CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-384 / S-031

Trade Name: **Noroxin**

Generic Name: **Norfloxacin**

Sponsor: **Merck Research larboratories**

Approval Date: **January 15, 1997**

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APPLICATION NUMBER:

19-384 / S-031

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

DIV FILE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-384/S-031

JAN 15 1997

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

Dear Dr. Ukwu:

Please refer to your February 1, 1996 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Noroxin® (norfloxacin) Tablets.

The supplemental application provides for revisions to the **CLINICAL PHARMACOLOGY**, **PRECAUTIONS**, and **DOSAGE AND ADMINISTRATION** sections of the package insert.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the November 1995, " 7898525", final printed labeling submitted February 1, 1996. Accordingly, the supplemental application is approved effective on the date of this letter.

However, at the next printing, revise the following sections of the final printed labeling to read as follows:

CLINICAL PHARMACOLOGY

Revise the sentence that now reads "

PRECAUTIONS - Information for Patients subsection

Revise the proposed statement to read:

"that norfloxacin should be taken at least one hour before or at least two hours after a meal or ingestion of milk and/or other dairy products."

DOSAGE AND ADMINISTRATION

Revise the first sentence to read:

"NOROXIN tablets should be taken at least one hour before or at least two hours after a meal or ingestion of milk and/or other dairy products."

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

If you have any questions, please contact Ms. Frances V. LeSane, Project Manager, at (301) 827-2125.

Sincerely yours,

David W. Feigal, Jr., M.D., M.P.H.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc: Orig NDA 19-384/S-031
HFD-520/Div.File
HFD-104/TNearing
HFD-735 (with labeling)
HFD-40/DDMAC (with labeling)
HF-2/Medwatch (with labeling)
HFD-92 (with labeling)
DISTRICT OFFICE
HFD-613 (with labeling)
HFD-520/MO/NMoledina
HFD-520/CHEM/BShetty
HFD-520/PHARM/AEllis
HFD-520/MICRO/PDionne
HFD-520/BIOPHARM/FAjayi
HFD-520/PMS/FVLeSane/12-9-96/**revised 12-12-96**

Concurrence Only:
HFD-520/TLMO/MAlbuerne
HFD-520/CPMS/JBona

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-384 / S-031

LABELING

19-384/S-031

APPROVED

JAN 15 1997

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

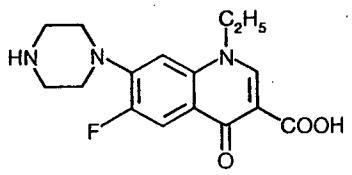
TABLETS

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 µg/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 µg 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 µg/mL or more are attained in the urine. In healthy volunteers, mean urinary concentrations of norfloxacin remain above 30 µg/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

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.)

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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-µg 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-µg norfloxacin disk should be interpreted according to the following criteria **(these criteria apply to isolates from urinary tract or prostatic 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/prostatic tissue 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-µg 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-µg 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 apply to isolates from urinary tract or prostatic infections):**

MIC (µg/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 (µg/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.*

Prostatitis:

Prostatitis due to *Escherichia coli.*

(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

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

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therapeutic effect of the antimicrobial agents but also on the possible emergence of bacterial resistance.

CONTRAINDICATIONS

NOROXIN (norfloxacin) is contraindicated in persons with a history of hypersensitivity, tendinitis, or tendon rupture associated with the use of norfloxacin or any member of the quinolone group of antimicrobial 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.)

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.)

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

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

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

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Ruptures of the shoulder, hand, and Achilles tendons that required surgical repair or resulted in prolonged disability have been reported with norfloxacin. Norfloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded. Tendon rupture can occur at any time during or after therapy with norfloxacin.

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.

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.

Rarely, hemolytic reactions have been reported in patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity who take quinolone antibacterial agents, including norfloxacin. (See ADVERSE REACTIONS.)

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 or milk ingestion.

— 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.

— 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 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*.)

Laboratory Tests

As with any potent antibacterial agent, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy.

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.

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** 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** 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** 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** 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** 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.

