiac arrest, edema, hypertension, hypotension, palpitations, vasodilation
Gastrointestinal System:	dyspepsia
Genital/Reproductive System:	burning, irritation, pain and rash of the female genitalia; dysmenorrhea; menorrhagia; metrorrhagia
Musculoskeletal System:	arthralgia, myalgia
Nervous System:	seizures, anxiety, cognitive change, depression, dream abnormality, euphoria, hallucinations, paresthesia, syncope, vertigo, tremor, confusion
Nutritional/Metabolic:	thirst, weight loss
Respiratory System:	respiratory arrest, cough, rhinorrhea
Skin/Hypersensitivity:	angioedema, diaphoresis, urticaria, vasculitis
Special Senses:	decreased hearing acuity, tinnitus, photophobia
Urinary System:	dysuria, urinary frequency, urinary retention

The following laboratory abnormalities appeared in $\geq 1.0\%$ of patients receiving multiple doses of ofloxacin. It is not known whether these abnormalities were caused by the drug or the underlying conditions being treated.

Hematopoietic:	anemia, leukopenia, leukocytosis, neutropenia, neutrophilia, increased band forms, lymphocytopenia, eosinophilia, lymphocytosis, thrombocytopenia, thrombocytosis, elevated ESR
Hepatic:	elevated: alkaline phosphatase, AST (SGOT), ALT (SGPT)
Serum chemistry:	hyperglycemia, hypoglycemia, elevated creatinine, elevated BUN
Urinary:	glucosuria, proteinuria, alkalinuria, hyposthenuria, hematuria, pyuria

Post-Marketing Adverse Events:

Additional adverse events, regardless of relationship to drug, reported from worldwide marketing experience with quinolones, including ofloxacin:

Clinical:

Cardiovascular System:	cerebral thrombosis, pulmonary edema, tachycardia, hypotension/shock, syncope
Endocrine/Metabolic:	hyper- or hypoglycemia, especially in diabetic patients on insulin or oral hypoglycemic agents (See PRECAUTIONS: General and Drug Interactions.)

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Gastrointestinal System:	hepatic dysfunction including: hepatic necrosis, jaundice (cholestatic or hepatocellular), hepatitis; intestinal perforation; pseudomembranous colitis (the onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment), GI hemorrhage; hiccough, painful oral mucosa, pyrosis (See WARNINGS .)
Genital/Reproductive System:	vaginal candidiasis
Hematopoietic:	anemia, including hemolytic and aplastic; hemorrhage, pancytopenia, agranulocytosis, leukopenia, reversible bone marrow depression, thrombocytopenia, thrombotic thrombocytopenic purpura, petechiae, ecchymosis/bruising (See WARNINGS .)
Musculoskeletal:	tendinitis/rupture; weakness; rhabdomyolysis (See WARNINGS .)
Nervous System:	nightmares; suicidal thoughts or acts, disorientation, psychotic reactions, paranoia; phobia, agitation, restlessness, aggressiveness/hostility, manic reaction, emotional lability; peripheral neuropathy, ataxia, incoordination; possible exacerbation of: myasthenia gravis and extrapyramidal disorders; dysphasia, lightheadedness (See WARNINGS and PRECAUTIONS .)
Respiratory System:	dyspnea, bronchospasm, allergic pneumonitis, stridor (See WARNINGS .)
Skin/Hypersensitivity:	anaphylactic (-toid) reactions/shock; purpura, serum sickness, erythema multiforme/Stevens-Johnson Syndrome, erythema nodosum, exfoliative dermatitis, hyperpigmentation, toxic epidermal necrolysis, conjunctivitis, photosensitivity, vesiculobullous eruption (See WARNINGS and PRECAUTIONS .)
Special Senses:	diplopia, nystagmus, blurred vision, disturbances of: taste, smell, hearing and equilibrium, usually reversible following discontinuation
Urinary System:	anuria, polyuria, renal calculi, renal failure, interstitial nephritis, hematuria (See WARNINGS and PRECAUTIONS .)
Laboratory:	
Hematopoietic:	prolongation of prothrombin time
Serum chemistry:	acidosis, elevation of: serum triglycerides, serum cholesterol, serum potassium, liver function tests including: GGTP, LDH, bilirubin
Urinary:	albuminuria, candiduria

In clinical trials using multiple-dose therapy, ophthalmologic abnormalities, including cataracts and multiple punctate lenticular opacities, have been noted in patients undergoing treatment with other quinolones. The relationship of the drugs to these events is not presently established.

