

These records are from CDER's historical file of information previously disclosed under the Freedom of Information Act (FOIA) for this drug approval and are being posted as is. They have not been previously posted on Drugs@FDA because of the quality (e.g., readability) of some of the records. The documents were redacted before amendments to FOIA required that the volume of redacted information be identified and/or the FOIA exemption be cited. These are the best available copies.

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APPL #: 019384

FIRM: MSD RES LABS

1 OF 4

TRADE NAME: NOROXIN (NORFLOXACIN) 400MG TABLET

GENERIC NAME: NORFLOXACIN

Summary Basis of Approval
Cover Form

Appl #: 019384

Firm: MS&D RES LASS
Reviewing Div: 520
Trade Name: NOROXIN (NORFLOXACIN) 400MG TABLET
Generic Name:

NORFLOXACIN

Approval Letter: Y	Statistician Review: N
SBA Form: N	Bio/Dissolution Review: Y
Final Printed Labeling: Y	Microbiologist Review: N
Medical Officer Review: Y	NAS/NRC Review: N
Chemist Review: Y	Pharmacologist Review: Y
Federal Register Notice: N	Completion Date: 19-NOV 90

APRVL

LTR



JUL 31 1986

NDA 19-384

David W. Blois, Ph.D.
Merck Sharp & Dohme Laboratories
West Point, PA 19486

Dear Dr. Blois:

Reference is made to your New Drug Application (NDA) dated January 14, 1985 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Noroxin (norfloxacin) Tablets, 400 mg.

We also acknowledge your additional correspondence dated February 7, February 11, March 15, March 21, April 2, April 3, April 23, July 3, July 11, July 23, August 1, September 13, October 3, October 10, October 18, November 4, November 6, December 19, 1985, January 20, February 12, February 14, February 24(3), March 11, March 17, March 18, March 21, March 31, April 4, April 22, May 1, May 8(2), May 15, May 19, July 25, August 26, and September 19, 1986.

We have completed our review of your submission and the application is approved as of the date of this letter.

However, prior to marketing, you must submit final printed labeling identical to draft labeling dated September 19, 1986, except that:

1. The title of the subsection in the DOSAGE AND ADMINISTRATION labeled "Renal Impairment (including the Elderly with Renal Impairment)" should be changed to "Renal Impairment;" the first sentence of this section should also have the parenthetical statement removed;
2. Recommended dosage for elderly patients should be added to a different part of the DOSAGE AND ADMINISTRATION section;
3. The footnote after the asterisk in the INDICATIONS AND USAGE section must read: "Efficacy for this organism in this organ system was studied in fewer than 10 infections."
4. An asterisk must be placed after each of the indole positive Proteus species in the INDICATIONS.

These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as requested, in the product's final printed labeling (FPL) may render the product misbranded and an unapproved new drug.

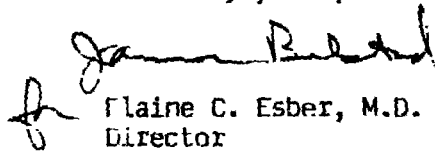
Please submit twelve copies of the revised FPL when it is available. This submission should be designated for administrative purposes as "FPL Supplement" to the approved NDA 12-384. Approval of the supplement by FDA is not required before the labeling is used.

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

Please submit one market package of the drug when it is available.

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

Sincerely yours,



Elaine C. Esber, M.D.
Director
Office of Biologics Research and Review
Center for Drugs and Biologics

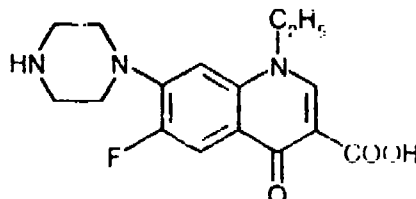
FPL

TABLETS

MSD | **NOROXIN®**
 (NORFLOXACIN, MSD)

NOROXIN®
 (Norfloxacin, MSD)
DESCRIPTION

NOROXIN® (Norfloxacin, MSD) 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-quinolincarboxylic acid. Its empirical formula is $C_{18}H_{18}FN_2O_3$, 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, iron oxide, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, and titanium dioxide.

Norfloxacin, a fluoroquinolone, differs from quinolones by having a fluorine atom at the 6 position and a piperazine moiety at the 7 position. Examples of antibacterial drugs which are quinolones include nalidixic acid and cinoxacin.

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 and 400 mg. At the respective doses, mean peak serum and plasma concentrations of 0.8 and 1.5 mcg/mL are attained approximately one hour after dosing. The presence of food may decrease absorption. The effective half-life of norfloxacin in serum and plasma is 3 - 4 hours. Steady-state concentrations of norfloxacin will be attained within two days of dosing.

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

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

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

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

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

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

Microbiology

Norfloxacin has *in vitro* activity against a broad spectrum 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 NOROXIN 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). Resistance of the organism has developed 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
 Enterococci

For this reason, when there is a lack of satisfactory clinical

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response, 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 demonstrates activity against indicated organisms resistant to the aminoglycosides (including gentamicin), penicillins, cephalosporins, tetracyclines, macrolides, and sulfonamides, including combinations of sulfamethoxazole and trimethoprim. Antagonism has been demonstrated *in vitro* between norfloxacin and nitrofurantoin.

While *in vitro* studies have demonstrated the susceptibility of most strains of the following organisms, clinical efficacy for infections other than those included in the INDICATIONS AND USAGE section has not been documented.

Aerobic Bacteria

Gram-positive bacteria including:
Streptococcus faecalis (enterococci)
Staphylococcus aureus (including both penicillinase-producing and methicillin-resistant strains)
Staphylococcus epidermidis
Staphylococcus saprophyticus
Bacillus cereus

Gram-negative bacteria including:

Acinetobacter calcoaceticus

Aeromonas species

Alcaligenas species

Campylobacter species

Citrobacter diversus

Citrobacter freundii

Edwardsiella tarda

Enterobacter aerogenes

Enterobacter cloacae

Escherichia coli

Flavobacterium species

Haemophilus influenzae

Klebsiella oxytoca

Klebsiella pneumoniae

Klebsiella rhinoscleromatis

Morganella morganii

Neisseria gonorrhoeae

Proteus mirabilis

Proteus vulgaris

Providencia alkalifaciens

Providencia rettgeri

Providencia stuartii

Pseudomonas aeruginosa

Salmonella typhi

Salmonella species

Serratia marcescens

Shigella species

Vibrio cholerae

Vibrio parahaemolyticus

Yersinia enterocolitica

Other

Ureaplasma urealyticum

NOROXIN is not generally active against obligate anaerobes.

Susceptibility Tests

Quantitative methods that require measurement of zone diameters give precise estimates of bacterial susceptibility.

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One such procedure has been recommended for use with discs to test susceptibility to norfloxacin.

Reports from the laboratory giving results of the standard single disc susceptibility test with a 10 mcg norfloxacin disc should be interpreted according to the following criteria.

Susceptible organisms produce zones of 13 mm or greater, indicating that the test organism is likely to respond to therapy.

Resistant organisms produce zones of 12 mm or less, indicating that other therapy should be selected.

A bacterial isolate may be considered susceptible if the MIC value for norfloxacin is equal to or less than 16 mcg/mL. Organisms are considered resistant if the MIC is equal to or greater than 32 mcg/mL.

The standardized quality control procedure requires use of control organisms. The 10 mcg norfloxacin disc should give the zone diameters listed below for the quality control strains.

Organism	ATCC*	Zone Size Range
<i>E. coli</i>	25922	28 - 35 mm
<i>P. aeruginosa</i>	27853	22 - 29 mm
<i>S. aureus</i>	25923	17 - 28 mm

Dilution susceptibility tests should give MICs between the ranges listed below for the quality control strains.

Organism	ATCC*	MIC (mcg/mL)
<i>E. coli</i>	25922	0.03 - 0.125
<i>S. aureus</i>	29213	0.5 - 2.0
<i>S. faecalis</i>	29212	2.0 - 8.0
<i>P. aeruginosa</i>	27853	1.0 - 4.0

Based on urinary concentrations of norfloxacin achieved in men, breakpoint criteria have been established as listed below.

Category	Zone Diameter (mm)	Recommended MIC Breakpoint (mcg/mL)
Susceptible	≥ 13	≤ 16
Resistant	≤ 12	≥ 32

Norfloxacin susceptibility test results should not be used to predict susceptibility to other less potent quinolone antibacterial agents such as nalidixic acid.

INDICATIONS AND USAGE

Treatment

NOROXIN is indicated for the treatment of adults with complicated and uncomplicated urinary tract infections that are caused by susceptible strains of the designated microorganisms listed below:

Escherichia coli, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, indole positive *Proteus* species* (which include the organisms now called *Proteus vulgaris**, *Providencia rettgeri**, and *Morganella morganii*)*, *Pseudomonas aeruginosa*, *Citrobacter freundii**, *Staphylococcus aureus**, *Staphylococcus epidermidis**, and group D streptococci.

NOTE: Specimens for culture and susceptibility testing should be obtained prior to and during treatment if clinical response warrants.

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

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CONTRAINDICATIONS

NOROXIN is contraindicated in patients with a history of hypersensitivity to norfloxacin or the quinolone group of antibacterial agents (e.g., nalidixic acid and cinoxacin).

WARNINGS

Norfloxacin should not be used in children or pregnant women.

The oral administration of single doses of norfloxacin, 6 times the recommended human clinical dose, caused lameness in immature dogs. Histologic examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs (e.g., nalidixic acid and cinoxacin) also produced erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species.

PRECAUTIONS

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 crystaluria 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).

The effects of norfloxacin on brain function or on the electrical activity of the brain have not been tested. Until more information becomes available, quinolones should be used with caution in patients with known factors which predispose to seizures.

Drug Interactions

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.

The concomitant administration of norfloxacin with antacids is not recommended.

Information for Patients

Patients should be advised to take NOROXIN one hour before or two hours after a meal. Patients should also be advised to drink fluids liberally and not to take antacids concomitantly or within 2 hours after dosing.

NOROXIN may cause dizziness or lightheadedness; 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.

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.

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 dose. Norfloxacin had no mutagenic activity *in vitro* in the Ames microbial mutagen test. Chinese hamster

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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 33 times the usual human dose.

Pregnancy

Pregnancy Category C: Norfloxacin has been shown to produce embryonic loss in monkeys when given in doses 10 times the maximum human dose (400 mg 5.i.d.), with peak plasma levels that are 2 to 3 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 human dose. There were no adequate and well controlled studies in pregnant women. Since norfloxacin, like other drugs in this class, causes arthropathy in immature animals, it should not be used in pregnant women (see WARNINGS).

Nursing Mothers

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

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

Pediatric Use

Norfloxacin should not be used in children because it causes arthropathy in juvenile animals (see WARNINGS.)

ADVERSE REACTIONS

In clinical trials, NOROXIN was generally well tolerated.

The incidence of subjects reporting drug related adverse experiences in clinical trials involving 1127 subjects was 3.4%. However, the incidence figures below were calculated without reference to drug relationship.

The most common adverse experiences (1% - 3%) were either gastrointestinal or neurological: nausea 2.8%, headache 2.7%, and dizziness 1.8%.

Additional reactions (0.3% - 1%) were: fatigue, rash, abdominal pain, dyspepsia, somnolence, depression, insomnia, constipation, flatulence, and heartburn.

Less frequent reactions included: dry mouth, diarrhea, fever, vomiting, and erythema.

Visual disturbances have been reported with drugs in this class.

Abnormal laboratory values observed in these 1127 subjects in clinical trials were eosinophilia 1.8%, elevation of ALT (SGPT) and AST (SGOT) 1.8%, increased alkaline phosphatase 1.4%, and decreased WBC or neutrophil count 1.2%. Those occurring less frequently included increased BUN, serum creatinine, and LDH, and decreased hematocrit.

OVERDOSAGE

The acute oral LD₅₀ values in male and female mice and male and female rats were greater than 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.

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DOSAGE AND ADMINISTRATION

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

Normal Renal Function

The recommended dosage of NOROXIN is:
Uncomplicated urinary tract infections: 400 mg twice daily for 7 to 10 days.

Complicated urinary tract infections: 400 mg twice daily for 10 to 21 days.

Maximum total daily dosage should not exceed 800 mg per day.

Renal Impairment

NOROXIN may be used for the treatment of urinary tract infections in patients with renal insufficiency. In patients with a creatinine clearance rate of 30 mL·min⁻¹·73m² or less, the recommended dosage is one 400 mg tablet once daily for the duration given above. At this dosage, the urinary concentration exceeds the MICs for most urinary pathogens susceptible to norfloxacin, even when the creatinine clearance is less than 10 mL·min⁻¹·73m².

