CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-384 / S-024

Trade Name: **Noroxin**

Generic Name: **norfloxacin**

Sponsor: **Merck**

Approval Date: **July 1, 1994**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-384 / S-024

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-384 / S-024

APPROVAL LETTER

NDA 19-384/S-024

Henrietta Ukwu, M.D.
Director
Regulatory Liaison
Merck Sharp & Dohme Research Laboratories
West Point, PA 19486

JUL 1 1994

Dear Dr. Ukwu:

Reference is made to your supplemental new drug application (NDA) dated May 21, 1993, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tablets Noroxin® (norfloxacin) providing for revisions to the **ADVERSE REACTIONS** section of the labeling.

We have completed our review of the supplement and the final printed labeling (FPL) dated February 1993, and it is approved as of the date of this letter. However, we request that, at the next FPL printing, the information below be incorporated.

Under the **WARNINGS** section, please add the following paragraphs so that they become the last three paragraphs of that section:

This approval affects only those changes specifically submitted in this supplemental application. Other changes which may be approved or are pending are not affected.

Should additional information relating to the safety and effectiveness of this drug product become available, further revision of the labeling may be required.

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

Should you have any question concerning this issue, please contact Ms. Pauline Fogarty, of the Project Management Staff, at 301-443-6797.

Sincerely yours,

6/28/94

for Lillian Gavrilovich, M.D.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:Orig NDA 19-384
HFD-130
HFD-82
HFD-500
HFD-638
HFD-735
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HFD-520/ActDivDir/LGavrilovich
HFD-520/MO/Blum 6/27/94
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HFD-520/Micro/PDionne
HFD-521/PMS/PDeSantis
HFD-521/PMS/Fogarty 6/27/94
fogarty6/8/94
APPROVAL

Concurrences:
HFD-520/SMO/Albuerne

HFD-521/SPMS/TDeSantis

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

MERCK & CO., INC.
West Point, PA 19486, USA

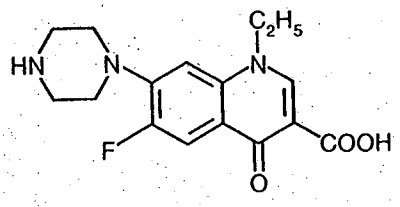
TABLETS

NOROXIN®

(NORFLOXACIN)

DESCRIPTION

NOROXIN* (Norfloxacin) is a synthetic, broad-spectrum antibacterial agent for oral administration. Norfloxacin, a fluoroquinolone, is 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is $C_{16}H_{18}FN_3O_3$ and the structural formula is:



Norfloxacin is a white to pale yellow crystalline powder with a molecular weight of 319.34 and a melting point of about 221°C. It is freely soluble in glacial acetic acid, and very slightly soluble in ethanol, methanol and water.

NOROXIN is available in 400-mg tablets. Each tablet contains the following inactive ingredients: cellulose, croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, and titanium dioxide.

Norfloxacin, a fluoroquinolone, differs from non-fluorinated quinolones by having a fluorine atom at the 6 position and a piperazine moiety at the 7 position.

CLINICAL PHARMACOLOGY

In fasting healthy volunteers, at least 30 - 40% of an oral dose of NOROXIN is absorbed. Absorption is rapid following single doses of 200 mg, 400 mg and 800 mg. At the respective doses, mean peak serum and plasma concentrations of 0.8, 1.5 and 2.4 mcg/mL are attained approximately one hour after dosing. The presence of food may decrease absorption. The effective half-life of norfloxacin in serum and plasma is 3 - 4 hours. Steady-state concentrations of norfloxacin will be attained within two days of dosing.

In healthy elderly volunteers (65 - 75 years of age with normal renal function for their age), norfloxacin is eliminated more slowly because of their slightly decreased renal function. Drug absorption appears unaffected. However, the effective half-life of norfloxacin in these elderly subjects is 4 hours.

The disposition of norfloxacin in patients with creatinine clearance rates greater than 30 mL/min/1.73m² is similar to that in healthy volunteers. In patients with creatinine clearance rates equal to or less than 30 mL/min/1.73m², the renal elimination of norfloxacin decreases so that the effective serum half-life is 6.5 hours. In these patients, alteration of dosage is necessary (see DOSAGE AND ADMINISTRATION). Drug absorption appears unaffected by decreasing renal function.