CRYSTALLURIA and CYLINDRURIA HAVE BEEN REPORTED with other quinolones.

OVERDOSAGE

Information on overdose with ofloxacin is limited. One incident of accidental overdose has been reported. In this case, an adult female received 3 grams of ofloxacin intravenously over 45 minutes. A blood sample obtained 15 minutes after the completion of the infusion revealed an ofloxacin level of 39.3 µg/mL. In 7 h, the level had fallen to 16.2 µg/mL, and by 24 h to 2.7 µg/mL. During the infusion, the patient developed drowsiness, nausea, dizziness, hot and cold flushes, subjective facial swelling and numbness, slurring of speech, and mild to moderate disorientation. All complaints except the dizziness subsided within 1 h after discontinuation of the infusion. The dizziness, most bothersome while standing, resolved in approximately 9 h. Laboratory testing reportedly revealed no clinically significant changes in routine parameters in this patient.

In the event of an acute overdose, the stomach should be emptied. The patient should be observed and appropriate hydration maintained. Ofloxacin is not efficiently removed by hemodialysis or peritoneal dialysis.

DOSAGE AND ADMINISTRATION

The usual dose of FLOXIN[®] (ofloxacin tablets) Tablets is 200 mg to 400 mg orally every 12 h as described in the following dosing chart. These recommendations apply to patients with normal renal function (i.e., creatinine clearance >50 mL/min). For patients with altered renal function (i.e., creatinine clearance ≤50 mL/min), see the *Patients with Impaired Renal Function* subsection.

Patients with Normal Renal Function:

Infection†	Unit Dose	Frequency	Duration	Daily Dose
Acute Bacterial Exacerbation of Chronic Bronchitis	400 mg	q12h	10 days	800 mg
Comm. Acquired Pneumonia	400 mg	q12h	10 days	800 mg
Uncomplicated Skin and Skin Structure Infections	400 mg	q12h	10 days	800 mg
Acute, Uncomplicated Urethral and Cervical Gonorrhea	400 mg	single dose	1 day	400 mg
Nongonococcal Cervicitis/Urethritis due to <i>C. trachomatis</i>	300 mg	q12h	7 days	600 mg
Mixed Infection of the urethra and cervix due to <i>C. trachomatis</i> and <i>N. gonorrhoeae</i>	300 mg	q12h	7 days	600 mg
Acute Pelvic Inflammatory Disease	400 mg	q12h	10-14 days	800 mg
Uncomplicated Cystitis due to <i>E. coli</i> or <i>K. pneumoniae</i>	200 mg	q12h	3 days	400 mg
Uncomplicated Cystitis due to other approved pathogens	200 mg	q12h	7 days	400 mg

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Complicated UTI's	200 mg	q12h	10 days	400 mg
Prostatitis due to <i>E.Coli</i>	300 mg	q12h	6 weeks	600 mg

†DUE TO THE DESIGNATED PATHOGENS (See **INDICATIONS AND USAGE**.)

Antacids containing calcium, magnesium, or aluminum; sucralfate; divalent or trivalent cations such as iron; or multivitamins containing zinc; or Videx[®] (didanosine) should not be taken within the two-hour period before or within the two-hour period after taking ofloxacin. (See **PRECAUTIONS**.)

Patients with Impaired Renal Function:

Dosage should be adjusted for patients with a creatinine clearance ≤ 50 mL/min. **After a normal initial dose**, dosage should be adjusted as follows:

Creatinine Clearance	Maintenance Dose	Frequency
20-50 mL/min	the usual recommended unit dose	q24h
<20 mL/min	1/2 the usual recommended unit dose	q24h

When only the serum creatinine is known, the following formula may be used to estimate creatinine clearance.

$$\text{Men: Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Women: 0.85 x the value calculated for men.

The serum creatinine should represent a steady-state of renal function.

Patients with Cirrhosis:

The excretion of ofloxacin may be reduced in patients with severe liver function disorders (e.g., cirrhosis with or without ascites). A maximum dose of 400 mg of ofloxacin per day should therefore not be exceeded.