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

$$\begin{aligned} \text{Males:} &= \frac{(\text{weight in kg}) \times (140 - \text{age})}{(72) \times \text{serum creatinine (mg/100 mL)}} \\ \text{Females:} &= (0.85) \times (\text{above value}) \end{aligned}$$

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Elderly

Elderly patients with a creatinine clearance of greater than 30 mL·min⁻¹·73m² should receive the dosages recommended under *Normal Renal Function*.

Elderly patients with a creatinine clearance of 30 mL·min⁻¹·73m² or less should receive 400 mg once daily as recommended under *Renal Impairment*.

HOW SUPPLIED

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

- NDC 0006-0705-68 bottles of 100
- 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.

MSD MERCK SHARP & DOHME
DIV. OF MERCK & CO., INC., WEST POINT, PA 19380, USA

MED

REV

NDA - 19384

March 14, 1986

MEDICAL OFFICER'S REVIEW OF LABELING
and

MEMORANDUM OF CONFERENCE TELEPHONE CONVERSATION

Applicant: Merck Sharp & Dohme Research Laboratories
West Point, PA

Name of Drug: Generic: Norfloxacin

Trade: NOROXIN^R

Review of Labeling: Labeling dated December 11, 1984 filed on January 14, 1985 in the original application (page I-09306 ff in Volume 2.25) was reviewed. Comments on the labeling were discussed with David W. Blois, Ph.D., Senior Director of Regulatory Affairs, and his staff (215-834-2304). (Underlining below, means new additions. Editorial changes are not mentioned.)

Description: (Page 1, Line 3) Insert the class name "fluoroquinolone" on the third line.

(Page 2) At the end, add "Examples of other antibacterial drugs that are quinolones are nalidixic acid, cinoxacin, and oxolinic acid."

Clinical Pharmacology:

1. (Page 3, Lines 1-12) Revise the first paragraph to read

"In healthy volunteers, at least 30-40% of an oral dose of NOROXIN is absorbed. Absorption is rapid following single doses of 200 and 400 mg. The presence of food may affect absorption. Mean peak serum and plasma concentrations of 0.8 and 1.5 mcg/mL, respectively, are attained approximately one hour after dosing. Levels in bile exceed serum levels. 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 on either regimen."

2. (Page 4, Line 7) Add "Alteration of dosage is necessary." in regard to patients with impaired renal function.

3. (Page 4, Line 18) "Within 24 hours of drug administration, approximately 28-30%," instead of 30%, "of the dose is recovered in the urine as norfloxacin with an additional 5-8% being recovered as six active metabolites of less-r antimicrobial potency."

4. (Page 5) On the first line, insert "Fecal recovery accounts for another 30% of the dose."

5. (Page 5 Lines 6-8) "The antibacterial efficacy of norfloxacin is not affected by the pH of the urine but its solubility is."

6. The Clinical Pharmacology section should end with a new paragraph to say that following oral administration, norfloxacin has been detected in bile,

prostatic fluid, umbilical cord blood, and amniotic fluid, and to give these concentrations. However, this information should only be added if these concentrations are clinically significant. Dr. Blois will check these concentrations.

Microbiology: The Microbiology section is being prepared by our microbiologist. This section will be discussed with the applicant later.

(Page 6, lines 7-8) The statement that "There is generally no cross-resistance between norfloxacin and other antibacterial agents presently marketed." is not true. Cross resistance with nalidixic acid has been reported. (See page 37 or the paper by Duckworth and Williams in the Jo. of Antimicrob. Chemother. (1984; Volume 13: Suppl. B).)

Indications and Usage:

1. (Page 10) Begin this section with the sentence, "NOROXIN is indicated for the treatment of complicated and uncomplicated urinary tract infections in adults that are caused by susceptible strains of"(give names of micro-organisms). Micro-organisms cannot be named until the summary table in Volume 2.23 (Pages I-08282-08286) has been corrected. The Medical Officer's preliminary review shows that we might have Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Pseudomonas aeruginosa, Citrobacter species, and Staphylococcus species to complete this sentence.

Delete everything else on pages 10 and 11.

Insert, at the end of the Indications section, "Uropathogens should be tested in vitro for their susceptibility to norfloxacin prior to administration of the drug and when clinically indicated." This is a class labeling sentence for the quinolones.

Contraindications: (Page 12) Revise this section to read, "NOROXIN is contraindicated in patients with a history of hypersensitivity to norfloxacin or other members of the quinolone group of antibacterial agents (e.g., nalidixic acid, oxolinic acid, cinoxacin).

Warnings: In keeping with the Anti-Infective Drug Advisory Committee recommendations, a Warnings section should be added. The first sentence should be in heavy print or bold type. The section should read as follows:

WARNINGS: "THE USE OF NORFLOXACIN IN PREPUBERTAL CHILDREN AND DURING PREGNANCY IS NOT RECOMMENDED. The oral administration of single doses of norfloxacin, four times the recommended human dose, caused lameness in immature dogs. Histologic examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs (e.g., nalidixic acid, cinoxacin, and oxolinic acid) also produced erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species.

"Crystalluria has been reported in patients receiving doses that are 1/2 and 2 times the recommended daily dosage. Although crystalluria is not expected to occur under normal conditions with a dosage regimen of 400 mg

b.i.d., as a precaution, preventive measures to be taken include keeping the dose as low as possible, maintaining an adequate rate of urine flow, maintaining a urine pH below 7.0, and keeping the patient well hydrated.

Precautions:

1. (Page 12, line 7) Insert the following new paragraphs at the beginning of the section.

"Alteration in dosage regimens is necessary for patients with impaired renal function (See Dosage and Administration)."

"Norfloxacin should be used with caution in patients with a history of hepatic disease or in patients with impaired hepatic function."

The effects of norfloxacin on brain function or on the electrical activity of the brain have not been tested. Central nervous system-type adverse experiences, such as headache, dizziness, lightheadedness, hyperactivity, visual changes, and insomnia, have been reported with some antibacterial agents in the quinolone drug class. Seizures which were not thought to be drug related occurred in two norfloxacin-treated patients that had existing CNS disorders that predispose to seizures and that fully accounted for the events. Until more information becomes available, quinolones should be used with caution in patients with known factors that predispose to seizures."

2. (Page 12, Lines 7-9) Revise the sentence to read, "Diminished urinary excretion of norfloxacin has been reported following the concomitant administration of probenecid and norfloxacin. Serum concentrations, however, are not affected."
3. (Page 12, Line 10) Revise this sentence to read, "The concomitant use of nitrofurantoin is not recommended since nitrofurantoin may antagonize the antibacterial effect of NOROXIN in the urinary tract."
4. (Page 12, Line 12) Add the following new paragraphs:

"The concomitant administration of norfloxacin with antacids is not recommended."

"Information for the Patient:

"Patients should be advised to drink fluids liberally and that antacids should not be given concomitantly or within two hours after dosing."

"Patients should know how they react to norfloxacin before they operate automobiles and machinery or engage in other tasks requiring mental alertness and coordination."

5. (Page 13, Line 16) The Pregnancy Category letter should be "C" instead of "3".

Dr. Blois agreed with the Category C letter.

We shall postpone further consideration of the pregnancy paragraph temporarily because the review team is waiting for the report of a monkey study. Norfloxacin is an known abortifacient in monkeys.

Dr. Blois will file the report of this monkey study next week.

The Medical Officer added that in keeping with our advisory committee recommendations, class labeling for the quinolones calls for this section to end with the sentence, "Since norfloxacin, like other drugs in this class, causes arthropathy in immature animals, its use during pregnancy is not recommended (See Warnings)."

6. (Page 14, line 11) Revise the Nursing Mothers paragraph to read as follows:

"It is not known whether norfloxacin is excreted in human milk. When a 200 mg dose of NOROXIN was administered to nursing mothers, norfloxacin was not detected in human milk. However, because the dose studied was low, because other drugs in this class are excreted 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."

7. (Page 14, Line 21) Delete the first sentence of the Pediatric Use paragraph. The full section shall read, "NOROXIN is not recommended for use in prepubertal children (See Warnings)."

Adverse Reactions: Recommendations for this section are deferred until the applicant files a revised adverse reaction table with corrected rates and a revised adverse laboratory experiences table.

Dosage and Administration:

1. (Page 17, Line 10) Revise the first section to read, "In patients with normal renal function and in patients with creatinine clearance rates greater than 30 ml/min/1.73 m²." Delete the word "apparently" and the phrase "including elderly patients."

2. (Page 17, Lines 15-17) Revise the recommendation to read, "Uncomplicated urinary tract infections: The recommended dosage is 400 mg with a glass of water twice daily one hour before or two hours after meals for 7 to 10 days."

3. (Page 17, Lines 18-20) Revise the recommendation to read, "Complicated urinary tract infections: The recommended dosage is 400 mg with a glass of water twice daily one hour before or two hours after meals for 10 to 30 days."

We discussed the mealtime relationship that the MO added. This will be adjusted for the appropriate time of the day. We also discussed the

possibility of taking the tablet with fruit juice as an innocuous way of acidifying the urine. The original 60-day maximum treatment period was changed to 30 days. The 60-day period did not appear to be supported by clinical studies.

4. (Page 17, end) Insert the following two paragraphs.

"Patients receiving norfloxacin should be well hydrated to prevent crystallization of norfloxacin in the urinary tract."

"Doses higher than 800 mg/day are not recommended."

The medical officer explained that the Division of Biopharmaceutics recommended a ceiling dose. She arbitrarily selected a 1000 mg/day ceiling because drug crystals have been reported at 1200 mg/day. However, the applicant stated that they are not recommending a dose higher than 800 mg/day.

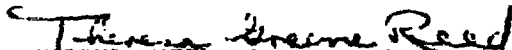
5. (Page 18, Lines 1-9 are deleted.) (Page 18, Line 10) Revise the renal impairment paragraph to read as follows:

"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/1.73 m² or less, the recommended dosage is one 400-mg tablet with a glass of water once daily one hour before or two hours after meals. At this dosage, the urinary concentration exceeds the MICs for most urinary pathogens susceptible to norfloxacin, even when the creatinine clearance rate is less than 10 mL/min/1.73 m². The serum creatinine should represent a steady state of renal function and..."
(Continue on page 19.)

Animal Pharmacology: In keeping with the advisory committee recommendations, there should be an animal pharmacology section after the How Supplied section. The wording of this section is being prepared by our pharmacologist. Examples are the Animal Pharmacology sections in cinoxacin, nalidixic acid, and oxolinic acid package inserts.

Dr. Blois will review these comments and recommendations with his staff and will prepare a revised draft of proposed labeling for additional revision and comment. We have gone as far as we can go without the unfinished sections. He may change the recommended wording in these suggestions to be in keeping with Merck's labeling policy and the firm's views on these subjects.

Conclusion and Recommendation: Labeling is unsatisfactory but labeling discussions with the applicant are progressing very well.


Theresa Greene Reed, M.D., M.P.H.

cc
Orig MDA 19-384 HFN-815/CSO
HFN-815-21 4/1/82 HFN-815/Reed

4717b

DISPATCH

MEDICAL OFFICER'S REVIEW OF NDA 19-384

Safety Update Dated May 19, 1986

Applicant: Merck Sharp and Dohme Research Laboratories
West Point, Pennsylvania 19486

Name of Drug: Trade: NOROXIN
Generic: Norfloxacin

In keeping with our request, the applicant files a safety update report covering the period from the NDA cut-off date, June 26, 1984, through September 30, 1985. This report gives adverse clinical and laboratory events from domestic and international controlled trials and compassionate therapy. Also, serious adverse experiences from the period since September 30, 1985 are presented. Since the NDA was compiled, an additional 1,797 patients have been treated with norfloxacin in controlled clinical trials, and over 17 million patients have been treated in worldwide marketing experience.

The following patients have been treated with norfloxacin since June 27, 1984:

Study	Approximate Number to 3-31-86
MSDRL controlled (domestic)	708
MSDRL controlled (international)	1,089
Japan Marketing Experience	11,900,000
Local Registration Studies	30,000
Clinical Development Study Program (CDSF)	1,945
MSDI Marketing Experience (excluding Japan)	5,600,000

Domestic and Foreign Applicant-Sponsored Studies: Between June 27, 1984 and Sept. 30, 1985, case report forms were received for the following 806 patients and volunteers who received norfloxacin in MSDRL-sponsored clinical trials:

Program	Dosage	No. Pts./Volunteers
Urinary tract infection (UTI)	400 mg bid	327
Travelers diarrhea (prophylaxis)	400 mg qd	60
Gastroenteritis (treatment)	400 mg bid	10
Gastroenteritis (treatment)	400 mg tid	30
Neutropenia (infection prophylaxis)	400 mg bid	27
Neutropenia (infection prophylaxis)	400 mg qid	9
Gonorrhea (treatment)	600 mg x 2 doses	8
Gonorrhea (treatment)	800 mg single dose	222
Compassionate program (U.S.)	400 mg qd, bid, tid	14
Compassionate program (Intern't)	400 mg bid	57
Pharmacology study	400 mg x 2 doses	24
Pharmacology study	400 mg single dose	18
	Total	806

(The number 806 differs from the number 708 because there were different cut off dates.)