Norfloxacin is eliminated through metabolism, biliary excretion, and renal excretion. After a single 400-mg dose of NOROXIN, mean antimicrobial activities equivalent to 278, 773, and 82 mcg of norfloxacin/g of feces were obtained at 12, 24, and 48 hours, respectively. Renal excretion occurs by both glomerular filtration and tubular secretion as evidenced by the high rate of renal clearance (approximately 275 mL/min). Within 24 hours of drug administration, 26 to 32% of the administered dose is recovered in the urine as norfloxacin with an additional 5 - 8% being recovered in the urine as six active metabolites of lesser antimicrobial potency. Only a small percentage (less than 1%) of the dose is recovered thereafter. Fecal recovery accounts for another 30% of the administered dose.

Two to three hours after a single 400-mg dose, urinary concentrations of 200 mcg/mL or more are attained in the urine. In healthy volunteers, mean urinary concentrations of norfloxacin remain above 30 mcg/mL for at least 12 hours following a 400-mg dose. The urinary pH may affect the solubility of norfloxacin. Norfloxacin is least soluble at urinary pH of 7.5 with greater solubility occurring at pHs above and below this value. The serum protein binding of norfloxacin is between 10 and 15%.

The following are mean concentrations of norfloxacin in various fluids and tissues measured 1 to 4 hours post-dose after two 400-mg doses, unless otherwise indicated:

Renal Parenchyma	7.3 µg/g
Prostate	2.5 µg/g
Seminal Fluid	2.7 µg/mL
Testicle	1.6 µg/g
Uterus/Cervix	3.0 µg/g
Vagina	4.3 µg/g
Fallopian Tube	1.9 µg/g
Bile	6.9 µg/mL (after two 200-mg doses)

Microbiology

Norfloxacin has *in vitro* activity against a broad range of gram-positive and gram-negative aerobic bacteria. The fluorine atom at the 6 position provides increased potency against gram-negative organisms, and the piperazine moiety at the 7 position is responsible for antipseudomonal activity.

Norfloxacin inhibits bacterial deoxyribonucleic acid synthesis and is bactericidal. At the molecular level, three specific events are attributed to norfloxacin in *E. coli* cells:

1) inhibition of the ATP-dependent DNA supercoiling reaction catalyzed by DNA gyrase,
2) inhibition of the relaxation of supercoiled DNA,
3) promotion of double-stranded DNA breakage.

Resistance to norfloxacin due to spontaneous mutation *in vitro* is a rare occurrence (range: 10^{-9} to 10^{-12} cells). Resistant organisms have emerged during therapy with norfloxacin in less than 1% of patients treated. Organisms in which development of resistance is greatest are the following:

Pseudomonas aeruginosa
Klebsiella pneumoniae
Acinetobacter species
Enterococcus species

For this reason, when there is a lack of satisfactory clinical response, repeat culture and susceptibility testing should be done. Nalidixic acid-resistant organisms are generally susceptible to norfloxacin *in vitro*; however, these organisms may have higher MICs to norfloxacin than nalidixic acid-susceptible strains. There is generally no cross-resistance between norfloxacin and other classes of antibacterial agents. Therefore, norfloxacin may demonstrate activity against indicated organisms resistant to some other antimicrobial agents including the aminoglycosides, penicillins, cephalosporins, tetracyclines, macrolides, and sulfonamides, including combinations of sulfamethoxazole and trimethoprim. Antagonism has been demonstrated *in vitro* between norfloxacin and nitrofurantoin.

Norfloxacin has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections (see INDICATIONS AND USAGE):

Gram-positive aerobes:
Enterococcus faecalis
Staphylococcus aureus
Staphylococcus epidermidis
Staphylococcus saprophyticus
Streptococcus agalactiae

Gram-negative aerobes:
Citrobacter freundii
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Klebsiella pneumoniae
Neisseria gonorrhoeae
Proteus mirabilis
Proteus vulgaris
Pseudomonas aeruginosa
Serratia marcescens

*Registered trademark of MERCK & CO., INC.

Norfloxacin has been shown to be active *in vitro* against most strains of the following organisms; however, the clinical significance of these data is unknown.