HOW SUPPLIED

FLOXIN[®] (ofloxacin tablets) Tablets are supplied as 200 mg light yellow, 300 mg white, and 400 mg pale gold oval, straight-edged, coated tablets. Each tablet is distinguished by an imprint of "FLOXIN" and the appropriate strength. FLOXIN Tablets are packaged in bottles in the following configurations:

200 mg tablets - bottles of 50 (NDC 0062 - 1540-02)

300 mg tablets - bottles of 50 (NDC 0062 - 1541-02)

400 mg tablets - bottles of 100 (NDC 0062 - 1542-01)

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FLOXIN Tablets should be stored in well-closed containers. Store below 86°F (30°C).

ANIMAL PHARMACOLOGY

Ofloxacin, as well as other drugs of the quinolone class, has been shown to cause arthropathies (arthrosis) in immature dogs and rats. In addition, these drugs are associated with an increased incidence of osteochondrosis in rats as compared to the incidence observed in vehicle-treated rats. (See **WARNINGS**.) There is no evidence of arthropathies in fully mature dogs at intravenous doses up to 3 times the recommended maximum human dose (on a mg/m² basis or 5 times based on mg/kg basis), for a one-week exposure period.

Long-term, high-dose systemic use of other quinolones in experimental animals has caused lenticular opacities; however, this finding was not observed in any animal studies with ofloxacin.

Reduced serum globulin and protein levels were observed in animals treated with other quinolones. In one ofloxacin study, minor decreases in serum globulin and protein levels were noted in female cynomolgus monkeys dosed orally with 40 mg/kg ofloxacin daily for one year. These changes, however, were considered to be within normal limits for monkeys.

Crystalluria and ocular toxicity were not observed in any animals treated with ofloxacin.

FLOXIN[®] is a trademark of ORTHO-McNEIL PHARMACEUTICAL, INC.

U.S. Patent No. 4,382,892

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically - Fourth Edition. Approved Standard NCCLS Document M7-A4, Vol. 17, No. 2, NCCLS, Wayne, PA, January, 1997.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests - Sixth Edition. Approved Standard NCCLS Document M2-A6, Vol. 17, No. 1, NCCLS, Wayne, PA, January 1997.

(Ortho-McNeil logo)

ORTHO-McNEIL

Text of Proposed Labeling
PHARMACEUTICAL, INC.
Raritan, NJ USA 08869
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Revised March 2003

7516002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-735 / S-052, S-053

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

Labeling and Clinical Review of Supplemental Labeling Revisions (SLRs):

Executive Summary:

This review describes and reviews the proposed labeling revisions to the **WARNINGS** and **PRECAUTIONS, Information for Patients** sections in these "Changes Being Effected" (CBE) supplemental labeling applications to add quinolone class labeling information to the package insert. These changes were requested in our supplement request letter dated November 26, 2003, and in our facsimiles to the sponsor dated March 10, 2004 and July 12, 2004.

The sponsor had also had included information on _____ to quinolone therapy and included that in the **CLINICAL STUDIES** section (S-053). That information was subsequently removed from the labeling per the Division's request. b(4)

This review recommends approval of these proposed labeling changes.

Products: FLOXIN[®] (ofloxacin tablets) Tablets, 200 mg, 300 mg, 400mg

Sponsor: Johnson & Johnson

Materials Reviewed:

NDA 19-735

<u>SLR</u>	<u>Date submitted</u>	<u>Date received</u>	<u>Date completed</u>
052/053	March 19, 2004	March 23, 2004	September 14, 2004

Amendment

<u>SLR</u>	<u>Date submitted</u>	<u>Date received</u>	<u>Date completed</u>
052	April 9, 2004	April 12, 2004	September 14, 2004
052	August 23, 2004	August 24, 2004	September 14, 2004

- FDA CBE request letter to sponsor concerning quinolone class labeling dated November 26, 2003
- FDA facsimiles to the sponsor dated March 10, 2004 and July 12, 2004
- Approved package insert for NDA 19-735 dated March 6, 2004

Background:

NDA 19-735 was originally approved on December 28, 1990. The last approved labeling change occurred on March 6, 2004 for SLR-051 when antibacterial class labeling was approved. There have been no other approved labeling changes since that time.

Quinolone Class Labeling

Supplement S-052 was submitted as CBE and provided for the addition of quinolone class labeling as was requested in our supplement request letter dated November 26, 2003 and in our facsimile to the sponsor dated March 10, 2004.