**Based on a patient weight of 50 kg.

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

Single-Dose Studies

In clinical trials involving 82 healthy subjects and 228 patients with gonorrhea, treated with a single dose of norfloxacin, 6.5% reported drug-related adverse experiences. However, the following incidence figures were calculated without reference to drug relationship.

The most common adverse experiences (>1.0%) were: dizziness (2.6%), nausea (2.6%), headache (2.0%), and abdominal cramping (1.6%).

Additional reactions (0.3%-1.0%) were: anorexia, diarrhea, hyperhidrosis, asthenia, anal/rectal pain, constipation, dyspepsia, flatulence, tingling of the fingers, and vomiting.

Laboratory adverse changes considered drug-related were reported in 4.5% of patients/subjects. These laboratory changes were: increased AST (SGOT) (1.6%), decreased WBC (1.3%), decreased platelet count (1.0%), increased urine protein (1.0%), decreased hematocrit and hemoglobin (0.6%), and increased eosinophils (0.6%).

Multiple-Dose Studies

In clinical trials involving 52 healthy subjects and 1980 patients with urinary tract infections or prostatitis, treated with multiple doses of norfloxacin, 3.6% reported drug-related adverse experiences. However, the incidence figures below were calculated without reference to drug relationship.

The most common adverse experiences (>1.0%) were: nausea (4.2%), headache (2.8%), dizziness (1.7%), and asthenia (1.3%).

Additional reactions (0.3%-1.0%) were: abdominal pain, back pain, constipation, diarrhea, dry mouth, dyspepsia/heartburn, fever, flatulence, hyperhidrosis, loose stools, pruritus, rash, somnolence, and vomiting.

Less frequent reactions (0.1%-0.2%) included: abdominal swelling, allergies, anorexia, anxiety, bitter taste, blurred vision, bursitis, chest pain, chills, depression, dysmenorrhea, edema, erythema, foot or hand swelling, insomnia, mouth ulcer, myocardial infarction, palpitation, pruritus ani, renal colic, sleep disturbances, and urticaria.

Abnormal laboratory values observed in these patients/subjects were: eosinophilia (1.5%), elevation of ALT (SGPT) (1.4%), decreased WBC and/or neutrophil count (1.4%), elevation of AST (SGOT) (1.4%), and increased alkaline phosphatase (1.1%). Those occurring less frequently included increased BUN, increased LDH, increased serum creatinine, decreased hematocrit, and glycosuria.

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, photosensitivity

Gastrointestinal

Pseudomembranous colitis, hepatitis, jaundice including cholestatic jaundice, pancreatitis (rare), stomatitis. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. (See WARNINGS.)

Renal

Interstitial nephritis, renal failure

Nervous System/Psychiatric

Peripheral neuropathy, Guillain-Barré syndrome, ataxia, paresthesia; psychic disturbances including psychotic reactions and confusion

Musculoskeletal

Tendinitis, tendon rupture, possible exacerbation of myasthenia gravis

Hematologic

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

Special Senses

Transient hearing loss (rare), tinnitus, diplopia

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

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 or milk ingestion. Tablets NOROXIN should be taken 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
Prostatitis	Acute or Chronic	400 mg	q12h	28 days	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/1.73m^2 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/1.73m^2.

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.

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

$$\text{Females: } (0.85) \times (\text{above value})$$

Elderly

Elderly patients being treated for urinary tract infections who have a creatinine clearance of greater than 30 mL/min/1.73m^2 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/1.73m^2 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 November 1995
Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-384 / S-031

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DIV

JAN 26 1998

Division of Special Pathogens and Immunologic Drug Products

PROJECT MANAGEMENT OFFICER REVIEW
OF
FINAL PRINTED LABELING (FPL)

Application Number: 19-384/SLR-026, SLR-031, SLR-036

Name of Drug: NOROXIN™ (norfloxacin) Tablets

Sponsor: Merck & Co., Inc.