Adverse reactions which were not seen in the NDA patients treated for urinary tract infections are listed below:

Adverse Reaction	No. Pts.	No. Drug Related
Malaise	5	0
Jaundice	1	0
Stomatitis	1	1
Muscle cramps	1	0
Hypertonia	1	0
Irritability	1	1
Lung cancer	1	0
Hyperhydrosis	1	1

Among post-NDA urinary tract infection cases, the most frequent adverse reactions were those related to the digestive system. Nausea was the most common complaint. The second most common complaint was neuropsychiatric in nature, namely, headache. Most common complaints are shown below:

System	All NDA	Drug Related NDA	All Post-NDA	Drug Related Post-NDA
Digestive:				
Nausea	2.75%	1.15%	2.45%	0.92%
Dyspepsia	0.44%	0.35%	0.31%	0.31%
Neuropsychiatric:				
Headache	2.66%	0.35%	1.83%	0.61%
Dizziness	1.77%	0.53%	0.61%	0.61%
Skin/Allergic:				
Rash	0.53%	0.27%	0.61%	0
Erythema	0.27%	0.17%	-	-

Adverse reactions with frequencies greater than five in combined data from the NDA and safety update and the total number are shown in the next table.

Adverse Experience	NDA UTI & Volunteer N=1127	Safety Update UTI N=327	Combined NDA & Safety Update N=1454	Combined % of pts. with AEs	Combined % with drug- related AEs
Constipation	4	2	6	.41	0.41
Diarrhea	3 (1)	2 (1)	5 (2)	.34	.14
Dry mouth	3 (2)	2 (1)	5 (3)	.34	.21
Dyspepsia	5 (4)	1 (1)	6 (5)	.41	.34
Nausea	31 (13)	8 (3)	39 (16)	2.68	1.10
Depression	4 (1)	1 (1)	5 (2)	.34	.14
Dizziness	20 (6)	2 (2)	22 (8)	1.51	.55
Headache	30 (4)	6 (2)	36 (6)	2.47	.41
Somnolence	5 (1)	-	5 (1)	.34	.07
Rash	6 (3)	2	8 (3)	.55	.21

(The number that were drug related is shown in parentheses.)

In the NDA, there were 196 adverse reaction reports for 1127 UTI patients and volunteers: 55 were drug related. In the safety update, there are 61 adverse reaction reports for 327 patients: 21 were drug related. Combined, there were 256 reactions of which 76 were drug related.

There were ten deaths. None of the deaths were considered to be drug related. Adverse experiences that were considered to be serious were convulsive disorders in two patients, intracerebral hemorrhage, jaundice, and confusion. One convulsive disorder and the intracerebral hemorrhage were probably not drug related. The other three were definitely not drug related.

Adverse clinical experiences resulted in discontinuation of therapy in 14 of 534 (2.6%) of all safety update report patients (including patients treated for diagnoses other than UTI), excluding the two-dose and single-dose gonorrhea studies. The most common reasons were nausea and rash.

The most common laboratory adverse experiences were elevated AST, ALT, followed by eosinophilia, elevated creatinine, elevated alkaline phosphatase, and leukopenia. None of the leukopenias or elevated creatinines were drug-related while one each of the other aforementioned observations were considered related to norfloxacin. Others were thrombocytosis (2 cases), increased serum GGT (1), increased blood glucose (2), decreased serum sodium (2), and decreased creatinine clearance (1). None of these were considered drug-related.

As with clinical adverse experiences, the types of laboratory adverse experiences from NDA and post-NDA patients are similar.

Adverse laboratory experiences resulted in discontinuation of therapy in 6 of 534 (1.1%) of safety update report patients, excluding the two-dose and single dose gonorrhea and pharmacology studies. The most common reasons for discontinuation were elevated liver function tests. None of the adverse laboratory experiences were considered related to norfloxacin therapy.

The applicant concludes that the safety profile for norfloxacin during the post-NDA period covered by this report is consistent with that seen in NDA data and described in the package circular.

Safety Update Report - Japan: The applicant reports that safety data from Japan have been derived from the post-marketing surveillance study (PMS) and spontaneous reports from prescribing physicians using marketed drug. The PMS study is a compulsory study required for all drugs after launching, maintained for three years after approval, and reported annually. Adverse experiences are looked for and reported in accordance with Koseisho Regulations. As of February 14, 1986, 8,827 patients had been enrolled in the PMS study. Between March 1984 and March 31, 1986, it is estimated that approximately 11,900,000 people received treatment with norfloxacin manufactured by Kyorin and Torii Pharmaceutical Companies.

Two deaths are listed: the cause was unknown for one and the other was due to acute renal failure which was reported as probably drug related. The patient had a history of hypertensive cerebral hemorrhage and asthma. The attacks led to a pulmonary infection followed by disseminated intravascular coagulation.

Twenty-four serious adverse experiences are listed in the report. The most frequent clinical AK's were allergic-type reactions, while the most frequently reported laboratory adverse events were elevated liver function tests. Their frequency is far below those described in clinical trials.

Local Registration Studies: In addition to the Japanese and clinical development studies, local studies to support product registration are on-going worldwide. The studies are conducted by the local Merck subsidiary and do not have case report forms. Approximately 30,000 patients had been treated in these local studies as of March 31, 1986. Prompt reporting of any deaths or serious adverse experiences are required and these are the only data that are available for the period between June 27, 1984 and March 31, 1986.

There are 21 reports. Eleven were deaths: ten of the eleven deaths were definitely not drug related. One death was due to interstitial nephritis and was listed as probably drug related. Other reactions are consistent with previous information.

Clinical Development Study Program: The Clinical Development Study Program supplements Merck's program in which the drug has been established as safe and effective. It gives physicians overseas an opportunity to form their own opinion concerning the efficacy and safety of norfloxacin. A total of 1,945 patients have received treatment with norfloxacin in CDSP studies through March 31, 1986. Three deaths have been reported to FDA on Form 1639. None were drug-related. No serious adverse laboratory experiences were reported.

Marketing Experience (Excluding Japan): In addition to Japan, norfloxacin was being marketed in the following countries as of March 31, 1986:

Argentina	El Salvador	Mexico
Austria	Germany	New Zealand
Belgium	Guatemala	Pakistan
Brazil	Holland	Peru
Columbia	Honduras	Portugal
Costa Rica	Italy	Spain
Equador	Lebanon	Switzerland

Excluding Japan, approximately 5,600,000 patients have received marketed norfloxacin worldwide. As with the clinical studies, deaths and serious adverse experiences occurring within 14 days of norfloxacin therapy are promptly reported to FDA on Form 1639. One death due to exfoliative dermatitis has been reported. Reports which were possibly or probably drug related included one anaphylactic reaction, thrombocytopenia, and thrombophlebitis. Drug relationship was not stated for one case of anuria, and one case of increased prothrombin time and hematuria. A congenital malformation was definitely not drug related.

Recommendation: Approval of norfloxacin is recommended.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc Orig ND/ HFN-815, HFN-815/Reed, HFN-815/CSO, HFN-815/Norton, 4806b

Dr. [Signature]

NDA
19-384

May 16, 1986

MEDICAL OFFICER'S REVIEW OF LABELING
and MEMORANDUM OF TELEPHONE CONVERSATION
Amendment ()

Applicant: Merck Sharp & Dohme Research Laboratories
West Point, Pennsylvania

Name of Drug: Trade: NOROXIN

Generic: Norfloxacin

Pharmacological Category: Fluoroquinolone

The applicant submits another revised version of proposed labeling.

Medical Officer's Comments: Revised proposed labeling is satisfactory.

Telephone Conversation May 16, 1986: I called Dr. Blois (215-834-2304) to tell him that I had received this amendment. He told me that the safety update is ready and will be delivered to me Monday, May 19, 1986.

Recommendation: Approval is recommended.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc
Orig NDA 575/23/86 HFN-815, HFN-815/Reed, HFN-815/CSO, HFN-815/Norton, 4802b

575/23/86

NDA 19-384

May 2, 1986

**MEDICAL OFFICER'S REVIEW OF LABELING
and MEMORANDUM OF TELEPHONE CONVERSATIONS**

Amendment ()

Applicant: Merck Sharp & Dohme Research Laboratories
West Point, Pennsylvania

Name of Drug: Trade: NOROXIN

Generic: Norfloxacin

Pharmacological Category: Fluoroquinolone

The applicant submits another revised version of proposed labeling.

Medical Officer's Comments: Revised proposed labeling has greatly improved and we are essentially in agreement. This new version was discussed with Mr. Norton. There are a few recommended sentences that have been omitted and there are a number of suggestions regarding sentence structure.

April 29 and 30, 1986: I called Dr. David Blois to discuss labeling.

May 2, 1986: I received the new version and I called Dr. David Blois, Senior Director of Regulatory Affairs (215-834-2304), to discuss these changes and to dictate my recommendations. Dr. Blois will consider these changes with his staff and will file revised proposed labeling in two or three days.

Recommendation: Approval is recommended but labeling is still unsatisfactory.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc

Orig NDA

SHFN-840

HFN-840/Reed

HFN-845/CSO

4783b

WRO 5/11/86

8:5 S.T. 5/23/86

August 18, 1986

AMENDMENT TO MEDICAL OFFICER'S REVIEW OF NDA 19-384

Applicant: Merck Sharp & Dohme Research Laboratories
Division of Merck & Co., Inc.
West Point, Pennsylvania 19486

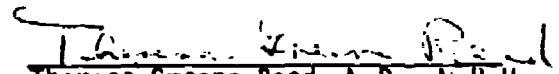
Name of Drug: Generic: Norfloxacin, MSD

Trade: NOROXIN™

The reader is referred to page 24 of the Medical Officer's Review dated Nov. 14, 1985. This is a review of the domestic multiclinic randomized controlled trial to compare norfloxacin with TMP/SMZ in the treatment of uncomplicated and complicated urinary tract infections. This review is amended to add the following information taken from Volume 2.6, page 1-01667:

CLINICAL RESPONSE

UTI	Susceptible to both drugs		Regardless to Susceptibility		Susceptible to Drug Received	
	Norflox.	TMP/SMZ	Norflox.	TMP/SMZ	Norflox.	TMP/SMZ
Complicated	95% (19)	83% (12)	81% (37)	87% (15)	85% (34)	83% (12)
Uncomplicated	94% (33)	82% (38)	95% (42)	82% (39)	95% (39)	82% (38)


Theresa Greene Reed, M.D., M.P.H.

cc
Orig NDA
HFN-815
HFN-815/Reed
HFN-815/CSO
5040b

MSD for E.T. 18 Aug 86

April 19, 1986

**MEDICAL OFFICER'S REVIEW OF NDA 19-384
and MEMORANDUM OF TELEPHONE CONVERSATIONS**

Amendments

**Applicant: Merck Sharp and Dohme Research Laboratories
West Point, PA**

Name of Drug: Generic: Norfloxacin

Trade: NOROXIN[®]

Pharmacological Category: Fluoroquinolone antibacterial agent for oral use

Amendment In response to our requests, the applicant files the following two items:

1. An overall summary for the patient diary data previously submitted on Feb. 14, 1986. Additional diaries had been filed but no diaries were summarized.

These data characterize and compare the number of patients with, and days of, each complaint. The percentage of complaints per person was obtained by dividing the number of persons voicing a complaint by the total number of persons receiving each drug. The percentage of days for each complaint was determined by dividing the total number of days of each complaint by the total number of treatment days. Corrected frequencies were obtained by subtracting the percents for placebo-treated subjects from the percents for norfloxacin-treated patients. A negative percent denotes a higher frequency in the placebo group.