The sponsor had also had included information on _____ to quinolone therapy and included that in the **CLINICAL STUDIES** section. That labeling change was administratively split into SLR-053, and was subsequently removed from the labeling per the Division's request.

b(4)

An internal team meeting was held on June 23, 2004 with Dr. Robert Temple, CDER Associate Director for Policy, and Dr. Mark Goldberger, Office Director concerning the quinolone class labeling issue for QT/*Torsades de Pointes* labeling. It was determined that it was acceptable for the sponsor to omit the Division's proposed QT/*Torsades de Pointes* wording in **WARNINGS**.

The sponsor was called on July 9, 2004, was advised of that decision and additional labeling revisions were proposed by the Division. A fax was then sent to the company on July 12, 2004 that included the following comments:

~~Strikethrough~~=deleted text

1. You may remove the following paragraph from **WARNINGS** and move it to **PRECAUTIONS**. If you determine that it is not necessary to include this paragraph in **PRECAUTIONS**, please include a justification in the cover letter when you submit the revised label. Please note that the word "very" should be deleted in the first sentence:

Torsades de pointes

~~Very r~~Rare cases of torsades de pointes have been spontaneously reported during post-marketing surveillance in patients receiving quinolones, including levofloxacin. Levofloxacin should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia, and patients receiving class IA (quinidine, procainamide), or class III (amiodarone, sotalol) antiarrhythmic agents. (see **PRECAUTIONS**)

2. You also have the option of removing the existing text regarding QTc from **PRECAUTIONS**.
3. Please propose wording in the **PRECAUTIONS, Geriatric Use** subsection to address the higher frequency of torsades de pointes among the elderly in post-marketing adverse event reports.
4. Please delete the following information from the **CLINICAL STUDIES** section (including text and tables):

QT/QTc studies

~~In a study of 48 healthy volunteers receiving single doses of levofloxacin 500, 1000, and 1500 mg and placebo, a dose-related increase from baseline to post dose of average QTc (Bazett) or QTc (Fridericia) was observed^x. No effect on~~

1 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Withheld Track Number: Administrative-_____

in healthy adults after single doses. Clin Pharmacol Ther 2003; 73:292-303

5. In **WARNINGS**, please add the subheading "**Tendon Effects**" for the tendon rupture paragraph, and "**Peripheral Neuropathy**" for the peripheral neuropathy paragraph.
6. In **PRECAUTIONS**, please delete the following paragraph under **General**:

[b(4)

~~PRECAUTIONS: Information for Patients~~

7. Please add rhabdomyolysis to **ADVERSE REACTIONS, Post-marketing Adverse Reactions**.

Electronic Labeling Comparison:

The approved label dated March 6, 2004 was electronically compared to the proposed draft labeling dated August 23, 2004. The changes were as follows:

~~Strikethrough~~=deleted

Double underline=added

1. "FLOXIN[®] (ofloxacin) Tablets" was changed to "FLOXIN[®] (ofloxacin tablets) Tablets" throughout the label.
2. References to "Videx[®] (Didanosine) chewable/ buffered tablets or the pediatric powder for oral solution" have been changed to just "Videx[®] (didanosine)" throughout the label.

3. WARNINGS

- A **Peripheral neuropathy** subsection was added to read:

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 ofloxacin. Ofloxacin should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness or other alterations of sensation including light touch, pain, temperature, position sense, and vibratory sensation in order to prevent the development of an irreversible condition.

- The **Tendon effects** subsection was revised to read:

Tendon effects: Ruptures of the shoulder, hand, and 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 increased in patients receiving corticosteroids, with ofloxacin and other quinolones especially the elderly. (see PRECAUTIONS). Ofloxacin 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 ofloxacin.

4. PRECAUTIONS

- A **Torsades de pointes** subsection was added to read:

Torsades de pointes: Some quinolones, including ofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. Rare cases of torsades de pointes have been spontaneously reported during post-marketing surveillance in patients receiving quinolones, including ofloxacin. Ofloxacin should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia, and patients receiving class IA (quinidine, procainamide), or class III (amiodarone, sotalol) antiarrhythmic agents.

