

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-384 / S-027

Trade Name: **Noroxin**

Generic Name: **norfloxacin**

Sponsor: **Merck**

Approval Date: **November 29, 1995**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-384 / S-027

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APPLICATION NUMBER:

19-384 / S-027

APPROVAL LETTER

NDA 19-384/S-027

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

NOV 29 1995

Dear Dr. Ukwu:

Please refer to your September 29, 1995, supplemental new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tablets NOROXIN® (norfloxacin).

The supplemental application provides for revisions to the **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS** sections of the package insert in accordance with the Divisional letter dated June 2, 1995, to all quinolone NDA holders.

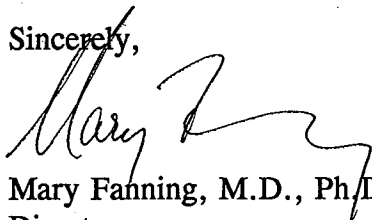
We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the August 1995, "097 017 002" final printed labeling submitted September 29, 1995. Accordingly, the supplemental application is approved effective on the date of this letter.

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. Pauline Fogarty
Regulatory Health Project Manager
(301) 443-6797

Sincerely,



Mary Fanning, M.D., Ph.D., FACP
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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cc:orig NDA 19-384

HF-2/MedWatch(lab)

District Office

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HFD-730(lab)

HFD-240(lab)

HFD-613(lab)

HFD-735/DBarash(lab)

HFD-520

HFD-520/Div.Dir/MFanning *MF 11/22/95*

HFD-520/MO/NMoledina

HFD-521/PM/PFogarty *PF 11/13/95*

fogarty10/26/95

PF11/13/95

APPROVAL

Concurrence only:

HFD-520/SMO/MAlbuerne *msb 11/14/95*

HFD-521/CPM/JBona *JB 11/14/95*

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APPLICATION NUMBER:

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LABELING



097 017 002
7945301

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NOROXIN

NOROXIN® (Norfloxacin)

(norfloxacin)

Distributed by:

ROBERTS®
PHARMACEUTICALS

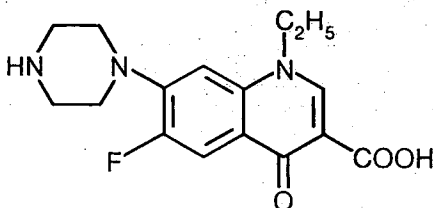
Roberts Laboratories Inc., a subsidiary of
ROBERTS PHARMACEUTICAL CORPORATION
Eatontown, NJ 07724, USA

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.

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

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 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 norfloxacin 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.

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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

Haemophilus

Klebsiella oxytoca

Klebsiella rhinoscleromatis

Morganella morganii

Providencia alcalifaciens

Providencia rettgeri

Providencia stuartii

Salmonella species

Shigella species

Vibrio cholerae

Vibrio parahaemolyticus

Yersinia enterocolitica

Other:

Ureaplasma urealyticum

Normal renal function		
Ingestion	Destruction	Number of Doses Frequency Duration
The recommended daily dose of NITROXIN is as described in the following chart. The dose can be brought to a level that the patient can tolerate if needed. The following chart is for patients with normal renal function.		
100 mg	100 mg	100 mg
200 mg	200 mg	200 mg
300 mg	300 mg	300 mg
400 mg	400 mg	400 mg
500 mg	500 mg	500 mg
600 mg	600 mg	600 mg
700 mg	700 mg	700 mg
800 mg	800 mg	800 mg
900 mg	900 mg	900 mg
1000 mg	1000 mg	1000 mg
1100 mg	1100 mg	1100 mg
1200 mg	1200 mg	1200 mg
1300 mg	1300 mg	1300 mg
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2600 mg	2600 mg	2600 mg
2700 mg	2700 mg	2700 mg
2800 mg	2800 mg	2800 mg
2900 mg	2900 mg	2900 mg
3000 mg	3000 mg	3000 mg
3100 mg	3100 mg	3100 mg
3200 mg	3200 mg	3200 mg
3300 mg	3300 mg	3300 mg
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3600 mg	3600 mg	3600 mg
3700 mg	3700 mg	3700 mg
3800 mg	3800 mg	3800 mg
3900 mg	3900 mg	3900 mg
4000 mg	4000 mg	4000 mg
4100 mg	4100 mg	4100 mg
4200 mg	4200 mg	4200 mg
4300 mg	4300 mg	4300 mg
4400 mg	4400 mg	4400 mg
4500 mg	4500 mg	4500 mg
4600 mg	4600 mg	4600 mg
4700 mg	4700 mg	4700 mg
4800 mg	4800 mg	4800 mg
4900 mg	4900 mg	4900 mg
5000 mg	5000 mg	5000 mg
5100 mg	5100 mg	5100 mg
5200 mg	5200 mg	5200 mg
5300 mg	5300 mg	5300 mg
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5500 mg	5500 mg	5500 mg
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6900 mg	6900 mg	6900 mg
7000 mg	7000 mg	7000 mg
7100 mg	7100 mg	7100 mg
7200 mg	7200 mg	7200 mg
7300 mg	7300 mg	7300 mg
7400 mg	7400 mg	7400 mg
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7600 mg	7600 mg	7600 mg
7700 mg	7700 mg	7700 mg
7800 mg	7800 mg	7800 mg
7900 mg	7900 mg	7900 mg
8000 mg	8000 mg	8000 mg
8100 mg	8100 mg	8100 mg
8200 mg	8200 mg	8200 mg
8300 mg	8300 mg	8300 mg
8400 mg	8400 mg	8400 mg
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9100 mg	9100 mg	9100 mg
9200 mg	9200 mg	9200 mg
9300 mg	9300 mg	9300 mg
9400 mg	9400 mg	9400 mg
9500 mg	9500 mg	9500 mg
9600 mg	9600 mg	9600 mg
9700 mg	9700 mg	9700 mg
9800 mg	9800 mg	9800 mg
9900 mg	9900 mg	9900 mg
10000 mg	10000 mg	10000 mg

NOROXIN® (Norfloxacin)

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-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)
<i>E. coli</i> ATCC 25922	28 - 35
<i>P. aeruginosa</i> ATCC 27853	22 - 29
<i>S. aureus</i> 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)
<i>E. coli</i> ATCC 25922	0.03-0.12
<i>E. faecalis</i> ATCC 29212	2.0-8.0
<i>P. aeruginosa</i> ATCC 27853	1.0-4.0
<i>S. aureus</i> ATCC 29213	0.05-2.0

INDICATIONS AND USAGE

TABLETS NOROXIN® (NORFLOXACIN)

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NOROXIN®
TABLETS
(NORFLOXACIN)

(See DOSAGE AND ADMINISTRATION for appropriate dosing instructions.)

Penicillinase production should have no effect on norfloxacin activity.

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

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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 (norfloxacin) is contraindicated in persons with a history of hypersensitivity, tendonitis, tendon rupture, associated with the use of norfloxacin or any member of the quinolone group of antimicrobial agents. **WARNINGS**
NOROXIN (norfloxacin) should be used with caution in patients with a history of tendonitis, tendon rupture, associated with the use of norfloxacin or any member of the quinolone group of antimicrobial agents.

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 400 mg to 800 mg in patients with a history of tendonitis, tendon rupture, associated with the use of norfloxacin or any member of the quinolone group of antimicrobial agents, has caused tendonitis, tendon rupture, associated with the use of norfloxacin or any member of the quinolone group of antimicrobial agents.

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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.