ANALYSIS OF PATIENT DIARIES

Complaints	<u>Placebo Cases</u> (N=51)		<u>Norfloxacina Cases</u> (N=170)		<u>Norfl. vs Placebo</u>	
	Total 468 days of Rx # Cases	Days of Complaint	Total 995 days of Rx # Cases	Days of Complaint	# Cases	% of total days of Complaint
Tired, etc	12 (24%)	21 (4%)	22 (22%)	61 (6%)	-2%	2%
Headache	13 (25%)	31 (7%)	22 (22%)	58 (6%)	-3%	-1%
Sleepy, etc	5 (10%)	6 (1%)	12 (12%)	25 (2.5%)	2%	1.5%
Nausea, etc.	2 (4%)	2	18 (18%)	49 (5%)	14%	5%
Dizzy, etc.	1 (2%)	3 (0.6%)	3 (3%)	5 (0.5%)	1%	0.1%
Lightheaded			2 (2%)	6 (0.6%)	2%	0.6%
Eye Complaints	2 (4%)	6 (1%)	4 (4%)	14 (1.4%)	0%	0.4%
Stomachache	2 (4%)	2	8 (8%)	11 (1%)	4%	1%
Rotten, sick, etc.			5 (5%)	5 (0.5%)	5%	0.5%
Hyperactive	1 (2%)	1	1 (1%)	1	-1%	0
Numbness, etc.			2 (2%)	3	2%	0.2%
Flank pain			1 (1%)	1	1%	0.1%
Lump in throat			1 (1%)	3	1%	0.3%
Diarrhea			2 (2%)	2	2%	0.2%
Depressed	1 (2%)	1			-2%	-0.2%
Metallic taste	1 (2%)	1			-2%	-0.2%
Poor sleep			8 (8%)	13 (1.3%)	8%	1.3%
Backache			3 (3%)	10 (1%)	3%	1%
Nervous, etc.			2 (2%)	3	2%	0.2%
Constipated			1 (1%)	1	1%	0.1%
Anorexia	1 (2%)	1	1 (1%)	2	-1%	0
Itching, rash			2 (2%)	5 (0.5%)	2%	0.5%
Swollen hands, etc.			2 (2%)	7 (0.7%)	2%	0.7%
Vaginal itching			4 (4%)	7 (0.7%)	4%	0.7%
Dry mouth			1 (1%)	1	1%	0.1%
Tinnitus			1 (1%)	2	1%	0.2%
Joint complaints			1 (1%)	1	1%	0.1%
No comments	28 (55%)	412 (88%)	37 (37%)	768 (77%)		

About 400 placebo treatment days are compared to about 1000 days norfloxacin treatment days. The rates were greater for norfloxacin than placebo, particularly for two complaints, nausea (14% greater), and poor sleep (8% greater). Others that were greater for norfloxacin were stomachache, feeling rotten or sick, and vaginal itching. Rates were greater for placebo than for norfloxacin for several complaints but none were as high as those given above.

2. Two issues that this medical officer asked to be clarified are explained. "Qual no" means qualitative numbers. Computer coding used a scale of 0-4+ for some reports. This scale was used to report urine protein and urine glucose concentrations and appeared on the computer printout as "Qual no." In like manner, words on the case report forms were converted to numerical figures for platelets and other laboratory reports. Therefore, "Many" epithelial cells and nonspherical crystals on Dr. Cohn's case report #302 was converted to 50 per high power field in the computer printout.

Amendment In response to the medical officer's request, the bacterial efficacy tables for urinary tract infection studies have been revised to exclude underage patients, to include micro-organisms which were not evaluable for the microbiological evaluation for a number of reasons, and to provide separate counts for individual species in five genera. Compassionate cases that had been excluded are included.

These revised bacterial outcome tables should be disregarded because the applicant failed to include data from the control groups. This revision is superseded by the Amendment which includes data from the controls.

Amendment The applicant files final reports of the three following studies which were requested by the FDA pharmacologist at the January 14, 1986 meeting with the firm:

1. Teratology study of norfloxacin in cynomolgus monkeys,
2. Metabolism study of norfloxacin in pregnant and nonpregnant cynomolgus monkeys, and
3. Embryotoxicity study of norfloxacin in cynomolgus monkeys.

The reader is referred to the review by the pharmacologist.

The results of the teratology study indicate that the oral administration of norfloxacin during organogenesis in the cynomolgus monkey at doses of 75 mg/kg/bid and greater induced dose-related embryotoxicity. The no-effect dose was 50 mg/kg/bid. Doses sufficient to cause embryonic loss are not tolerated in some monkeys. The mechanism of norfloxacin-induced embryotoxicity is most likely hormonal (some aspect of placental progesterone synthesis) and not a direct effect on the embryo. Norfloxacin was not teratogenic in any species.

The applicant concludes that in view of the embryoletality in monkeys, although the relevance of this to humans is not known, norfloxacin should be used in pregnancy only if the benefits justify the potential risk to the fetus.

Reviewer's Comment: Like other quinolones, norfloxacin already is not to be recommended for use in pregnancy because of the development of arthropathy in juvenile animals of all species tested. Embryotoxicity is a second reason.

Amendment

1. In response to the medical officer's request the bacterial efficacy tables for urinary tract infection studies have been revised to exclude underage patients, to include micro-organisms which were not evaluable for the microbiological evaluation for a number of reasons, and to provide separate counts for individual species in five genera. Data from control groups have been added. Compassionate cases that had been excluded are included.

The applicant's revised summary of efficacy data for urinary tract infections for evaluable patients in this application is shown below. (Number eradicated/No. Isolated. Protocol numbers are in parentheses.)

Indication & Claim No.	Organism	Controlled Trials			Uncontrolled Trials - Proto-	
		Norflor- acin	Control	Protocol #	Trials - Proto- #E/#I	col #
1.1	<u>E. coli</u>	46/46	44/44	(#001)	13/13	(#011)
		27/27	17/22	(#002)	28/29	(#017)
					0/1	(#019)
	Total	53/53 126/126 (100.0%)	52/55 113/121 (93.4%)	(#504/505)	61/63 102/106 (96.2%)	(#506/508)
1.2	<u>Klebsiella pneumoniae</u>	1/1	2/2	(#001)	5/5	(#011)
		6/8	5/5	(#002)	3/3	(#017)
		1/5	3/4	(#504/505)	6/6	(#506/508)
	Total	8/14 (57.1%)	10/11 (90.9%)		14/14 (100.0%)	
	<u>K. oxytoca Klebsiella sp.</u>	0	1/1	(#504/505)	2/2	(#506/508)
1.3	<u>Enterobacter aerogenes</u>	1/1	1/1	(#002)	2/3	(#011)
		0/1	1/1	(#504/506)		
		Total	1/2	2/2		2/3
		<u>E. cloacae E. agglomerans Enterobacter sp.</u>	4/4 1/1 0	1/1 0 2/2	(#504/505) (#504/505) (#504/505)	1/2 1/1
1.4	<u>Proteus mirabilis</u>	3/3	1/1	(#001)	4/4	(#011)
		5/5	3/4	(#002)	4/4	(#017)
		9/9	8/9	(#504/505)	15/15	(#506/508)
	Total	17/17 (100%)	12/14 (85.7%)		23/23 (100%)	
1.5	<u>Proteus, indole positive group (3 species)</u> Total	1/1	1/1	(#002)	4/4	(#506/508)
		2/2	1/1	(#504/505)		
		3/3	2/2		4/4 (100%)	
1.6	<u>Pseudomonas aeruginosa</u>	4/4	0	(#001)	11/13	(#011)
		4/8	0	(#002)	2/3	(#017)
					2/6	(#019)
		5/5	0/1	(#504/505)	8/9	(#506/508)
	Total	13/17 (76.5%)	0/1		23/31 (74.2%)	
	<u>Pseudomonas cepacia P. fluorescens</u>	0	1/1	(#002)	1/1	(#506/508)

Indication & Claim No.	Organism	Controlled Trials			Uncontrolled Trials - Proto-	
		Norfloxac- acin	Control	Protocol #	#E/#I	col #
1.7	<u>Serratia marcescens</u>	0	1/1	(#504/505)		
1.8	<u>Providencia stuartii</u> and <u>Providencia sp.</u>	2/2	0/0	(#504/505)		
1.9	<u>Citrobacter freundii</u>	1/2	0/0	(#002)	2/2	(#017)
	Total	1/2	0/0		2/2	(#506/508)
	<u>Citrobacter diversus</u>	0/0	0/0		1/1	(#506/508)
	<u>Citrobacter sp.</u>	0/0	1/1	(#001)		
		1/1	0/0	(#002)		
1.10	<u>Staphylococcus aureus</u>	1/1	0/0	(#001)	2/3	(#011)
		3/3	2/2	(#002)	3/3	(#017)
	Total	4/4	2/2		3/3	(#506/508)
					8/9	(88.9%)
	<u>Staphylococcus epidermidis</u>	3/3	0/0	(#002)	1/1	(#011)
		0/0	1/1	(#504/505)	2/2	(#017)
	Total	3/3	1/1		2/2	(#506/508)
					5/5	
	<u>Staphylococcus saprophyticus</u>	1/1	0/0	(#001)		
		0/0	1/1	(#002)		
	1/1	0/0	(#504/505)	1/1	(#506/508)	
	<u>Staphylococcus coag. neg</u>				1/1	(#011)
					1/1	(#017)
1.11	Group D streptococci	7/8	0/1	(#002)	5/6	(#011)
	including <u>S. faecalis</u>	1/1	5/5	(#504/505)	1/2	(#017)
	Total	8/9	5/6		3/3	(#506/508)
		(88.9%)	(83.3%)		9/11	(81.8%)
1.12	Group B streptococci Beta-hemolytic strep.	1/1	1/1	(#002)	1/2	(#011)

Medical Officer's Comments: (Percents were added by the medical officer.)

a) This revised table responds to the medical officer's requests and is satisfactory. It is the final bacteriological outcome table and takes the place of the applicant's table shown on pages 88-89 and the medical officer's preliminary outcome table shown on pages 91-91 of the original

MOR of this application.

b) Therefore, satisfactory efficacy data have been filed to recommend norfloxacin in the treatment of urinary tract infections caused by Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus aureus, and Group D streptococci. Staphylococcus epidermidis, Citrobacter freundii, and Enterobacter cloacae should also be added to this list but with an asterisk to show that there were less than ten cases

Tallying individual species separately in this revised table deletes Enterobacter aerogenes (only 1/2 eradication in controlled trials and 2/3 eradication in uncontrolled trials).

c) Treatment of gastroenteritis will not be recommended.

2. In response to the medical officer's request, adverse reaction data and laboratory data have been retabulated to provide counts in separate categories by the size and frequency of the dose.

Distribution of Adverse Experiences by Dose
(Only rates greater than 0.15% are shown)

	200 mg bid 60 pts.	400 mg bid 1015 pts	400 mg bid 27 Vol.	400 mg tid 25 Vol.	Total N=1127	% hav- ing AE	% of Drug- Related AEs
Abdominal Swelling		1	1		2	0.17	0
Fatigue		3	3		6	0.53	0
Fever		2		1	3	0.27	0
Myocardial Infarct.		2			2	0.17	0
Abdominal Pain		4 (2)	1		5 (2)	0.44	3.5
Constipation		4			4	0.35	-
Diarrhea		3 (1)			3 (1)	0.27	1.8
Dry Mouth		3 (2)			3 (2)	0.27	3.5
Dyspepsia		5 (4)			5 (4)	0.44	7
Flatulence		3	1		4	0.35	-
G.I. Cramps		2 (1)			2 (1)	0.17	1.8
Heart Burn		4			4	0.35	-
Mouth Ulcer		2			2	0.17	-
Nausea		28 (13)	2	1	31 (13)	2.75	23
Vomiting		2	1		3	0.27	-
Depression		4 (1)			4 (1)	0.35	1.8
Dizziness		16 (6)	4		20 (6)	1.77	10.5
Headache		21 (4)		9	30 (4)	2.66	7
Insomnia		4 (2)			4 (2)	0.35	3.5
Somnolence		5 (1)			5 (1)	0.44	1.8
Pruritis		2 (2)			2	0.17	3.5
Rash		6 (3)			6 (3)	0.53	5.3
Taste Perversion		2 (2)			2 (2)	0.17	3.5
Other (Under 1X)		40 (13)	2	2	44 (15)		
Total		168 (57)	15	13	196 (57)		

The most frequently occurring adverse reactions for 1127 subjects in multiple-dose, non-neutropenic studies that were predominantly urinary tract infection studies with the recommended 400 mg bid dose schedule were nausea - 2.75%, headache - 2.66%, dizziness - 1.77%, rash - 0.53%, and fatigue - 0.53%.

