CENTRAL FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-384 / S-029

Trade Name: Noroxin

Generic Name: norfloxacin

Sponsor: Merck

Approval Date: September 12, 1996
**CONTENTS**

<table>
<thead>
<tr>
<th>Reviews / Information Included in this NDA Review.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Approval Letter</strong></td>
</tr>
<tr>
<td><strong>Approvable Letter</strong></td>
</tr>
<tr>
<td><strong>Labeling</strong></td>
</tr>
<tr>
<td><strong>Summary Review</strong></td>
</tr>
<tr>
<td><strong>Officer/Employee List</strong></td>
</tr>
<tr>
<td><strong>Office Director Memo</strong></td>
</tr>
<tr>
<td><strong>Cross Discipline Team Leader Review</strong></td>
</tr>
<tr>
<td><strong>Medical Review(s)</strong></td>
</tr>
<tr>
<td><strong>Chemistry Review(s)</strong></td>
</tr>
<tr>
<td><strong>Environmental Assessment</strong></td>
</tr>
<tr>
<td><strong>Pharmacology Review(s)</strong></td>
</tr>
<tr>
<td><strong>Statistical Review(s)</strong></td>
</tr>
<tr>
<td><strong>Microbiology Review(s)</strong></td>
</tr>
<tr>
<td><strong>Clinical Pharmacology/Biopharmaceutics Review(s)</strong></td>
</tr>
<tr>
<td><strong>Risk Assessment and Risk Mitigation Review(s)</strong></td>
</tr>
<tr>
<td><strong>Proprietary Name Review(s)</strong></td>
</tr>
<tr>
<td><strong>Administrative/Correspondence Document(s)</strong></td>
</tr>
</tbody>
</table>
APPLICATION NUMBER:

19-384 / S-029

APPROVAL LETTER
NDA 19-384/S-029

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 December 8, 1995 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 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, "7898524", final printed labeling submitted December 8, 1995. Accordingly, the supplemental application is approved effective on the date of this letter.

However, at the next printing, revise the CONTRAINDICATIONS section to read:

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-029
HFD-520/Div.File
HFD-80 (with labeling)
HFD-735 (with labeling)
HFD-40/DDMAC (with labeling)
HF-2/Medwatch (with labeling)
DISTRICT OFFICE
HFD-613 (with labeling)
HFD-520/MO/Moledina
HFD-520/CHEM/Shetty
HFD-520/PHARM/Buko
HFD-520/MICRO/Dionne
HFD-520/PMS/FVLeSane/8-12-96/revised 8-21-96

APPROVAL
NOROXIN® (Norfloxacin)

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:

<table>
<thead>
<tr>
<th>Fluid/Tissue</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resin Parenchyma</td>
<td>7.3 µg/g</td>
</tr>
<tr>
<td>Prostate</td>
<td>2.5 µg/g</td>
</tr>
<tr>
<td>Seminal Fluid</td>
<td>2.7 µg/mL</td>
</tr>
<tr>
<td>Testicle</td>
<td>1.6 µg/g</td>
</tr>
<tr>
<td>Uterus/Cervix</td>
<td>3.0 µg/g</td>
</tr>
<tr>
<td>Vagina</td>
<td>6.3 µg/g</td>
</tr>
<tr>
<td>Fallopian Tube</td>
<td>1.9 µg/g</td>
</tr>
<tr>
<td>Bile</td>
<td>6.9 µg/mL (after two 400-mg doses)</td>
</tr>
</tbody>
</table>

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

- Norfloxacin inhibits bacterial deoxyribonucleic acid synthesis and is bactericidal. At the molecular level, several 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 vivo is rare (occurrence range: 10^{-6} to 10^{-7} 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. Nitrofurantoin-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 amino glycosides, 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
excretion, and renal excretion. After a single 400-mg dose of NOROXIN, mean antimicrobial activity is equivalent to 278, 773, and 82 μg of norfloxacin/mL, 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, 20 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 36% 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%.