Gram-positive aerobes:
Bacillus cereus

Gram-negative aerobes:
Acinetobacter calcoaceticus
Aeromonas species
Alcaligenes species
Campylobacter species
Citrobacter diversus
Edwardsiella tarda
Flavobacterium species
Hafnia alvei
Klebsiella oxytoca
Klebsiella rhinoscleromatis
Morganella morganii
Providencia alcalifaciens
Providencia rettgeri
Providencia stuartii
Salmonella species
Shigella species
Vibrio cholerae
Vibrio parahemolyticus
Yersinia enterocolitica

Other:
Ureaplasma urealyticum

NOROXIN is not generally active against obligate anaerobes.

Norfloxacin has not been shown to be active against *Treponema pallidum*. (See WARNINGS.)

Susceptibility Tests

Diffusion Techniques: Quantitative methods that require measurement of zone diameters give the most precise estimate of the susceptibility of bacteria to antimicrobial agents. One such procedure is the National Committee for Clinical Laboratory Standards (NCCLS) approved procedure (M2-A4--Performance Standards for Antimicrobial Disk Susceptibility Tests 1990). This method has been recommended for use with the 10-mcg norfloxacin disk to test susceptibility to norfloxacin. Interpretation involves correlation of the diameters obtained in the disk test with minimum inhibitory concentration (MIC) for norfloxacin. Reports from the laboratory giving results of the standard single-disk susceptibility test with a 10-mcg norfloxacin disk should be interpreted according to the following criteria **(these criteria only apply to isolates from urinary tract infections):**

Zone diameter (mm)	Interpretation
≥17	(S) Susceptible
13-16	(I) Intermediate
≤12	(R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable urine levels. A report of "Intermediate" indicates that the test results be considered equivocal or indeterminate. A report of "Resistant" indicates that achievable concentrations of the antibiotic are unlikely to be inhibitory and other therapy should be selected.

Standardized procedures require the use of laboratory control organisms. The 10-mcg norfloxacin disk should give the following zone diameter:

Organism	Zone diameter (mm)
E. coli ATCC 25922	28 - 35
P. aeruginosa ATCC 27853	22 - 29
S. aureus ATCC 25923	17 - 28

Other quinolone antibacterial disks should not be substituted when performing susceptibility tests for norfloxacin because of spectrum differences with norfloxacin. The 10-mcg norfloxacin disk should be used for all *in vitro* testing of isolates using diffusion techniques.

Dilution Techniques: Broth and agar dilution methods, such as those recommended by the NCCLS (M7-A2--Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically 1990), may be used to determine the minimum inhibitory concentration (MIC) of norfloxacin. MIC test results should be interpreted according to the following criteria **(these criteria only apply to isolates from urinary tract infections):**

NOROXIN® (Norfloxacin)

MIC (mcg/mL)	Interpretation
≤4	(S) Susceptible
8	(I) Intermediate
≥16	(R) Resistant

As with standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard norfloxacin powder should give the following MIC values:

Organism	MIC range (mcg/mL)
E. coli ATCC 25922	0.03-0.12
E. faecalis ATCC 29212	2.0-8.0
P. aeruginosa ATCC 27853	1.0-4.0
S. aureus ATCC 29213	0.05-2.0

INDICATIONS AND USAGE

NOROXIN is indicated for the treatment of adults with the following infections caused by susceptible strains of the designated microorganisms:

Urinary tract infections:
Uncomplicated urinary tract infections (including cystitis) due to *Enterococcus faecalis, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus epidermidis, Staphylococcus saprophyticus, Citrobacter freundii*, Enterobacter aerogenes*, Enterobacter cloacae*, Proteus vulgaris*, Staphylococcus aureus*,* or *Streptococcus agalactiae**.

Complicated urinary tract infections due to *Enterococcus faecalis, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa,* or *Serratia marcescens**.

Sexually transmitted diseases (See WARNINGS.):
Uncomplicated urethral and cervical gonorrhea due to *Neisseria gonorrhoeae.*

(See DOSAGE AND ADMINISTRATION for appropriate dosing instructions.)

Penicillinase production should have no effect on norfloxacin activity.