Distribution of Adverse Laboratory Experiences by Dose
(Only rates greater than are shown)

	200 mg bid 60 pts.	400 mg bid 1015 pts	400 mg bid 27 Vol.	400 mg tid 25 Vol.	Total N=1127	% hav- ing AEs	% of Drug- Related AEs
Hemoglobin Dec.		4			4	0.35	0
Hematocrit Dec		2	3		5	0.44	0
WBC Count Dec.*		6 (3)	8		14 (3)	1.2	30
WBC Count Inc.		3	1		4	0.35	0
Neutrophils Dec.*		7 (3)			7 (3)	0.62	30
Lymphocytes Rel Inc.		3 (1)			3 (1)	0.17	10
Eosinophilia		19 (1)	1		20 (1)	1.8	10
Thrombocytopenia		4			4	0.35	0
BUN Elevated		11			11	0.98	0
Ser. Creat. Elev.		5			5	0.44	0
Tot. Biliru. Elev.	1	3			4	0.35	0
AST, ALT Inc.		20 (1)			20 (1)	1.8	10
Alk. Phos. Inc.		16 (1)			16 (1)	1.4	10
Ser. LDH inc.		7			7	0.62	0
Ser. Chloride Dec.		4			4	0.35	0
Ser. Chloride Inc.		3			3	0.27	0
Urine Protein Inc.		3	1		4	0.35	0
Urine RBCs Inc.		3			3	0.27	0
Other (Under 2%)	0	14	1		15		
Total	1	137 (10)	15	0	153 (10)		

*In most instances, WBC decreases and neutrophil decreases came from the same patients.

In both tables, numbers in parentheses are the number of reactions thought to be drug-related.

The most frequently occurring laboratory adverse experiences were eosinophilia - 1.8%, AST or ALT increase - 1.8%, increased alkaline phosphatase - 1.4%, decreased WBC count - 1.2%, and elevated BUN - 0.98%. No single adverse laboratory experience in urinary tract infection studies was as high as 2%.

Amendment The applicant responds to the request from FDA's Division of Biopharmaceutics for in vitro dissolution data on various lots and formulations of norfloxacin tablets. Dissolution data as agreed upon in a telephone conversation with Dr. Gene Mason of this Division are filed.

The final market image 400-mg formulation, the Kyoria 400 mg-tablet, the Merck Sharp & Dohme Research Laboratories direct compression 400 mg-tablet, and

production scale tablets are compared. The final market image formulation dissolves faster and peaks faster than any of the previous products and has less coating. Eighty percent of the tablet dissolved in 30 minutes. The reader is referred to the chemist's review and to the review by Dr. Gene Mason of the Division of Biopharmaceutics. That Division has accepted this report.

Amendments (): Revised proposed labeling is filed. Many of the comments listed in my MOR dated March 14, 1986 have been included. Some were not included. Comments on the new version are listed below.

Clinical Pharmacology:

1. (Page 6, line 7) Insert "Alteration of dosage is necessary (See DOSAGE AND ADMINISTRATION)." in regard to patients with impaired renal function.
2. (Page 6, line 19) Insert "in the urine" in the sentence, "Within 24 hours of drug administration, 26 to 32% of the dose is recovered in the urine as norfloxacin ..."

Microbiology:

1. (Page 9, lines 4-6) Revise this sentence to read, "Nalidixic acid resistant organisms are generally susceptible to norfloxacin in vitro; however, these organisms (particularly P. aeruginosa, K. pneumoniae, Acinetobacter, and enterococci) may have higher MICs to norfloxacin than nalidixic acid-susceptible strains. For this reason, cultures and susceptibility testing may have to be repeated.

Indications and Usage:

(Page 15) Revise the first paragraph to read as follows:

"NOROXIN is indicated for the treatment of adults with complicated and uncomplicated urinary tract infections that are caused by susceptible strains of the designated micro-organisms listed below:

Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,
Pseudomonas aeruginosa, Staphylococcus aureus, Staphylococcus epidermidis,* Citrobacter freundii,* Enterobacter cloacae,* and group D streptococci.

*Efficacy for these micro-organisms in urinary tract infections was studied in fewer than ten infections."

Warnings:

1. (Page 16, lines 14-15) Revise the sentence to read, "The oral administration of single doses of norfloxacin, 4 times the recommended human clinical dose, caused lameness in immature dogs."
2. (Page 16, lines 7-12) Switch phrases and revise the first sentence so

that it will read "Needle-shaped crystals in the urine were found in some volunteers who received either 800 mg norfloxacin, 1600 mg norfloxacin (at or twice the recommended dose), or placebo while participating in a single double-blind, crossover study comparing single doses of norfloxacin with placebo." Delete the next sentence "These crystals were not identified."

3. (Page 15, line 17) Add "and an adequate rate of urine flow" to the end of the last sentence.

Precautions:

1. (Page 18, line 3) Insert two paragraphs that were recommended in the last labeling discussion.

"Norfloxacin should be used with caution in patients with a history of hepatic disease or in patients with impaired hepatic function."

"The effects of norfloxacin on brain function or on the electrical activity of the brain have not been tested. Central nervous system-type adverse experiences such as headache, dizziness, lightheadedness, hyperactivity, visual changes, and insomnia have been reported with some antibacterial agents in the quinolone drug class. Seizures which were not thought to be drug related occurred in two norfloxacin-treated patients that had existing CNS disorders that predispose to seizures and that fully accounted for the events. Until more information becomes available, quinolones should be used with caution in patients with known factors that predispose to seizures."

2. (Page 19, lines 2-7) Revise the Information for Patients section to read as follows:

"Patients should be advised to drink fluids liberally and that antacids should not be taken concomitantly or within two hours after dosing.

"NOROXIN may cause dizziness or lightheadedness; therefore, patients should know how they react to norfloxacin before they operate automobiles and machinery or engage in activities requiring mental alertness and coordination."

3. (Page 20, lines 12-19) Switch the first two sentences in the Pregnancy Category C section.

(Page 21, lines 1-3) The last sentence in the pregnancy section should be revised to read, "Since norfloxacin, like other drugs in this class, causes arthropathy in immature animals, its use during pregnancy is not recommended (See Warnings)."

Adverse Reactions: (Pages 22-23) Revise this whole section to read as follows:

"NOROXIN generally is well tolerated. The overall incidence of drug-related side effects in clinical trials involving 1127 subjects was approximately _____%" (Percent figure will be inserted.)

"The most common side effects (less than 3%) observed during clinical trials were either gastrointestinal or neurological and include nausea-2.8%, headache-2.7%, and dizziness-1.8%. Additional reactions with frequencies greater than 0.3% were fatigue, rash, abdominal pain, dyspepsia, somnolence, depression, insomnia, flatulence, and heart burn. Less frequent reactions were dry mouth, diarrhea, fever, vomiting, and erythema. Although not reported with norfloxacin, visual disturbances have been reported with other drugs in this class."

"Abnormal laboratory values observed in clinical trials were eosinophilia-1.8%, elevation of ALAT (SGPT) and ASAT (SGOT)-1.8%, increased alkaline phosphatase-1.4%, and decreased WBC-1.2%. Those occurring less frequently were elevated BUN, serum creatinine, and LDH, and decreased hematocrit.

Dosage and Administration: (Page 24, lines 1-12) Revise this section to read as follows:

"Norfloxacin should be taken orally one hour before or two hours after a meal with a glass of water. Patients receiving norfloxacin should be well hydrated to prevent crystallization of norfloxacin in the urinary tract.

Normal Renal Function

"The recommended norfloxacin dose is 400 mg twice daily for adults with normal renal function, and for patients with creatinine clearance rates greater than 30 mL/min/1.73 m².

For uncomplicated urinary tract infections, the recommended treatment period is 7 to 10 days.

For complicated urinary tract infections, the recommended treatment period is 10 to 30 days.

Doses higher than 800 mg/day are not recommended.

Animal Pharmacology: The Anti-Infective Advisory Committee has recommended that labeling for members of the quinolone drug class have an Animal Pharmacology section. The following text is recommended:

Animal Pharmacology: Norfloxacin and related drugs have been shown to cause arthropathy in immature animals of most species tested (See Warnings).

Crystalluria occurs in laboratory animals treated with norfloxacin. In dogs, needle-shaped drug crystals were seen in the urine at doses as low as 50 mg/kg/day. In cats, crystals were reported following doses of 50 mg/kg/day. In cynomolgus monkeys, drug crystals were seen in the urine at doses of 50 mg/kg/day and higher.

Embryolethality and slight maternotoxicity were observed in cynomolgus monkeys at doses of 50 mg/kg/day or higher.

Oculotoxicity, seen with some related drugs, was not observed in any norfloxacin-treated animal."

Memoranda of Telephone Conversations: A number of telephone conversations were held with Dr. David W. Blois, Senior Director of Regulatory Affairs (215-661-2304) to discuss these amendments and proposed labeling.

April 16, 1986 I called to dictate labeling recommendations. Dr. Blois will edit the brain function paragraph.

April 17, 1986 I called to discuss adverse reaction data. Dr. Blois discussed the Indications section. Dr. Blois wants E. cloacae, freundii, and indole positive Proteus listed in the Indications section.

April 19, 1986 In a conference call, Mr. Norton and I gave them comments on the Microbiology section. We agreed to add E. cloacae and C. freundii with asterisks. These pathogens are exquisitely susceptible to norfloxacin. Indole positive Proteus, however, represents a

Conclusion: All requests have been answered satisfactorily and the applicant has responded to all comments except a few labeling comments.

Recommendation: This application should be made approvable. Labeling is unsatisfactory but labeling discussions are progressing very well.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc
Orig NDA
HFN-815
HFN-815/Reed
HFN-815/CSO
4731b

BRD 22 Apr 86

4/24/86 Division Director's
wording of the "asterisk" for
should be consistent with
other recent drug labeling
identical. S. Tabor

August 26, 1986

MEDICAL OFFICER'S REVIEW OF NDA 19-384

Amendment [REDACTED]

Applicant: Merck Sharp & Dohme Research Laboratories
West Point, Pennsylvania

Name of Drug: Trade: NOROXIN^R
Generic: Norfloxacin

Pharmacological Category: Fluoroquinolone antibacterial agent

The applicant submits revised proposed labeling and answers to Dr. Tabor's questions in response to my telephone conversation August 18, 1986.

Labeling:

1. Microbiology Section (page 7, line 3) The phrase "of the organism" has been inserted as requested.
2. Indications and Usage Section (page 13, line 12) An asterisk (*) has been added following the listing of the organism "Staphylococcus aureus."
3. Indications and Usage Section (page 13, lines 14-16) The sentence after the asterisk has not been revised to add "in this organ system" as requested. The applicant feels that this addition would lead the reader to think that norfloxacin was indicated for more organ systems than the urinary tract.
4. Precautions Section (pages 18 and 19) These two paragraphs have not been revised as requested to say that norfloxacin should not be used in pregnancy or in children. The applicant indicates that the wording is identical to that used in the approved labeling for cinoxacin, a related drug. It is felt that the reasons for the wording in these sections is the same for both drugs and, therefore, that the wording should be identical.

Medical Officer's Comment: The wording in the Precautions section of the cinoxacin labeling, that use of norfloxacin in pregnancy and in children is not recommended, was one of several recommended wordings for quinolones given us by the Anti-Infective Drug Advisory Committee.

Microbiological outcome:

In response to our request, the applicant reports the microbiological outcome for norfloxacin in Study No. 2 according to organism for both complicated and uncomplicated urinary tract infections as follows:

Study No. 2	Number Eradicated/Total Number	
	Complicated UTI	Uncomplicated UTI
<u>S. epidermidis</u>	1/1	2/2
Group D streptococci	5/6	4/4
Citrobacter species	1/1	
<u>C. freundii</u>	1/2	1/1
<u>E. coli</u>	13/13	24/24
<u>K. pneumoniae</u>	2/4	4/5
<u>M. morgani</u>	1/1	
<u>P. vulgaris</u>	1/1	
<u>P. mirabilis</u>	3/3	3/3
<u>F. rettgeri</u>	2/2	
<u>P. aeruginosa</u>	9/12	1/1
<u>Corynebacterium</u>		0/1
Group B streptococci		1/1
<u>F. aerogenes</u>		1/1
<u>Lactobacillus</u> species		1/1
Total	39/46 (85%)	42/44 (95%)

A similar table is provided for all evaluable norfloxacin cases as follows:

All evaluable norfloxacin cases	Number Eradicated/Total Number	
	Complicated UTI	Uncomplicated UTI
<u>Gram Positive Bacteria</u>		
<u>Corynebacterium</u> sp.		0/1
<u>Lactobacillus</u> sp.		1/1
<u>Micrococcus</u> species		1/1
<u>Staphylococcus</u> species		1/1
<u>S. aureus</u>	1/1	5/6
<u>S. epidermidis</u>	2/2	7/7
<u>S. saprophyticus</u>	2/2	4/4
Coag. Neg. Staph.		1/1
Gp. B <u>Streptococcus</u>		1/1
Gp. D streptococci	10/11	9/11
Beta hemolytic Strep.	1/1	
Total	15/16 (94%)	30/34 (88%)

(Continued on next page)

All evaluable norfloxacin cases	Number Eradicated/Total Number	
	Complicated UTI	Uncomplicated UTI
<u>Gram Negative Bacteria</u>		
<u>Acinetobacter sp.</u>	0/1	
<u>Alcaligenes species</u>		1/1
<u>Citrobacter species</u>	2/2	1/1
<u>C. diversus</u>	1/1	
<u>C. freundii</u>	3/4	4
<u>Enterobacter species</u>	1/1	1/1
<u>E. aerogenes</u>	1/3	2/2
<u>E. agglomerans</u>		3/3
<u>E. cloacae</u>	2/4	3/3
<u>E. coli</u>	66/68	207/210
<u>Klebsiella species</u>		1/2
<u>K. oxytoca</u>	1/1	2/2
<u>K. pneumoniae</u>	11/14	15/19
<u>M. morgani</u>	1/1	
<u>Proteus species</u>	1/1	1/1
<u>Proteus indole pos.</u>	1/1	1/1
<u>Proteus rettgeri</u>	2/2	
<u>P. vulgaris</u>	2/2	2/2
<u>P. mirabilis</u>	21/21	27/27
<u>Providencia rettgeri</u>	2/2	
<u>P. stuartii</u>	1/1	
<u>Providencia species</u>		1/1
<u>P. aeruginosa</u>	27/34	16/17
<u>P. cepacia</u>	1/1	
<u>S. liquefaciens</u>	1/1	
<u>S. marcescens</u>	1/1	
<u>Total</u>	149/167 (89%)	290/297 (98%)

Duration of Treatment:

In response to one of the questions, the applicant gives the duration of treatment in days for all patients who received norfloxacin for complicated urinary tract infections as follows:

<u>Duration of Treatment</u>	<u>Number of Norfloxacin Cases</u>
1-9 days	39
10-20 "	221
21-24 "	2
25-30 "	12
31-99 "	4
<u>Total</u>	<u>278</u>

No. with 10 days or more 239

Since only three adverse experiences occurred beyond 9 days of therapy, it appears that prolonging norfloxacin therapy up to 30 days does not significantly increase the rate of adverse experiences.