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NOROXIN® (Norfloxacin)

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-A8—Performance Standards for Antimicrobial Disk Susceptibility Tests 1980). 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):

<table>
<thead>
<tr>
<th>Zone diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥21</td>
<td>(S) Susceptible</td>
</tr>
<tr>
<td>12-20</td>
<td>(I) Intermediate</td>
</tr>
<tr>
<td>11-11</td>
<td>(R) Resistant</td>
</tr>
</tbody>
</table>

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable urinary/prostatic tissue levels. A report of "Intermediate" indicates that the test results are 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:

<table>
<thead>
<tr>
<th>Organism</th>
<th>Zone diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli ATCC 25922</td>
<td>≥20</td>
</tr>
<tr>
<td>P. aeruginosa ATCC 27853</td>
<td>≥20</td>
</tr>
<tr>
<td>S. aureus ATCC 25923</td>
<td>≥17</td>
</tr>
</tbody>
</table>

Other quinolones 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-A8—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):

<table>
<thead>
<tr>
<th>MIC (μg/ml)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.064</td>
<td>(S) Susceptible</td>
</tr>
<tr>
<td>0.125-3.125</td>
<td>(I) Intermediate</td>
</tr>
<tr>
<td>≥6.25</td>
<td>(R) Resistant</td>
</tr>
</tbody>
</table>

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

Efficacy for this organism in this organ system was studied in fewer than 10 infections. Based on a patient weight of 60 kg.
NOROXIN® (Norfloxacin)

ADVERSE REACTIONS
- Norfloxacin is usually well tolerated. Adverse reactions are similar to those of other quinolone antibacterials. The frequency and severity of adverse reactions have been related to the duration of therapy, and the type and severity of infections treated. In clinical studies, adverse reactions were reported more frequently with multiple daily dosing than with single daily dosing. Adverse reactions include nausea, abdominal pain, diarrhea, headache, dizziness, tinnitus, insomnia, and rash. Serious reactions, such as fever, rash, liver function abnormalities, and eosinophilia, have also occurred. Pseudomembranous colitis has been reported in association with quinolones.

DOSE AND ADMINISTRATION
- The recommended dose of NOROXIN® is 400 mg orally, twice daily, for 7 to 10 days, with meals.

OVERDOSAGE
- There is no specific antidote for norfloxacin. In case of overdose, symptomatic and supportive treatment should be employed. Adequate hydration must be maintained.

WARNING
- Patients with epilepsy or other central nervous system disorders may be more sensitive to norfloxacin. Therefore, patients with central nervous system disorders should be treated with caution.

NURSE’s DRUG GUIDE
- Norfloxacin is a member of the quinolone class of antibiotics. It is effective against a wide range of Gram-negative and Gram-positive bacteria. Norfloxacin is available in two formulations: NOROXIN® and NOROXIN® capsules. NOROXIN® capsules are indicated for the treatment of urinary tract infections, acute pelvic inflammatory disease, and acute uncomplicated cervicitis. NOROXIN® capsules are indicated for the treatment of acute exacerbation of chronic bronchitis. NOROXIN® capsules are also indicated for the treatment of acute otitis media.

NOROXIN® (Norfloxacin)

796854

NOROXIN® (Norfloxacin)

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APPLICATION NUMBER:

19-384 / S-029

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
PROJECT MANAGER'S REVIEW OF LABELING

NDA NUMBERS: NDA 19-384/S-029

DATE OF SUBMISSIONS: December 8, 1995

SPONSOR: Merck & Co., Inc.
West Point, PA  19486-0004
Abbott Park, IL  60060-3500

DRUGS: NOROXIN® (norfloxacin)

DOSAGE FORM: Tablets

Description of Submission: On June 2, 1995, the Division issued a letter to all quinolone holders requesting that the CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of their package insert be revised to include information about the association of tendinitis and/or tendon rupture and fluoroquinolones. The final printed labeling was revised as follows:

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 not acceptable. However, at the next printing, this section should be revised to read:

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
These revisions are acceptable.

PRECAUTIONS
Information for Patients

The following new phrase has been added under the heading "Patients 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 dated August 1995 (7898524) is approved.

However, at the next printing, revisions to the CONTRAINdications section of the package insert should be made.

Frances V. LeSane
Project Manager
cc:Orig NDA 19-384/S-029
HFD-520/Div. Files
HFD-520/MO/Moledina
HFD-520/CHEM/Shetty
HFD-520/MICRO/Dionne
HFD-520/PHARM/Buko
HFD-520/PMS/FVLcSane/8-11-96/revised 8-21-96

Concurrence Only:
HFD-520/Act Dir./DFeigal
HFD-520/TLMO/Albuerne
HFD-520/CPMS/Bona

FINAL PRINTED LABELING REVIEW