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 norfloxacin. Therapy with norfloxacin may be initiated before results of these tests are known; once results become available, appropriate therapy should be given. Repeat culture and susceptibility testing performed periodically during therapy will provide information not only on the therapeutic effect of the antimicrobial agents but also on the possible emergence of bacterial resistance.

CONTRAINDICATIONS

NOROXIN is contraindicated in patients with a history of hypersensitivity to norfloxacin or the other members of the quinolone group of antibacterial agents.

WARNINGS

THE SAFETY AND EFFICACY OF ORAL NORFLOXACIN IN CHILDREN, ADOLESCENTS (UNDER THE AGE OF 18), PREGNANT WOMEN, AND NURSING MOTHERS HAVE NOT BEEN ESTABLISHED. (See PRECAUTIONS-*Pregnancy, Nursing Mothers* and *Pediatric Use.*)

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.)

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.

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, tin-

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.
†Based on a patient weight of 50 kg.

gling, 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.

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.)

PRECAUTIONS

General:

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

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

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

Information for Patients

Patients should be advised:

— to drink fluids liberally.

— that norfloxacin should be taken at least one hour before or at least two hours after a meal.

— that multivitamins or other products containing iron or zinc, or antacids should not be taken within the two-hour period before or within the two-hour period after taking norfloxacin. (See *Drug Interactions.*)

— that norfloxacin can cause dizziness and lightheadedness and, therefore, patients should know how they react to norfloxacin before they operate an automobile or machinery or engage in activities requiring mental alertness and coordination.

— that norfloxacin may be associated with hypersensitivity reactions, even following the first dose, and to discontinue the drug at the first sign of a skin rash or other allergic reaction.

— to avoid undue exposure to excessive sunlight while receiving norfloxacin and to discontinue therapy if phototoxicity occurs.

— that some quinolones may increase the effects of theophylline and/or caffeine. (See *Drug Interactions.*)

Drug Interactions

Elevated plasma levels of theophylline have been reported with concomitant quinolone use. There have been reports of theophylline-related side effects in patients on concomitant therapy with norfloxacin and theophylline. Therefore, monitoring of theophylline plasma levels should be considered and dosage of theophylline adjusted as required.

Elevated serum levels of cyclosporine have been reported with concomitant use of cyclosporine with norfloxacin. Therefore cyclosporine serum levels should be monitored and appropriate cyclosporine dosage adjustments made when these drugs are used concomitantly.

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

Diminished urinary excretion of norfloxacin has been reported during the concomitant administration of probenecid and norfloxacin.

The concomitant use of nitrofurantoin is not recommended since nitrofurantoin may antagonize the antibacterial effect of NOROXIN in the urinary tract.

NOROXIN® (Norfloxacin)

Multivitamins, or other products containing iron or zinc, antacids or sucralfate should not be administered concomitantly with, or within 2 hours of, the administration of norfloxacin, because they may interfere with absorption resulting in lower serum and urine levels of norfloxacin.

Some quinolones have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its plasma half-life.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No increase in neoplastic changes was observed with norfloxacin as compared to controls in a study in rats, lasting up to 96 weeks at doses 8 - 9 times[1] the usual human dose (on a mg/kg basis).

Norfloxacin was tested for mutagenic activity in a number of *in vivo* and *in vitro* tests. Norfloxacin had no mutagenic effect in the dominant lethal test in mice and did not cause chromosomal aberrations in hamsters or rats at doses 30 - 60 times[1] the usual human dose (on a mg/kg basis). Norfloxacin had no mutagenic activity *in vitro* in the Ames microbial mutagen test, Chinese hamster fibroblasts and V-79 mammalian cell assay. Although norfloxacin was weakly positive in the Rec-assay for DNA repair, all other mutagenic assays were negative including a more sensitive test (V-79).

Norfloxacin did not adversely affect the fertility of male and female mice at oral doses up to 30 times[1] the usual human dose (on a mg/kg basis).

Pregnancy

Teratogenic Effects. Pregnancy Category C. Norfloxacin has been shown to produce embryonic loss in monkeys when given in doses 10 times[1] the maximum daily total human dose (on a mg/kg basis). At this dose, peak plasma levels obtained in monkeys were approximately 2 times those obtained in humans. There has been no evidence of a teratogenic effect in any of the animal species tested (rat, rabbit, mouse, monkey) at 6 - 50 times[1] the maximum daily human dose (on a mg/kg basis). There are, however, no adequate and well controlled studies in pregnant women. Norfloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether norfloxacin is excreted in human milk.