Indole-positive Proteus cases:

The following seven indole-positive cases were reported in the NDA:

<u>Protocol No.</u>	<u>Study No.</u>	<u>Alloc. No.</u>	<u>Micro-organism</u>
002	8	810	<u>Morganella morganii</u>
504/505	529	1093	<u>Proteus rettgeri</u>
504/505	529	1099	<u>Proteus rettgeri</u>
506/508	516	2002	<u>Proteus, indole pos.</u>
506/508	516	2009	<u>Proteus, indole pos.</u>
506/508	533	2028	<u>Proteus vulgaris</u>
506/50'	535	2150	<u>Proteus vulgaris</u>
Total			7 of 7 eradicated

Recommendation: Revised proposed labeling is satisfactory. Approval is recommended.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc Orig NDA, HFN-815 HFN-815/Reed, HFN-815/CSO 5008b

DRD 27 Aug 86

ET 8/27/86

August 18, 1986

MEDICAL OFFICER'S REVIEW OF NDA 19-384
and MEMORANDUM OF TELEPHONE CONVERSATION

Labeling amendment dated July 25, 1986

Applicant: Merck Sharp & Dohme Research Laboratories
West Point, Pennsylvania

Name of Drug: Trade: NOROXIN[®]
Generic: Norfloxacin

Pharmacological Category: Fluoroquinolone antibacterial agent

The applicant submits revised proposed labeling to comply with comments from Dr. Ed Tabor which were given to the firm by Mr. Robert Linkous in a telephone conversation on July 21, 1986. Revised proposed labeling is satisfactory except for the following recommendations:

1. Microbiology Section (page 7, line 3) Insert "of the organism" after the first word. The new sentence will read, "Resistance of the organism has developed during therapy with norfloxacin in less than 1% of patients treated."
2. Indications and Usage Section (page 13, lines 14-16) Revise the sentence after the asterisk to read, "* Efficacy for this organism in this organ system was demonstrated in fewer than ten infections."
3. Precautions Section (page 18, lines 10-13) The last sentence in the Pregnancy paragraph should be revised to read, "Since norfloxacin, like other drugs in this class, causes arthropathy in immature animals, it should not be used in pregnancy (see WARNINGS)."
4. Precautions Section (page 19, lines 5-6) The Pediatric Use sentence should be revised to read, "NOROXIN should not be used in children (See WARNINGS)."

In Dr. David Blois' absence, I called Dr. Gerard D. Picot, Assistant Director of Regulatory Affairs at Merck to give him these comments. Dr. Mike Corrado participated in the conversations. I also asked other questions that the Division Director has raised. Did all complicated UTI patients get 10-30 days of therapy? How many patients got 30 days? What were the eradication rates for indole-positive Proteus species (P. vulgaris, P. rettgeri, and M. morganii) and give the study numbers where these uropathogens were isolated? What were the eradication rates for S. aureus and what were these study numbers?

Some of these questions were answered in attachments to the second version of the proposed labeling.

1. The report gives microbiological outcomes for complicated and uncomplicated urinary tract infections after cases which were originally classified as unevaluable had been deleted.

	Norfloxacin			TMP/SMZ		
	Eradi- cated	Pers- isted	Total	Eradi- cated	Pers- isted	Total
Complicated Cases						
Gram Positive Cocci	15 (94%)	1	16	8 (88%)	1	9
Gram Neg. Bacilli	149 (89%)	18	167	34 (87%)	5	39
Uncomplicated Cases						
Gram Positive Cocci	30 (88%)	4	34	7 (88%)	1	8
Gram Negative UTIs	290 (97%)	9	299	174 (91%)	18	192

2. The majority of complicated urinary tract infections were treated for 10-30 days.

Treatment Period	Number of Evaluable Cases
1-9 days	9
10-30 days	147 (92.5%)
31-99 days	3
Total	159

Approximately 90% of all adverse reactions occurred within the first four days of norfloxacin therapy. Dyspepsia, nausea, headache, dizziness, etc. appeared to occur very early in the course of treatment and continued therapy did not seem to appreciably increase the incidence of adverse experiences. Three adverse experiences occurred in patients treated beyond ten days for complicated urinary tract infections: rash on day 12 was probably related to treatment, hemorrhagic shock on day 31 was definitely not related to treatment, and eosinophilia on day 11 was probably not related to treatment. Of the 150 patients receiving therapy beyond 10 days, 147 did not experience adverse reactions.

Dr. Picot will confer with his coworkers and respond as soon as possible.

Recommendation: Approval is recommended but labeling is still unsatisfactory.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc Orig NDA, HFN-815, HFN-815/Reed, HFN-815/CSO 5008b

WAD 19 Aug 86

ET 8/27/86

May 9, 1986

MEDICAL OFFICER'S REVIEW OF LABELING
and MEMORANDUM OF TELEPHONE CONVERSATIONS

Amendment ~~XXXXXXXXXX~~

Applicant: Merck Sharp & Dohme Research Laboratories
West Point, Pennsylvania

14 287

Name of Drug: Trade: NOROXIN

Generic: Norfloxacin

Pharmacological Category: Fluoroquinolone

The applicant submits another revised version of proposed labeling.

Medical Officer's Comments: Revised proposed labeling is satisfactory except for two sentences.

1. Clinical Pharmacology section (Page 5, line 9): The sentence about pH was deleted by mistake. The following sentence should be inserted in its place:

"The urinary pH may effect the solubility of norfloxacin: at pH 7.5, there is minimum solubility."

2. Dosage and Administration (Page 21): Now that I have a copy of the written Biopharmaceutics review, I am reminded that the dosage of norfloxacin needs to be adjusted in the elderly as well as in patients with impaired renal function. Appropriate information should be added to address this problem.

May 5 through 9, 1986: I called Dr. David Blois and he called me several times to discuss labeling.

May 9, 1986: I called Dr. David Blois, Senior Director of Regulatory Affairs (215-834-2304), to discuss these two changes given above. Dr. Mason, the Biopharmaceutics reviewer, and I discussed the problem of dosing in the elderly. We talked to Dr. Blois about this. and all agreed upon the following changes in the Dosage and Administration section:

1. Change the subheading from "Renal Impairment" to "Renal Impairment and the Elderly."
2. Revise the first sentence to add "and the elderly," to read "NOROXIN may be used for the treatment of urinary tract infections in patients with renal insufficiency and in the elderly."

Recommendation: Approval is recommended. Revised labeling, as agreed upon, is satisfactory.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

915/11/86

cc
Orig NDA HFN-815, HFN-815/Reed, HFN-815/CSO, HFN-815/Norton, 4792b

FD 915/11/86

NDA 19-384

David W. Blois, Ph.D.
Merck Sharp & Dohme Laboratories
West Point, PA 19486

Dear Dr. Blois:

Reference is made to your New Drug Application (NDA) dated January 14, 1985 submitted pursuant to section 505(b) of the Federal, Food, Drug, and Cosmetic Act for Noroxin (norfloxacin) Tablets, 400 mg.

We also acknowledge your additional correspondence dated February 7, February 11, March 15, March 21, April 2, April 3, April 23, July 3, July 11, July 23, August 1, September 13, October 3, October 10, October 18, November 4, November 6, December 19, 1985, January 20, February 12, February 14, February 14, February 24(3), March 11, March 17, March 18, March 21, March 31, April 4, April 22, May 1, May 8(2), May 15, May 19, July 25, August 26, and September 19, 1986.

We have completed our review of your submission and the application is approved.

However, prior to marketing, you must submit final printed labeling identical to draft labeling dated September 19, 1986, except that:

1. The title of the subsection in the DOSAGE AND ADMINISTRATION labeled "Renal Impairment (including the Elderly with Renal Impairment)" should be changed to "Renal Impairment;" the first sentence of this section should also have the parenthetical statement removed;
2. Recommended dosage for elderly patients should be added to a different part of the DOSAGE AND ADMINISTRATION section;
3. The footnote after the asterisk in the INDICATIONS AND USAGE section must read: "Efficacy for this organism in this organ system was studied in fewer than 10 infections."
4. An asterisk must be placed after each of the indole positive Proteus species in the INDICATIONS.

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

Sincerely yours,

cc: PHI-DO

ORIG. NDA 19-384

HFN-82

HFN-220

HFN-710

HFN-815

HFN-815/RLinkous/8/29/86/sdj/9/5/86

HFN-815/MO

HFN-815/PHARM

HFN-815/CHEM

F/T: 9/26/86/9/29/86

APPROVABLE 0476u

Elaine C. Esber, M.D.

Director

Office of Biologics Research and Review
Center for Drugs and Biologics

*prior to retyping, this was
initialed by all superiors except
Dr. Stanley, who was on sick leave.
See attached copy.*

HFN-815

November 14, 1985

MEDICAL OFFICER'S REVIEW OF NDA 19-384

Initial 148 Volume Submission Dated January 14, 1985
and Amendments

Applicant: Merck Sharp & Dohme Research Laboratories
Division of Merck & Co., Inc.
West Point, Pennsylvania 19486

40R

Name of Drug: Generic: Norfloxacin, MSD

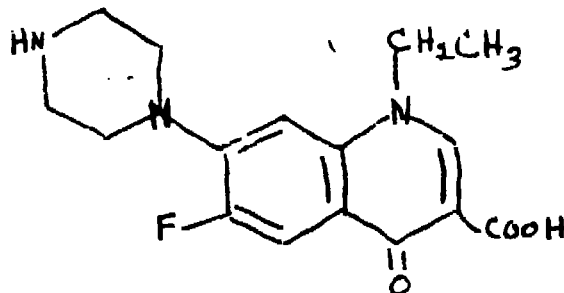
Trade: NOROXINTM

Empirical: C₁₆H₁₈FN₃O₃

Mol. Wt. 319.34

Chemical: 1-ethyl-6-fluoro-1,4-dehydro-4-oxo-7-(1-piperazinyl)-
-3-quinoline carboxylic acid

Structural:



Pharmacological Category: Orally absorbed antibacterial agent, a fluoroquinolone member of the quinolone drug class

Proposed Indications: For treatment of complicated and uncomplicated infections of the urinary tract, gonorrheal urethritis, bacterial gastro-enteritis, and for prophylactic use in neutropenia.

Related Submissions:

Microbiology and Manufacturing Controls: Norfloxacin is a synthetic broad spectrum pyridone carboxylic acid for oral administration. It was discovered and developed by investigators at the Kyorin Pharmaceutical Co., Ltd., in Japan. Norfloxacin is chemically and pharmacologically related to nalidixic acid, oxolinic acid, and pipemidic acid but with a fluoride ion at the 6-position and is much more potent.

Norfloxacin is bactericidal and is active against aerobic gram-negative and gram-positive bacteria including all species of staphylococci, all species of Enterobacteriaceae, N. gonorrhoeae, H. influenzae, G. vaginalis, U. urealyticus, P. aeruginosa, Acinetobacter species, and C. trachomatis. Norfloxacin MIC's are outstanding when compared to MIC's for other nonfluoridated antimicrobial agents shown in the next table. Norfloxacin is not active against anaerobes.