- The following bullet concerning peripheral neuropathy was added under **Information for Patients:**

- that peripheral neuropathies have been associated with ofloxacin use. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness develop, they should discontinue treatment and contact their physicians;

- The following paragraph was added to the **Geriatric Use** subsection:

Elderly patients may be more sensitive to drug-associated effects on the QT interval. Therefore, precaution should be taken when using ofloxacin with concomitant drugs that can result in prolongation of the QT interval (e.g. class IA or class III antiarrhythmics) or in patients with risk factors for Torsade de pointes (e.g. known QT prolongation, uncorrected hypokalemia). (See **PRECAUTIONS: GENERAL: Torsades de pointes**)

5. HOW SUPPLIED

- The first two sentences in this section were revised to read:

FLOXIN[®] (ofloxacin tablets) Tablets are supplied as 200 mg light yellow, 300 mg white, and 400 mg pale gold oval, straight-edged, film coated tablets. Each tablet is distinguished by an imprint of "FLOXIN" and the appropriate strength.

Conclusions/Recommendations:

These labeling changes are acceptable. An approval letter should be sent advising the applicant that these supplemental NDA submissions are approved.

Robin Anderson, R.N., M.B.A.
Labeling Reviewer

Renata Albrecht, M.D.
Division Director

Concurrence:

HFD-590/DivDir/ R. Albrecht 9/15/04

HFD-590/PM/R. Saville (cc only)

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

/s/

Robin Anderson
9/15/04 02:23:01 PM
INTERDISCIPLINARY

Renata Albrecht concurred with this review on 9/15/04.

Renata Albrecht
9/15/04 04:05:24 PM
MEDICAL OFFICER

09 APR 2004

920 U.S. Highway 202, P.O. Box 300
Raritan NJ 08869

Renata Albrecht, MD, Director
Division of Special Pathogens and Immunologic
Drug Products (HFD-590)
Center For Drug Evaluation and Research
Attn.: Document Control Room
Food and Drug Administration
9201 Corporate Blvd.
Rockville, Maryland 20850

NDA 19-735
FLOXIN® Tablets

REQUEST FOR A MEETING

**SPECIAL SUPPLEMENT:
PROPOSED LABELING**

Dear Dr. Albrecht:

Reference is made to Johnson & Johnson Pharmaceutical Research and Development (JJPRD) on behalf of Ortho-McNeil Pharmaceutical's approved New Drug Application 19-735 for FLOXIN® (ofloxacin) Tablets. Reference is also made to the Agency's October 27, 2003 Special Supplement Request for Fluoroquinolone Class Labeling, and to the March 19, 2004 labeling submission.

Two teleconferences between JJPRD and the Agency were held to discuss the Agency's request for class labeling for QTc prolongation/torsades de pointe and peripheral neuropathy, one on February 09 and the other on April 1, 2004. The minutes of the April 1 meeting are attached.

During this teleconference, the Agency agreed to accept an updated proposed text for the FLOXIN® label which would address the sponsor's as well as the Agency's concerns regarding fluoroquinolone information to consumers and clinicians.

In this correspondence, we are providing an updated version of the March 19th 2004 proposed FLOXIN® labeling which contains text on torsades de pointe in the WARNING Section. Based on the discussions in the April 1, 2004 teleconference the text on peripheral neuropathy and Tendon rupture in the WARNING section has not changed from the March 19, 2004 version.

Also, based on the discussions of April 1, we are requesting for a follow-up meeting/teleconference (type C) to further discuss the data that has been provided as

well as the proposed label changes. We would like to request this meeting for April 22 from 11-12 am. The teleconference details are as follows:

Dial In Number: 877-214-5637
Participant Code: 663308

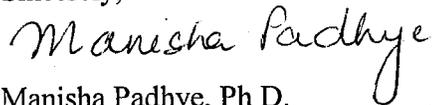
The JJPRD Attendee list for this teleconference is as follows:

David Grewcock, Director of Marketing, Anti-infectives
Larry Johnson, Drug Safety Leader
Sam Maldonado, MD, Regulatory Leader
Gary Noel, MD. Clinical Team Leader
Manisha Padhye, Ph.D, Regulatory Liason
Hamish Ross, Ph.D. Clinical Development Team Leader

We look forward to meeting with you to further discuss these important issues about FLOXIN®.

If there are any questions or concerns please contact me at 908-704-4587.

Sincerely,



Manisha Padhye, Ph D.
Associate Director, Regulatory Affairs
Johnson & Johnson Pharmaceutical Research & Development, L.LC.

Desk Copy: Cover Letter - Ms. Susan Peacock, MS, M(ASCP)