When a 200-mg dose of NOROXIN was administered to nursing mothers, norfloxacin was not detected in human milk. However, because the dose studied was low, because other drugs in this class are secreted in human milk, and because of the potential for serious adverse reactions from norfloxacin in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of oral norfloxacin in children and adolescents below the age of 18 years have not been established. Norfloxacin causes arthropathy in juvenile animals of several animal species. (See WARNINGS and ANIMAL PHARMACOLOGY.)

ADVERSE REACTIONS

Urinary Tract Infections

In clinical trials involving 1869 patients/subjects, 3.5% reported drug-related adverse experiences. However, the incidence figures below were calculated without reference to drug relationship.

The most common adverse experiences (>1%) were: nausea (4.3%), headache (2.9%), dizziness (1.8%), and fatigue (1.1%).

Additional reactions (0.3% - 1%) were: rash, abdominal pain, dyspepsia, somnolence, depression, insomnia, constipation, flatulence, heartburn, dry mouth, diarrhea, fever, vomiting, pruritus, loose stools, back pain and hyperhidrosis.

Less frequent reactions included: erythema, anorexia, bitter taste, and asthenia.

Abnormal laboratory values observed in these patients/subjects were: elevation of ALT (SGPT) (1.6%), decreased WBC and neutrophil count (1.6%), elevation of AST (SGOT) (1.4%), eosinophilia (1.4%), and increased alkaline phosphatase (1.2%). Those occurring less frequently included increased BUN, serum creatinine, and LDH, and decreased hematocrit.

Gonorrhea

In clinical trials involving 228 patients who received a single 800-mg dose, 7.0% of patients reported drug-related adverse experiences. However, the following incidence figures were calculated without reference to drug relationship.

[1]Based on a patient weight of 50 kg.

The most common adverse experiences (1% - 3.5%) were: dizziness (3.5%), nausea (2.2%), abdominal cramping (1.8%), diarrhea (1.3%), anorexia (1.3%), headache (1.3%), and hyperhidrosis (1.3%).

Additional reactions (0.3% - 1%) were: vomiting, constipation, dyspepsia, and tingling of the fingers.

Laboratory adverse changes considered drug-related were reported in 2.2% of patients who received a single 800-mg dose of norfloxacin. These laboratory changes were: decreased hemoglobin and hematocrit (0.9%), decreased platelet count (0.9%), and increased AST (0.4%).

Post Marketing

The most frequently reported adverse reaction in post-marketing experience is rash.

CNS effects characterized as generalized seizures and myoclonus have been reported with NOROXIN. A causal relationship to NOROXIN has not been established (see WARNINGS). Visual disturbances have been reported with drugs in this class.

The following additional adverse reactions have been reported since the drug was marketed:

Hypersensitivity Reactions

Hypersensitivity reactions have been reported including anaphylactoid reactions, angioedema, dyspnea, vasculitis, urticaria, arthritis, arthralgia and myalgia (see WARNINGS).

Skin

Toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme, exfoliative dermatitis, pruritus, photosensitivity

Gastrointestinal

Pseudomembranous colitis, hepatitis, jaundice, including cholestatic jaundice, pancreatitis (rare), stomatitis, anorexia

Renal

Interstitial nephritis, renal failure

Nervous System/Psychiatric

Neurologic changes such as ataxia, diplopia and weakness, possible exacerbation of myasthenia gravis, psychic disturbances including psychotic reactions and confusion, paresthesia

Musculoskeletal

Tendinitis

Hematologic

Neutropenia, leukopenia, hemolytic anemia, thrombocytopenia

Special Senses

Transient hearing loss (rare), tinnitus

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, hypoglycemia, nystagmus, postural hypotension, prolongation of prothrombin time, and vaginal candidiasis.

OVERDOSAGE

No significant lethality was observed in male and female mice and rats at single oral doses up to 4 g/kg.

In the event of acute overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage, and the patient carefully observed and given symptomatic and supportive treatment. Adequate hydration must be maintained.