Norfloxacin inhibits bacterial DNA synthesis. It inhibits the ATP-dependent DNA supercoiling reaction by E. coli DNA gyrase. It inhibits the relaxation of supercoiled DNA, an activity that is induced by DNA gyrase in the absence of ATP. It promotes double-stranded DNA breakage in E. coli cells. Collectively, these events cause filamentation of representative gram-negative bacterial cells, swelling of S. aureus, lysis of P. aeruginosa, and shrinkage when the cells are viewed by transmission and scanning electron microscopy.

The applicant has selected a disk content of 10 mcg. Organisms with zones of 17 mm or greater are considered to be susceptible, those with zones of 13-16 mm have intermediate susceptibility, and those with zones of 12 mm or less are considered to be resistant strains. Dilution susceptibility breakpoints are 16 mcg/ml or less - susceptible, and 32 mcg/ml or greater - resistant.

Table of Contents

	Page
Applicant, Name of Drug, Pharmacological Category	1
Proposed Indication, Related Submissions	
Dosage Form and Route of Administration	3
Microbiology and Manufacturing Controls	3
Animal Pharmacology	5
Clinical Background	8
Clinical Studies	
1. Special Studies	9
a) Human Pharmacology and Pharmacokinetics	9
b) Safety and Tolerance (Zinney - diaries)	12
c) Bioavailability (Two trials - Zinney - diaries)	17
d) Renal Function (Asscher)	18
2. Controlled Clinical Trials	
a) Uncomplicated UTI Domestic, Multiclinic	20
b) Complicated & Uncomp. UTI (N vs TMP-SMZ)	
(1) Domestic (Multiclinic)	24
(2) International (Multiclinic)	29
c) Bacterial Gastroenteritis	
(1) N vs Erythromycin vs Placebo (Cohn)	35
(2) N vs TMP-SMZ (Multiclinic)	39
d) Suppression of Bowel Flora in Granulocytopenia	
(1) N + Amphotericin B vs TMP-SMZ + Ampho. B	45
(2) N + Nystatin vs Polymyxin B + Vanco.+Nys.	51
e) Gonorrheal Infection	
(1) N vs Spectinomycin - Subic Bay (Berg)	56
(2) N vs Ampicillin + Probenecid	58
3. Uncontrolled Clinical Studies	
a) Acute Bacterial Gastroenteritis (Kunkel)	61
b) Urinary Tract Infections	
(1) Domestic (Multiclinic)	62
(2) International (Multiclinic)	64
c) Compassionate Treatment	
(1) Salmonellosis (Lyons & Nadworny)	70
(2) Multiple Antibiotic Resistant Infections	70
d) Suppression of Bowel Flora in Granulocytopenia	
(1) Rubin & Talbot	71
(2) LeFrock	74
4. Controlled UTI Trials Filed for Safety Only	
a) N vs TMP-SMZ International (Multiclinic)	75
b) N vs Nalidixic Acid- Un. Kingdom (Multiclinic)	77
c) N vs Nalidixic Acid- Canada (Ronald)	80
Amendment:	81
Applicant's Efficacy Summary	88
(Medical Officer's Preliminary Summary of Efficacy)	91
Applicant's Safety Summary	93
Summary of Medical Officer's Comments	102
Biopharmaceutics Consultation	109
Labeling Review	109
Foreign Clinical Data	109
Conclusion and Recommendation	109

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Comparison of Antibacterial Activities

Organism	MIC (mcg/ml)					
	Norflox- acin	Cinox- cin	Nalidix- ic acid	Oxolinic acid	Nitrofur- antoin	Trimeth- oprim
<u>L. monocytogenes</u>	4	>128	>128	>128	>128	≤ 0.03
<u>S. aureus</u>	2	>128	64	1	8	64
<u>S. epidermidis</u>	0.25	128	128	4	>128	2
<u>S. agalactiae</u>	16	>128	>128	>128	32	NT
<u>S. faecalis</u>	4	128	>128	32	32	NT
<u>S. pneumoniae</u>	4	>128	>128	64	4	NT
<u>S. pyogenes</u>	4	>128	>128	>128	4	NT
<u>Acinetobacter iwoffii</u>	0.5	32	8	1	>128	8
<u>Alcaligenes sp.</u>	4	2	4	0.25	64	128
<u>C. diversus</u>	0.015	4	2	0.25	32	0.25
<u>C. freundii</u>	0.03	8	8	1	32	0.5
<u>E. aerogenes</u>	0.06	8	8	1	128	1
<u>E. cloacae</u>	0.06	8	4	0.25	128	2
<u>E. coli</u>	0.5	>128	>128	4	16	0.5
<u>H. influenzae</u>	<0.06	NT	0.5	0.125	NT	NT
<u>K. oxytoca</u>	0.06	8	8	0.5	32	0.5
<u>K. pneumoniae</u>	0.06	4	2	0.125	16	1
<u>Morganella bovis</u>	0.06	32	4	0.25	4	16
<u>M. morganii</u>	0.015	2	1	0.125	8	64
<u>N. gonorrhoeae</u>	0.5	>128	32	2	32	<0.03
<u>P. mirabilis</u>	0.03	16	8	0.125	128	1
<u>P. alcalifaciens</u>	0.125	>128	>128	8	>128	32
<u>P. rettgeri</u>	0.05	4	4	0.25	64	2
<u>P. aeruginosa</u>	0.5	>128	>128	16	>128	>128
<u>S. paratyphi A</u>	4	>128	>128	8	16	2
<u>S. marcescens</u>	0.125	8	4	0.5	>128	16
<u>S. sonnei</u>	0.03	8	4	1	8	0.25

Norfloxacin significantly reduced the mortality of suckling piglets challenged orally with enterotoxigenic E. coli and eliminated diarrhea in surviving animals. Studies in rodents demonstrated that norfloxacin is effective in treating pulmonary infections, skin and skin structure infections, renal abscesses, intradermal abscesses, and in eliminating E. coli from granuloma pouch exudates.

Oral doses of 50 mg/kg for several days in pathogen-free mice lowered the number of enterobacteria in the fecal flora to near zero without affecting the numbers of lactobacilli, Bacteroides species, or gram positive cocci. In rats, norfloxacin significantly decreased both gram-positive and gram-negative bacteria from the ileum to the rectum, while anaerobic bacteria increased

Norfloxacin at a concentration of 2.5 mcg/ml in pooled serum was 13.8% bound to human protein.

Six metabolites identified in human urine, M-1, M-2, M-3, M-4, M-5, and M-6, are all microbiologically active. Eleven bacterial species were tested.

Animal Pharmacology: Animal studies of norfloxacin have been conducted in the rat, mouse, dog, and monkey. Norfloxacin is relatively nontoxic in adult male and female rats and mice. It is poorly absorbed from the gastrointestinal tract. Acute toxicity studies of norfloxacin are summarized as follows:

Species and Sex	LD ₅₀ (mg/kg)			
	PO	Sub Q	IM	IV
Mouse				
Male	Over 4,000	Over 1,500	470	220
Female	Over 4,000	Over 1,500	480	237
Rat				
Male	Over 4,000	Over 1,500	Over 500	270
Female	Over 4,000	Over 1,500	Over 500	245

In mouse and rat studies, six different metabolites were tested orally for their acute toxicities. LD₅₀ values were estimated to be over 2000 mg/kg for M-1, M-4 (2), and M-5 and over 4000 mg/kg for M-2, M-3, and M-4 (1).

One month oral toxicity studies were performed in rats (at doses of 250, 500, and 1000 mg/kg/day), dogs (at 50, 100, and 200 mg/kg/day or 25, 50, and 100 mg/kg bid), and monkeys (at 25, 50, and 100 mg/kg bid). There was no drug-induced toxicity in any species.

Six-month oral toxicity studies in rats conducted by Kyorin revealed body weight retardation in the 250 and 500 mg/kg/day groups but not in the 50 or 125 mg/kg/day group. A similar study in rats conducted by Merck using different doses revealed a slight decrease in body weight gain in the 600 mg/kg/day group. Cecal enlargement was seen in all dose groups. A decrease in body weight gain occurred in females in the 200 and 600 mg/kg/day dose groups in the one-year study in rats. An increase in urinary potassium excretion was seen in female rats given 500 and 1,000 mg/kg/day.

Crystalluria consisting of the dihydrate and the magnesium salts of norfloxacin occurred in rats in the two high dose groups in the Merck study (in the 200 and 600 mg/kg/day dose groups).

Crystalluria occurred in beagle dogs given norfloxacin at 50, 150, and 300 mg/kg/day for 26 weeks but not in the 25 mg/kg/day dose group. The incidence was dose related and was high in the 300 mg/kg/day group. Three dogs, one in the 150 mg/kg/day group and two in the 300 mg/kg/day group, were found dead or were sacrificed due to urinary obstruction from drug crystals.

The crystalluria in dogs and rats was attributed to low solubility of the drug in alkaline urine. This was supported by the observation of a significant decrease in the incidence of crystalluria and in the absence of urinary obstruction when urine was acidified by the administration of ammonium chloride. In this separate study, dogs received 50, 150, and 300 mg/kg/day for three months. Urine acidification to pH range between 5.5 and 6.5 was accomplished by adding ammonium chloride (1%) to drinking water. Emesis

occurred in all dogs and frequently occurred shortly after dosing. Drug crystals shaped as sea urchins and/or fine needles were occasionally seen in urine from dogs in each of the drug-treated groups. Those found during drug weeks 11, 12, and 13 were shown by HPLC to be norfloxacin. The severity and incidence of crystalluria was greatest in the 300 μ g/kg/day group. Four deaths due to aspiration pneumonia occurred.

An oral norfloxacin suspension was given to monkeys in doses of 25, 50, and 100 mg/kg bid six days a week for four weeks. There were two monkeys in each group. Controls received sterile distilled water. Monkeys were sacrificed at the end of treatment. The summary says that no findings attributable to treatment were seen.

Medical Officer's Comments:

1. The report indicates that proteinuria was observed in one of two 200 mg/kg/day monkeys and slight hemoglobinuria was observed in one of two 50 mg/kg/day dose monkeys. Upon further review, the report states in regard to urinalysis that, "One monkey in each of the 50 mg/kg/day group and 100 mg/kg/day group, however, were (sic) not examined because urine could not be obtained from the bladder." Therefore, hemoglobinuria occurred in 100% of monkeys at a dose which is 2-3 times the expected human dose. The "no-effect" dose for hemoglobinuria in monkeys is not known. (The higher doses in humans are 800-1200 mg daily or 16-24 mg/kg based upon a human weighing 50 kg.)
2. The presence of drug crystals in the urine of these monkeys cannot be evaluated because urine was not examined microscopically. Crystals may have been present and may have been the cause of the proteinuria and hemoglobinuria. The "no-effect" crystalluria dose in monkeys is not known.
3. Crystalluria occurred in dogs at 50 mg/kg/day, a dose which will be 2-3 times the recommended human dose. The 'no-effect' crystalluria dose is not known. There may be a possibility that crystalluria could occur at the recommended doses in some patients. Labeling should advise about this possibility.

In the cat, intravenous administration of norfloxacin in doses of 10 mg/kg resulted in modestly reduced (less than 30%) contractions of the nictitating membrane elicited by both pre- and post-ganglionic nerve stimulation.

The amplitude of spontaneous contractions of the pregnant and non-pregnant rat uterus and rabbit ileum were slightly reduced.

In vitro, in isolated perfused guinea pig hearts, one-gram bolus injections resulted in a slight increase in coronary flow and decreased heart rate while modestly depressing contractile force. In the isolated rabbit ear artery, a similar 1-mg bolus of norfloxacin produced a weak, transient change in blood flow.

In vivo, in urethane anesthetized rabbits and barbiturate anesthetized dogs, intravenous doses resulted in an increased respiratory rate. Rabbits received 30 mg/kg and dogs received 10 mg/kg. In these animals and in rats receiving 20 mg/kg IV, blood pressure tended to be reduced without substantial changes in heart rate. In rats, the reduced blood pressure was inhibited by diphenhydramine and was unaffected by atropine; propranolol, or phentolamine. Infusion of norfloxacin in dogs produced an elevation in respiratory rate (60% increase) with only modest changes in blood pressure and heart rate. These doses are well above those which are required for antimicrobial activity.

Results of several teratology studies revealed that rabbits were intolerant of oral doses of norfloxacin. There was, however, fetotoxicity in rabbits that was directly related to maternotoxicity due to its effects on the gastrointestinal flora.