Material Reviewed

Submission Date(s): November 3, 1997 and December 9, 1997

Receipt Date(s): November 6, 1997 and December 10, 1997

Background and Summary Description:

These supplemental new drug applications (SLR) S-026, S-031, and S-036 for NOROXIN™ were dated April 27, 1994, February 1, 1996, and June 6, 1997, respectively. The following FDA letters were issued in response to the SLRs identified above: an approvable letter for S-026 dated September 12, 1996, an approval letter for S-031 dated January 15, 1997, and an approval letter for S-036 dated June 20, 1997. S-031 and S-036 contained identical revisions. These supplements account for the two identical FPLs contained in the November 3, 1997, submission (for distribution (Roberts Pharmaceutical, Puerto Rico)), and (for manufacturing (Merck & Co.)).

Review

The FDA requested changes are incorporated in the FPLs dated May 1997. The changes to the applicable sections of the labeling are listed as stated in the FDA approvable and approval letters:

The [redacted] The Microbiology subsection should be revised in accordance with the enclosed copy." The following wording was provided to the sponsor.

CLINICAL PHARMACOLOGY
Microbiology

Susceptibility Tests
Dilution Techniques:

Organism	MIC range(μg/mL)
E. coli ATCC 25922	
E. faecalis ATCC 29212	
P. aeruginosa ATCC 27853	
S. aureus ATCC 29213	

Diffusion Techniques:

REFERENCES

1. National Committee for Clinical Laboratory Standards, Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically - 3rd ed., Approved Standard NCCLS Document M7-A3, Vol 13, No 25, NCCLS, Villanova, PA, 1993.

2. National Committee for Clinical Laboratory Standards, Performance standards for antimicrobial disk susceptibility tests - 5th ed., Approved Standard NCCLS Document M2-A5, Vol 13, No 24, NCCLS, Villanova, PA, 1993.

FDA approval letters dated **January 15, 1997**, (S-031) and **June 20, 1997**, (S-036)

stated that the following revisions should be made to the CLINICAL PHARMACOLOGY, PRECAUTIONS, AND DOSAGE AND ADMINISTRATION sections of the package insert at the next printing. The following wording was provided to the sponsor.

CLINICAL PHARMACOLOGY

[ ]

PRECAUTIONS - Information for Patients subsection

Revise the proposed statement to read:
"that norfloxacin should be taken at least one hour before or a least two hours after a meal or ingestion of milk and/or other dairy products."

DOSAGE AND ADMINISTRATION

Revise the first sentence to read:
"NOROXIN tablets should be taken at least one hour before or at least two hours after a meal or ingestion of milk and/or other dairy products."

The June 20, 1997, FDA approval letter stated that the following revisions should be made to the CLINICAL PHARMACOLOGY, PRECAUTIONS, AND DOSAGE AND ADMINISTRATION sections of the package insert at the next printing. The following wording was provided to the sponsor.

Conclusions

An acknowledge and retain letter will be issued accepting the FPLs enclosed in the submission dated November 3, 1997.

Brenda J. Althaus 1/23/98
Project Manager

Rigoberto A. Roca 1/26/98
Rigoberto Roca, Medical Officer

concurrence:
HFD-590/ActingTL/MMann/ MMann 2-2-98
HFD-590/MO/RRoca/

HFD-590/ActingSCSO/LHubbard/ 1/24/98
HFD-590/CSO/BAtkins/drafted012398

cc:
Original NDA
HFD-590/Div. Files
HFD-590/ActingTL/MMann
HFD-590/MO/RRoca
HFD-590/ActingSCSO/LHubbard
HFD-590/CSO/BAtkins

address: o:\atkins\n19264\971022.rev

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date FEB 2 1 1996

NDA No. 19-384

Henrietta N. Ukwu, M.D.
Merck Research Laboratories
Sumneytown Pike
West Point, PA 19486

Attention: Henrietta N. Ukwu, M.D.

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Noroxin Tablets

NDA Number: 19-384

Supplement Number: S-031

Date of Supplement: February 1, 1996

Date of Receipt: February 7, 1996

Unless we find the application not acceptable for filing, the filing date will be 60 days from the receipt date above.

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Attention: Document Control, Room 12B-30
5600 Fishers Lane
Rockville, MD 20857

Sincerely yours,

FOR Supervisory Consumer Safety Officer
Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research