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established, therapeutic measures should be initiated when 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. Evidence of tendon rupture 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 proper state of hydration and adequate urinary output. A few cases of both tendon rupture and tendonitis have been reported in patients receiving 400 mg b.i.d. to 800 mg b.i.d. to 1600 mg b.i.d. to 3200 mg b.i.d. to 6400 mg b.i.d. to 12800 mg b.i.d. to 25600 mg b.i.d. to 51200 mg b.i.d. to 102400 mg b.i.d. to 204800 mg b.i.d. to 409600 mg b.i.d. to 819200 mg b.i.d. to 1638400 mg b.i.d. to 3276800 mg b.i.d. to 6553600 mg b.i.d. to 13107200 mg b.i.d. to 26214400 mg b.i.d. to 52428800 mg b.i.d. to 104857600 mg b.i.d. to 209715200 mg b.i.d. to 419430400 mg b.i.d. to 838860800 mg b.i.d. to 1677721600 mg b.i.d. to 3355443200 mg b.i.d. to 6710886400 mg b.i.d. to 13421772800 mg b.i.d. to 26843545600 mg b.i.d. to 53687091200 mg b.i.d. to 107374182400 mg b.i.d. to 214748364800 mg b.i.d. to 429496729600 mg b.i.d. to 858993459200 mg b.i.d. to 1717986918400 mg b.i.d. to 3435973836800 mg b.i.d. to 6871947673600 mg b.i.d. to 13743895347200 mg b.i.d. to 27487790694400 mg b.i.d. to 54975581388800 mg b.i.d. to 109951162777600 mg b.i.d. to 219902325555200 mg b.i.d. to 439804651110400 mg b.i.d. to 879609302220800 mg b.i.d. to 1759218604441600 mg b.i.d. to 3518437208883200 mg b.i.d. to 7036874417766400 mg b.i.d. to 14073748835532800 mg b.i.d. to 28147497671065600 mg b.i.d. to 56294995342131200 mg b.i.d. to 112589990684262400 mg b.i.d. to 225179981368524800 mg b.i.d. to 450359962737049600 mg b.i.d. to 900719925474099200 mg b.i.d. to 1801439850948198400 mg b.i.d. to 3602879701896396800 mg b.i.d. to 7205759403792793600 mg b.i.d. to 14411518807585587200 mg b.i.d. to 28823037615171174400 mg b.i.d. to 57646075230342348800 mg b.i.d. to 115292150460684697600 mg b.i.d. to 230584300921369395200 mg b.i.d. to 461168601842738790400 mg b.i.d. to 922337203685477580800 mg b.i.d. to 1844674407370955161600 mg b.i.d. to 3689348814741910323200 mg b.i.d. to 7378697629483820646400 mg b.i.d. to 14757395258967641292800 mg b.i.d. to 29514790517935282585600 mg b.i.d. to 59029581035870565171200 mg b.i.d. to 118059162071741130342400 mg b.i.d. to 236118324143482260684800 mg b.i.d. to 472236648286964521369600 mg b.i.d. to 944473296573929042739200 mg b.i.d. to 1888946593147858085478400 mg b.i.d. to 3777893186295716170956800 mg b.i.d. to 7555786372591432341913600 mg b.i.d. to 15111572745182864683827200 mg b.i.d. to 30223145490365729367654400 mg b.i.d. to 60446290980731458735308800 mg b.i.d. to 120892581961462917470617600 mg b.i.d. to 241785163922925834941235200 mg b.i.d. to 483570327845851669882470400 mg b.i.d. to 967140655691703339764940800 mg b.i.d. to 1934281311383406679529881600 mg b.i.d. to 3868562622766813359059763200 mg b.i.d. to 7737125245533626718119526400 mg b.i.d. to 15474250491067253436239052800 mg b.i.d. to 30948500982134506872478105600 mg b.i.d. to 61897001964269013744956211200 mg b.i.d. to 123794003928538027489912422400 mg b.i.d. to 247588007857076054979824844800 mg b.i.d. to 495176015714152109959649689600 mg b.i.d. to 990352031428304219919299379200 mg b.i.d. to 1980704062856608439838598758400 mg b.i.d. to 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b.i.d. to 830767497365572420564879412675276800 mg b.i.d. to 1661534994731144841129758825350553600 mg b.i.d. to 3323069989462289682259517650701107200 mg b.i.d. to 6646139978924579364519035301402214400 mg b.i.d. to 13292279957849158729038070602804428800 mg b.i.d. to 26584559915698317458076141205608857600 mg b.i.d. to 53169119831396634916152282411217715200 mg b.i.d. to 106338239662793269832304564822435430400 mg b.i.d. to 212676479325586539664609129644870860800 mg b.i.d. to 425352958651173079329218259289741721600 mg b.i.d. to 850705917302346158658436518579483443200 mg b.i.d. to 1701411834604692317316873037158966886400 mg b.i.d. to 3402823669209384634633746074317933772800 mg b.i.d. to 6805647338418769269267492148635867545600 mg b.i.d. to 13611294676837538538534984297271735091200 mg b.i.d. to 27222589353675077077069968594543470182400 mg b.i.d. to 54445178707350154154139937189086940364800 mg b.i.d. to 108890357414700308308279874378173880729600 mg b.i.d. to 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22615642429163319418666208009511030095352565089289315967295565443891200 mg b.i.d. to 45231284858326638837332416019022060190705130178578631934591130887782400 mg b.i.d. to 90462569716653277674664832038044120381410260357157263869182261775564800 mg b.i.d. to 180925139433306555349329664076088240762820520714314527738364523551129600 mg b.i.d. to 361850278866613110698659328152176481525641041428629055476729047102259200 mg b.i.d. to 723700557733226221397318656304352963051282082857258110953458094204518400 mg b.i.d. to 1447401115466452442794637312608705926102564165714516221906916188409036800 mg b.i.d. to 2894802230932904885589274625217411852205128331429032443813832376818073600 mg b.i.d. to 5789604461865809771178549250434823704410256662858064887627664753636147200 mg b.i.d. to 11579208923731619542357098500869647408820513325716129775255329507272294400 mg b.i.d.