DOSAGE AND ADMINISTRATION

Tablets NOROXIN should be taken at least one hour before or at least two hours after a meal with a glass of water. Patients receiving NOROXIN should be well hydrated (see PRECAUTIONS).

Normal Renal Function

The recommended daily dose of NOROXIN is as described in the following chart:

Infection	Description	Unit Dose	Frequency	Duration	Daily Dose
Urinary Tract	Uncomplicated UTI's (cystitis) due to *E. coli, K. pneumoniae,* or *P. mirabilis*	400 mg	q12h	3 days	800 mg
	Uncomplicated UTI's due to other indicated organisms	400 mg	q12h	7-10 days	800 mg
	Complicated UTI's	400 mg	q12h	10-21 days	800 mg
Sexually Transmitted Diseases	Uncomplicated Gonorrhea	800 mg	single dose	1 day	800 mg

Renal Impairment

NOROXIN may be used for the treatment of urinary tract infections in patients with renal insufficiency. In patients with a creatinine clearance rate of 30 mL/min/1.73m² or less, the recommended dosage is one 400-mg tablet once daily for the duration given above. At this dosage, the urinary concentration exceeds the MICs for most urinary pathogens susceptible to norfloxacin, even when the creatinine clearance is less than 10 mL/min/1.73m².

When only the serum creatinine level is available, the following formula (based on sex, weight, and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

$$\text{Males: } \frac{(\text{weight in kg}) \times (140 - \text{age})}{(72) \times \text{serum creatinine (mg/100 mL)}}$$

Females: (0.85) x (above value)

Elderly

Elderly patients being treated for urinary tract infections who have a creatinine clearance of greater than 30 mL/min/1.73m² should receive the dosages recommended under *Normal Renal Function.*

Elderly patients being treated for urinary tract infections who have a creatinine clearance of 30 mL/min/1.73m² or less should receive 400 mg once daily as recommended under *Renal Impairment.*

HOW SUPPLIED

No. 3522 — Tablets NOROXIN 400 mg are dark pink, oval shaped, film-coated tablets, coded MSD 705 on one side and NOROXIN on the other. They are supplied as follows:

NDC 0006-0705-68 bottles of 100
(6505-01-258-9542 100's)
NDC 0006-0705-20 unit of use bottles of 20
NDC 0006-0705-28 unit dose packages of 100.

Storage

Tablets NOROXIN should be stored in a tightly-closed container. Avoid storage at temperatures above 40°C (104°F).

ANIMAL PHARMACOLOGY

Norfloxacin and related drugs have been shown to cause arthropathy in immature animals of most species tested (see WARNINGS).

Crystalluria has occurred in laboratory animals tested with norfloxacin. In dogs, needle-shaped drug crystals were seen in the urine at doses of 50 mg/kg/day. In rats, crystals were reported following doses of 200 mg/kg/day.

Embryo lethality and slight maternotoxicity (vomiting and anorexia) were observed in cynomolgus monkeys at doses of 150 mg/kg/day or higher.

Ocular toxicity, seen with some related drugs, was not observed in any norfloxacin-treated animals.

Dist. by:
MERCK & CO., INC., West Point, PA 19486, USA

Issued February 1993

Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-384 / S-024

MEDICAL REVIEW(S)

MAY 9 1994

Clinical Review of Supplement

NDA 19-384/S-024

Date of Supplement: May 21, 1993

Date of Review: May 3, 1994

Applicant: Merck & Co., Inc.

Drug - Generic: Norfloxacin
Trade: Noroxin

Route of Administration: Oral

Purpose of Submission

The applicant has filed this submission in response to a request from the Division of Anti-Infective Drug Products to include tendinitis/tendon rupture as adverse experiences to the labeling. The supplement is submitted in accordance with provisions found under 21 CFR 314.70 (c)(2)(i),i.e., changes to add or strengthen a contraindication, warning, precaution, or adverse reaction. These changes can be made before FDA approval with the submission marked: "Special Supplement - Changes Being Effected."

The following changes to the labeling have been made:

Title

The American Hospital Formulary Society (AHFS) category designation has been deleted to avoid confusion between an FDA approval and any unlabeled uses listed by the AHFS.

Comment

The deletion is acceptable.