Normal Renal Function: In patients with normal renal function, the elimination half-life of NOROXIN is approximately 11.7 hours. The clearance of NOROXIN is directly proportional to the creatinine clearance. In patients with renal impairment, the elimination half-life of NOROXIN is prolonged. The following table shows the elimination half-life of NOROXIN in patients with various degrees of renal impairment.

Renal Function	Elimination Half-life (hours)
Normal	11.7
Mild impairment (creatinine clearance 30-50 mL/min)	15.0
Moderate impairment (creatinine clearance 10-30 mL/min)	20.0
Severe impairment (creatinine clearance <10 mL/min)	25.0

Elderly: Elderly patients should receive the dosage recommended under "Dosage" with caution. Elderly patients may have a decreased renal function, which may result in a prolonged elimination half-life of NOROXIN. Elderly patients should be monitored for signs of toxicity.

Weight: The elimination half-life of NOROXIN is not significantly affected by body weight. The following table shows the elimination half-life of NOROXIN in patients with various body weights.

Weight (kg)	Elimination Half-life (hours)
50	11.7
75	11.7
100	11.7

Protein	Sex	Age	Weight (kg)	Elimination Half-life (hours)
Protein A	Male	18-24	70	11.7
	Male	25-34	75	11.7
	Male	35-44	80	11.7
	Male	45-54	85	11.7
	Male	55-64	90	11.7
	Male	65-74	95	11.7
	Male	75-84	100	11.7
	Male	85-94	105	11.7
	Male	95-104	110	11.7
	Male	105-114	115	11.7
Protein B	Male	18-24	70	11.7
	Male	25-34	75	11.7
	Male	35-44	80	11.7
	Male	45-54	85	11.7
	Male	55-64	90	11.7
	Male	65-74	95	11.7
	Male	75-84	100	11.7
	Male	85-94	105	11.7
	Male	95-104	110	11.7
	Male	105-114	115	11.7
Protein C	Male	18-24	70	11.7
	Male	25-34	75	11.7
	Male	35-44	80	11.7
	Male	45-54	85	11.7
	Male	55-64	90	11.7
	Male	65-74	95	11.7
	Male	75-84	100	11.7
	Male	85-94	105	11.7
	Male	95-104	110	11.7
	Male	105-114	115	11.7
Protein D	Male	18-24	70	11.7
	Male	25-34	75	11.7
	Male	35-44	80	11.7
	Male	45-54	85	11.7
	Male	55-64	90	11.7
	Male	65-74	95	11.7
	Male	75-84	100	11.7
	Male	85-94	105	11.7
	Male	95-104	110	11.7
	Male	105-114	115	11.7
Protein E	Male	18-24	70	11.7
	Male	25-34	75	11.7
	Male	35-44	80	11.7
	Male	45-54	85	11.7
	Male	55-64	90	11.7
	Male	65-74	95	11.7
	Male	75-84	100	11.7
	Male	85-94	105	11.7
	Male	95-104	110	11.7
	Male	105-114	115	11.7
Protein F	Male	18-24	70	11.7
	Male	25-34	75	11.7
	Male	35-44	80	11.7
	Male	45-54	85	11.7
	Male	55-64	90	11.7
	Male	65-74	95	11.7
	Male	75-84	100	11.7
	Male	85-94	105	11.7
	Male	95-104	110	11.7
	Male	105-114	115	11.7
Protein G	Male	18-24	70	11.7
	Male	25-34	75	11.7
	Male	35-44	80	11.7
	Male	45-54	85	11.7
	Male	55-64	90	11.7
	Male	65-74	95	11.7
	Male	75-84	100	11.7
	Male	85-94	105	11.7
	Male	95-104	110	11.7
	Male	105-114	115	11.7
Protein H	Male	18-24	70	11.7
	Male	25-34	75	11.7
	Male	35-44	80	11.7
	Male	45-54	85	11.7
	Male	55-64	90	11.7
	Male	65-74	95	11.7
	Male	75-84	100	11.7
	Male	85-94	105	11.7
	Male	95-104	110	11.7
	Male	105-114	115	11.7
Protein I	Male	18-24	70	11.7
	Male	25-34	75	11.7
	Male	35-44	80	11.7
	Male	45-54	85	11.7
	Male	55-64	90	11.7
	Male	65-74	95	11.7
	Male	75-84	100	11.7
	Male	85-94	105	11.7
	Male	95-104	110	11.7
	Male	105-114	115	11.7
Protein J	Male	18-24	70	11.7
	Male	25-34	75	11.7
	Male	35-44	80	11.7
	Male	45-54	85	11.7
	Male	55-64	90	11.7
	Male	65-74	95	11.7
	Male	75-84	100	11.7
	Male	85-94	105	11.7
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	Male	105-114	115	11.7
Protein K	Male	18-24	70	11.7
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	Male	105-114	115	11.7
Protein L	Male	18-24	70	11.7
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	Male	85-94	105	11.7
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	Male	35-44	80	11.7
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	Male	75-84	100	11.7
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	Male	95-104	110	11.7
	Male	105-114	115	11.7
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	Male	85-94	105	11.7
	Male	95-104	110	11.7
	Male	105-114	115	11.7
Protein O	Male	18-24	70	11.7
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	Male	35-44	80	11.7
	Male	45-54	85	11.7
	Male	55-64	90	11.7
	Male	65-74	95	11.7
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	Male	85-94	105	11.7
	Male	95-104	110	11.7
	Male	105-114	115	11.7
Protein P	Male	18-24	70	11.7
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	Male	65-74	95	11.7
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	Male	85-94	105	11.7
	Male	95-104	110	11.7
	Male	105-114	115	11.7
Protein Q	Male	18-24	70	11.7
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	Male	85-94	105	11.7
	Male	95-104	110	11.7
	Male	105-114	115	11.7
Protein R	Male	18-24	70	11.7
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	Male	85-94	105	11.7
	Male	95-104	110	11.7
	Male	105-114	115	11.7
Protein S	Male	18-24	70	11.7
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	Male	35-44	80	11.7
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	Male	95-104	110	11.7
	Male	105-114	115	11.7
Protein T	Male	18-24	70	11.7
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	Male	95-104	110	11.7
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Protein U	Male	18-24	70	11.7
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Protein W	Male	18-24	70	11.7
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	Male	105-114	115	11.7
Protein X	Male	18-24	70	11.7
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	Male	85-94	105	11.7
	Male	95-104	110	11.7
	Male	105-114	115	11.7
Protein Y	Male	18-24	70	11.7
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	Male	55-64	90	11.7
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	Male	85-94	105	11.7
	Male	95-104	110	11.7
	Male	105-114	115	11.7
Protein Z	Male	18-24	70	11.7
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	Male	35-44	80	11.7
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	Male	75-84	100	11.7
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	Male	105-114	115	11.7
Protein AA	Male	18-24	70	11.7
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	Male	75-84	100	11.7
	Male	85-94	105	11.7
	Male	95-104	110	11.7
	Male	105-114	115	11.7
Protein AB	Male	18-24	70	11.7
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	Male	35-44	80	11.7
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	Male	75-84	100	11.7
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	Male	105-114	115	11.7
Protein AC	Male	18-24	70	11.7
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	Male	85-94	105	11.7
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	Male	105-114	115	11.7
Protein AD	Male	18-24	70	11.7
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	Male	35-44	80	11.7
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	Male	105-114	115	11.7
Protein AE	Male	18-24	70	11.7
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Protein AF	Male	18-24	70	11.7
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Protein AG	Male	18-24	70	11.7
	Male	25-34	75	11.7
	Male	35-44	80	11.7
	Male	45-54	85	11.7
	Male	55-64	90	11.7
	Male	65-74		