ADVERSE REACTIONS

Post Marketing

Addition: *Musculoskeletal*
Tendinitis

In support of this addition, the applicant has included copies of adverse drug experience reports (1639's) concerning six patients who developed tendinitis while receiving norfloxacin therapy. A synopsis of each case report follows.

1. The first report concerns a 69-year-old physician with cholangitis and a previous Whipple procedure who developed muscle strain during exercise while on therapy with

norfloxacin (400 mg q12 hours). After six days of therapy, the dosing interval was changed to q18 hours. There was no concomitant medication. The patient experienced a sudden "pull" of his right gastrocnemius muscle and hamstring. Subsequently, he noted ecchymosis on his posterior calf and swelling of his right thigh. The dosage of norfloxacin was reduced to 200 mg q12 hours and two days later he experienced pain diagnosed as tendinitis of the right hip. Therapy was discontinued and the patient was treated with unspecified prescription drug therapy. At the time of the report, the patient was recovering slowly, but still reporting hamstring pain and tendinitis of the hip.

2. The second report describes an 84-year-old female on therapy with norfloxacin for an acute severe bladder infection who developed severe pain in both lower extremities. She was taking norfloxacin (400 mg bid), along with verapamil HCl (Calan). She was diagnosed as possibly having tendinitis and treated with cyclobenzaprine HCl. The norfloxacin was discontinued. Six days later she was seen with edema and pain of the lower extremities. She was treated with furosemide (Lasix) and subsequently recovered at the time of this report.

3. In the third report, a 72-year-old male with acute tubular necrosis, COPD, gastroenteritis, hypercalcemia, asthma and allergy to nifedipine (Procardia) was placed on therapy with norfloxacin (400 mg bid) for a persistent salmonella infection. Concomitant medications included theophylline (Theo-Dur), albuterol sulfate (Proventil), triamcinolone acetonide (Azmacort) and prednisone. The patient developed pain in his Achilles tendon, as well as across the shoulders and lower back, after the seventh day of therapy. The norfloxacin was discontinued and the patient subsequently recovered.

4. A 40-year-old female on therapy for approximately one week with norfloxacin (400 mg bid) and ampicillin (dosage not specified) for the treatment of a urinary tract infection developed tenderness and pain in the right thumb and fifth digit several weeks later. This condition progressed to an arthritis involving the wrist and hand. The patient's condition was worsening at the time of the report. No further details were provided.

5. The fifth report (foreign) concerns a 52-year-old female who was placed on norfloxacin therapy (400 mg bid) for five days for the treatment of a UTI. One week after therapy was discontinued, she developed pain in the ankles, hands, shoulders and knees. A rheumatologic examination revealed hand flexor tendinitis and bilateral edema of the heels. The patient recovered slowly within a period of six months.

6. The last report (foreign) describes a 78-year-old male who was placed on therapy with norfloxacin 400 mg three times a week for more than one year for a recurrent UTI. The patient experienced pain and difficulty in walking. A physical exam revealed edema of the left heel and tendinitis. Norfloxacin therapy was discontinued. The edema was resolved; however, the patient had not fully recovered at the time of this report.

Comments

The six adverse drug experience reports provided by the applicant support the addition of tendinitis as an adverse event that may be associated with norfloxacin therapy.

Review of tendon rupture cases.

At the Agency's request, the applicant reviewed its worldwide database and identified four case reports of tendon rupture in connection with norfloxacin therapy. All four cases involved French males who were between 60 and 78 years of age. In three cases, the Achilles tendon was affected and in the fourth case the thumb tendon was affected. All of the patients received 800 mg/day for a duration of 1 to 11 days until the onset of the tendon rupture.

In the three cases of Achilles rupture, the patients had received long term therapy with glucocorticoids, which have been associated with tendon rupture. In the fourth case, the tendon rupture occurred only one day after starting norfloxacin therapy.

Based on the above information, the applicant did not consider a causal relationship to exist between therapy with norfloxacin and tendon rupture. Therefore, tendon rupture was not added to the labeling as a possible adverse event.

Case reports from the Division of Epidemiology & Surveillance (HFD-730).

Since the submission of this supplement, two additional cases of tendon rupture associated with norfloxacin therapy have been submitted to the agency. Copies of the 1639's were sent to the medical officer in DAIDP for review and a summary of each report follows.

1. The first report was from ___, and submitted on August 18, 1993. A patient experienced a tendon rupture while on therapy with norfloxacin. The event was thought to be drug related; no other details were provided.

2. In the second report, a 51 year-old female from was taking norfloxacin (400 mg bid) for a 9-day course for the

treatment of a urinary tract infection. The woman was otherwise healthy with no underlying conditions; she was taking no concomitant medications. On the 16th day after completing the norfloxacin therapy, she was hospitalized for surgery to repair a ruptured Achilles tendon, which was thought to be drug related.

Comments

The second case report submitted to the agency provides strong evidence of a possible link between norfloxacin therapy and subsequent development of a tendon rupture. In this case, a healthy, middle-aged woman, taking no other medication, developed an Achilles tendon rupture 16 days after completing a course of norfloxacin therapy. This report, along with the four cases described by the applicant, provide sufficient information for the inclusion of tendon rupture as a possible adverse event associated with norfloxacin therapy. Thus, tendon rupture should be added to the labeling as originally proposed by the Agency.

Recommendation

It is recommended that supplement S-024 be approved after the addition of "tendon rupture" has been made to the Musculoskeletal subsection of the ADVERSE REACTIONS section. The subsection should read as follows:

Post Marketing

Musculoskeletal
Tendinitis, tendon rupture.

James Blank
James Blank, Ph.D.

Michael Blum
Michael Blum, M.D.

cc: Orig. NDA
HFD-638
HFD-520
HFD-520/MO/MBlum
SRT/JBlank
CSO/PFogarty
Pharm/ROsterberg
Chem/TDecamp
Micro/ASheldon
WP51; 19-384.024,5-5-94;5-9-94

Concurrence Only:
HFD-520/DivDir/LGavrilovich
HFD-520/SMO/MAlbuerne
MSA for LG 5/9/94

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-384 / S-024

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 19-384/S-024

JUN 19 1995

Henrietta H. Ukwu, M.D.
Director
Regulatory Liaison
Merck & Co., Inc.
P.O. Box 4, BLA-30A
West Point, PA 19486-0004

Dear Dr. Ukwu:

We acknowledge the receipt of your April 17, 1995, submission containing final printed labeling in response to our July 1, 1994, letter approving your supplemental new drug application for Tablets NOROXIN® (norfloxacin).

We have reviewed the labeling that you have submitted in accordance with our July 1, 1994, approval letter, and we find it acceptable.

Sincerely yours,

Mtk for L G 6/16/95

Lillian Gavrilovich, M.D.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:Orig NDA 19-384
HFD-500
HFD-520
HFD-520/ActDivDir/LGavrilovich
HFD-520/MO/Blum
HFD-521/PMS/Fogarty 6/16/95
fogarty10/11/94
ACKNOWLEDGE & RETAIN

Concurrences:
HFD-520/SMO/Albuerne
HFD-521/SPMS/JBona

ORF

JUN 15 1995

NDA 19-384/S-024

Review of Final Printed Labeling (FPL)

DATE OF SUBMISSION: April 17, 1995
DATE REVIEW STARTED: June 15, 1995
DATE REVIEW COMPLETED: June 15, 1995

APPLICANT: Merck Sharp & Dohme Research Laboratories
West Point, Pennsylvania 19486

DRUG: Generic - norfloxacin
Trade - Noroxin®

Description of Submission: Final printed labeling (FPL) submitted in responses to "Approval" letter dated July 1, 1994, to add the pseudomembranous colitis information to the **"WARNINGS"** section, and adverse reactions to the **ADVERSE REACTION**, Post-marketing subsection of the labeling.

Comments: I have reviewed the FPL and find that it is consistent with the approval letter dated July 1, 1994.

Recommendation: An "Acknowledge and Retain" letter should be issued.

6/15/95
Pauline Fogarty
Project Manager

cc:Orig NDA 19-384
HFD-520
HFD-520/Act.Div.Dir/LGavrilovich
HFD-520/MO/MBlum
HFD-520/PDionne
HFD-520/VShetty
HFD-520/LBuko
HFD-521/PMS/PFogarty
fogary6/15/94
FPL Review

Concurrence Only:

HFD-520/SMO/MAlbuerne MDA for LG 6/15/95

HFD-521/CPMS/JBona 6/15/95