CCN(C)C=CNC1CCNCC1

Resistance to norfloxacin due to spontaneous mutation *in vitro*

Elderly patients being treated for urinary tract infections who have a creatinine clearance of greater than 30 mL/min/1.73m² should receive the dosage recommended under **Major 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**. In the elderly, the drug should be given to those with normal renal function. **HOW SUPPLIED** TABLETS: NONOXIN 400 mg is dark pink, oval shaped, film coated tablets, coded MS-470 on one side and NONOXIN 400 on the other. They are supplied as follows: NDC 54092-097-01 bottles of 100 NDC 54092-097-01 bottles of 100 (6505-01-258-994-2 100's) NDC 54092-097-20 unit dose packages of 20 NDC 54092-097-52 unit dose packages of 100. **Storage** Tablets NONOXIN should be stored in a tightly-closed container. Avoid storage at temperatures above 40°C (104°F).

ANIMAL PHARMACOLOGY Nortloxicin and related drugs have been shown to cause antipathy in immature animals of most species tested (see **Warnings**). A study in young rats has occurred in laboratory animals tested with nortloxicin. In dogs, needle-shaped drug crystals were reported following doses of 200 mg/kg/day. In rats, crystals were reported following doses of 50 mg/kg/day. In mice, crystals were reported following doses of 200 mg/kg/day. **WARNINGS**

[illegible]

MOORE OSTEON
MOBOXING
1977012

CHERRY HILL, N.J. 08034

MOBOXIN®
EYE TABLETS

MOBOXIN®
201045697

MOBOXIMO
VBF12

the 1990s, the number of people in the world who are illiterate has increased from 1.2 billion to 1.5 billion. The number of illiterate people in the world is projected to reach 1.7 billion by the year 2015. The number of illiterate people in the world is projected to reach 1.7 billion by the year 2015. The number of illiterate people in the world is projected to reach 1.7 billion by the year 2015.

[illegible]

NOROXIN® (Norfloxacin)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-384 / S-027

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

NOV 22 1995

Review of Final Printed Labeling

NDA 19-384/S-027

DATE OF SUBMISSION: September 29, 1995
DATE REVIEW OF LABELING BEGUN: October 25, 1995
DATE REVIEW OF LABELING COMPLETED: October 26, 1995

APPLICANT: Merck & Co., Inc.
West Point, PA 19486-0004

DRUG: Generic - norfloxacin
Trade - NOROXIN®

DOSAGE FORM: Tablets

ROUTE OF ADMINISTRATION: Oral

DISCUSSION

On June 2, 1995, the Division issued a letter to all quinolone holders requesting that the **CONTRAINDICATIONS**, **WARNINGS**, and **PRECAUTIONS** sections of their package inserts be revised to include information about the association between tendinitis and/or tendon rupture and fluoroquinolones. This supplemental application with final printed labeling (FPL) provides for those revisions.

CONTRAINDICATIONS

This section has been revised to read: "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."

The revision is acceptable.

WARNINGS

This section has been reorganized, and a new paragraph added as follows:

Paragraph 1: The information on the use of the product in children

Paragraph 2-3: CNS information

Paragraph 4: Anaphylactoid or anaphylactic reaction information

Paragraph 5-7: Pseudomembranous colitis information

Paragraph 8:

[

These revisions are acceptable.

PRECAUTIONS

Information for Patients

The following new phrase has been added under the heading "Patient should be advised:"

- "- 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."

The revision is acceptable.

ADVERSE REACTIONS

Post Marketing

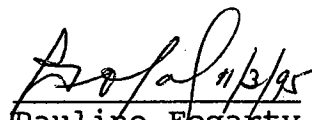
Musculoskeletal

"Tendon rupture" has been added to the list of adverse events under this heading.

The revision is acceptable.

Recommendation:

An approval letter should be issued informing the applicant that the FPL is approved.


Pauline Fogarty
Project Manager

Page 3
NDA 19-384

cc:Orig NDA 19-384

HFD-520

HFD-520/DivDir/MFanning *MF 11/22/95*

HFD-520/MO/NMoledina

HFD-521/PM/PFogarty

fogarty10/25/95

PF11/3/95

Concurrence only:

HFD-520/SMO/MAlbuerne *mda 11/1/95 (draft)*

HFD-521/CPM/JBona *11/8/95 (final)*
B 11/7/95