A preliminary report reveals that embryotoxicity and maternal toxicity resulted for 8 of 14 pregnant cynomolgus monkeys that received 300 or 200 mg/kg/day after 10-30 doses. The threshold for embryonic loss is at least 50 mg/kg/day. These doses were not tolerated in all monkeys. This study continues and the applicant is expanding it to evaluate a possible difference in the metabolism of norfloxacin in pregnant and non-pregnant monkeys.

Arthropathy - Lameness appeared on the second day of treatment in 3-5 month old dogs treated for seven days with doses greater than 60 mg/kg/day and persisted during treatment. Similar signs of lameness occurred in dogs given doses of nalidixic acid and pipemidic acid that were greater than 30 mg/kg/day. Lameness did not occur in norfloxacin-treated rabbits but there was blister formation on the articular cartilage in rabbits given 250 mg/kg/day or greater for seven days. In dogs, lameness was usually associated with joint lesions that were characterized by an increased amount of synovial fluid and blister formation and sometimes by erosions of the articular cartilage.

No evidence of retinal toxicity was observed in cats given doses up to 200 mg/kg/day for two weeks. However cats given nalidixic acid in doses of 100 mg/kg/day showed retinal toxicity as evidenced by electroretinographic changes (prolongation of latency and reduction amplitude) as well as histopathological changes characterized by wave-like arrangements of the outer nuclear layer.

Norfloxacin powder, 100 mg/eye, was found to be severely irritating to rabbit eyes as evidenced by conjunctival injection, discharge, and marked chemosis at 24 hours after treatment.

Serum pharmacokinetics and urinary excretion of norfloxacin suspension and tablets in single doses of 25 mg/kg were studied in three male rhesus monkeys over a period of six months. Peak serum concentrations varied from 1.12-2.35 mcg/ml at one hour. Urinary excretion was variable and ranged from 4.9 mg to 67.5 mg during the first 24 hours. Serum half-life was 165 minutes in monkeys.

The applicant concludes that there is no contraindication to the clinical administration of norfloxacin. However, norfloxacin should not be used in children or during pregnancy unless the benefits outweigh the risks.

Clinical Background:

Norfloxacin has been extensively investigated by Kyorin in Japan. Results of the Japanese studies show that norfloxacin is rapidly absorbed following oral administration. Serum concentrations after a single dose are approximately proportional to the dose in the range of 100 to 800 mg but are higher than expected at 1600 mg. Peak serum concentrations were 0.47, 0.77, 1.38, 2.33, and 9.70 mcg/ml at doses of 100, 200, 400, 800, and 1600 mg, respectively. Drug levels were measured by a microbiological technique and, therefore, include metabolites. The apparent serum half-life is approximately 4 hours and is independent of the dose up to and including 800 mg. At the 1600 mg dose, half-life was prolonged.

No accumulation of the drug in healthy volunteers was found after multiple dosing of 200 mg q 8 h for seven days. The peak serum level on the first day was approximately 0.9 mcg/ml and on the eighth day was approximately 1.0 mcg/ml. Absorption was slightly reduced in post prandial administration.

Urinary concentrations reached approximately 100 times the serum concentration in healthy volunteers. Urinary recovery was 33-48% of the dose within 24 hours after single oral doses.

Studies in five patients with biliary fistulas suggest that norfloxacin levels in bile are 5-10 times serum levels.

The major metabolite, one of six metabolites, was the 2-oxo form which accounted for 10% of the load excreted. Unchanged drug accounted for 70%.

A variety of urinary tract and systemic infections were studied by Kyorin workers but most were urinary tract infections. Outcome in a study of 949 cases is reported as follows:

<u>Diagnosis</u>	<u>No. cases</u>	<u>Treatment Success</u>
Acute, simple cystitis	469	96.2%
Simple pyelonephritis	15	93.3%
Complicated cystitis	307	83.5%
Complicated pyelonephritis	106	50.9%
Gonorrheal urethritis	14	92.9%
Nongonorrheal urethritis	21	42.9%
Prostatitis	13	61.5%
Acute epididymitis	4	100.0%

Of these, Pseudomonas aeruginosa was reported to be the pathogen in 59 and 57.6% of these were resolved with norfloxacin treatment.

Medical Officer's Comment: Adverse effects and abnormal laboratory reports in these 949 cases are not summarized. Also, the report does not say how these patients were monitored.

Clinical Studies:1. Special Studies

a) Human Pharmacology and Pharmacokinetics: The reader is referred to the Biopharmaceutics Review. Copies of Volumes 2.145-2.148 were sent to Biopharmaceutics on March 11, 1985.

(1) Study No. 1 Roger K. Ferguson, M.D., Clinical Pharmacology Unit, Thomas Jefferson Hospital, Philadelphia, PA, conducted a randomized, double-blind, single-dose escalation, placebo-controlled trial of norfloxacin by the oral route in 14 healthy adult male volunteers. Each subject received 200, 400, 800, 1200, and 1600 mg of norfloxacin in increasing order a week apart and two doses of placebo. Results are shown below.

	Single Norfloxacin Doses				
	200 mg	400 mg	800 mg	1200 mg	1600 mg
C_{max} (mcg/ml)	0.79	1.55	2.38	3.64	3.67
T_{max} (hrs)	1.1	1.1	1.4	1.7	1.8
$T_{1/2}$ (hrs)	2.18	2.19	2.29	2.39	2.48
AUC (mcg/hr/ml)	3.36	6.20	12.19	19.09	24.06
Mean 48 hr. Urinary Recovery (% of dose)	32.2	31.5	28.7	29.0	29.2

Serum levels were never higher than 6 mcg/ml. Maximum levels increased as the dose increased but did not increase in proportion to the dose escalations except at the 200 and 400 mg doses. Since the time to peak increased with higher doses, there may have been some delayed absorption as the dose increased.

The applicant reports that, "Although appreciable quantities of drug were recovered during the 24-48 hour urine collection interval, it appears that little drug would be recovered after 48 hours regardless of dose. The average total urinary recovery of MK-366 represents 30% of the dose administered at all dose levels." For a given individual, renal clearance is constant within a treatment and shows little variability between treatment. There was little change as a function of increasing dose. Renal clearance averaged 300 ml/min.

The applicant concludes that increasing the dose does not affect the total absorption although absorption is somewhat delayed at higher doses. The serum half-life is independent of the dose. The elimination of norfloxacin from serum is linear and the AUC increases in proportion to the dose. The average renal clearance is 300 mg/min. Urinary recovery is 30% in 48 hours. Norfloxacin was well tolerated.

Medical Officer's Comment: This report is incomplete because it fails to report the microscopic examinations of urine sediment examined in order to

ascertain the presence of drug crystals at the peak of the drug excretion period. When the protocol for this study was received, this was one of nine requests from FDA in the initial MOR for protocol revision. The IND was placed "on-hold" status because of this and other deficiencies. These requests were transmitted to the sponsor in a letter. The Agency also asked the sponsor to provide for the examination of urine sediment for the presence of drug crystals in subsequent pharmacokinetic studies until it could be established that drug crystallization was not a problem.

The protocol in this NDA (protocol on page 10, NDA page I-00119, Vol. 2.2) says that, "Following each act of urination, an aliquot (10 ml) of the freshly voided urine will be centrifuged and the resulting sediment examined for the presence of crystalline material." No reports of this examination can be located. Instead, the applicant tells us on page I-00142 of Volume 2.2 that, "In as much as the urinary concentrations of MK-366 can exceed the limits of drug solubility in urine at room temperature (see figure 1), thorough mixing of urine was essential prior to dispensing of urine for assay." Norfloxacin precipitation can probably be diminished by acidification of the urine.

The question as to whether norfloxacin precipitates in the urine and whether drug crystals can cause renal obstruction, as happened in dogs, has not been answered by this study.

Five subjects experienced nine episodes of adverse reactions, seven episodes followed norfloxacin dosing, and two followed placebo dosing. Adverse reactions after norfloxacin dosings were nausea, headache, tiredness, flatulence, and abdominal cramps. Abnormal laboratory values were protein in urine, increased WBC in urine, decreased platelets, elevated SGOT, decreased serum glucose, eosinophilia, and decreased hematocrit. The last two deviations were not considered to be drug related.

(2) Study No. 501 W. R. Kukovetz, Vorstand des Institute for Pharmakodynamik und Toxikologie der Universität, Universität Splatz-2, A-8010 Graz 1 Austria, conducted a double-blind, crossover, multiple-dose, placebo-controlled trial of the safety, tolerance, absorption, and excretion of norfloxacin tablets in oral doses of 200 mg three times a day for seven days in twelve healthy male adult volunteers. Treatments for each volunteer were separated by a six-day crossover interval. (The control number for norfloxacin tablets was SOY9890A and the control number for placebo was SOY9890P.)

Three of the twelve subjects experienced the following three adverse reactions after taking norfloxacin: tiredness - 3 subjects, and burning sensation upon voiding - one subject. Five of these reactions appeared on the third day. Two placebo subjects reported tiredness, one of these two had diarrhea.

Serum and urine levels of antimicrobial activity cannot be attributed to norfloxacin alone since the microbiological activities of six metabolites are included in the measurement.

Serum levels were below detectable limits in nearly 60% of the serum samples. Trough levels on the second and eighth days did indicate that antimicrobial activity was accumulating in serum on this eight-hour regimen. Following the last dose, antimicrobial activity persisted in serum for at least four hours with detectable levels in 75% of serum samples. On either the first or the eighth day, serum levels of antimicrobial activity rarely exceeded 1.0 mcg/ml equivalents and were generally near the sensitivity limits of the assay (0.1 mcg/ml).

The amount of antibiotic activity noted for urinary recovery at eight hours after the last dose is nearly twice that found after the first dose. Individual renal clearance appeared constant within a treatment and did not change from the first day to the eighth day. Clearance generally exceeded 400 ml/min. Urine levels of antimicrobial activity were 20 mcg/ml equivalents or higher for approximately 2-3 hours after the first dose and 5-8 hours after the last dose.

A significantly lower mean supine diastolic blood pressure was observed on the fifth day at zero hour for patients on norfloxacin than for those on placebo. Small but significant changes from pretreatment in lymphocytes, monocytes, and basophils were observed for norfloxacin and in WBC, basophils and SGPT for placebo. Significant differences between treatment were observed in lymphocytes, monocytes, and basophils.

The applicant concludes that norfloxacin in doses of 200 mg t.i.d. for seven days is safe and well tolerated.

(3) Study No. 661 Bernard K. Martin, Ph.D., BIOS (Consultancy & Contract Research), Ltd., Pinewood, College Ride, Bagship, Surrey, England, conducted an uncontrolled, single-dose study of pharmacokinetic parameters of norfloxacin in six healthy, elderly volunteers. Subjects were between 67 and 74 years of age. Each subject received one 400-mg film-coated tablet.

Norfloxacin was well tolerated in all subjects. There were no adverse reactions. After a short lag period of 20 minutes, the drug was rapidly absorbed, reaching a mean peak plasma concentration of 2 mcg/ml approximately 1.5 hours after administration.

Highest urine concentrations occurred between two and four hours after dosing and ranged from 79.5 to 254.1 mcg/ml for the six subjects.

The applicant reports that pharmacokinetic parameters indicate elimination of norfloxacin may be slightly reduced in the elderly. This results in small increases in plasma levels and may also result in small increases in drug half-life. Changes in norfloxacin disposition appear attributable to the slightly reduced renal function associated with a normal elderly population. No alteration of dosing regimen appears necessary for elderly subjects whose renal function is normal for this age group (creatinine clearance equal to or greater than 70 ml/min/1.73 m²). The applicant concludes that a single 400 mg tablet of norfloxacin appears safe in healthy, elderly subjects.

b. Safety and Tolerance

(1) Study No. 45 Miguel A. Zinney, M.D., Assistant Professor of medicine at Tufts University School of Medicine, and with Medical and Technical Research Assoc., Inc., Clinical Unit, Jamaica Plain, MA 02194, conducted a randomized, double-blind, multiple-dose, crossover study of norfloxacin and placebo to measure pharmacokinetic parameters and tolerance. Twenty-seven healthy adult volunteers (24 males and 3 females) received either a 400-mg film-coated tablet of norfloxacin q 12 h or placebo for 14 days. There was a seven-day crossover interval.

The applicant reports that nineteen volunteers experienced at least one adverse clinical experience during the course of the study, while on norfloxacin, 5 while on placebo, and 7 while on both regimens. No reactions were considered serious. The most common were central nervous system adverse reactions - 13 (11 of whom reported headache), respiratory tract adverse reactions - 6, and digestive tract reactions - 6. Norfloxacin was discontinued in three male volunteers because of adverse effects and one volunteer did not ingest one placebo dose.

All 27 subjects completed diary sheets for reporting adverse reactions.

Sixteen subjects had at least one adverse laboratory report. The most common were low WBC counts followed by high WBC counts, low hematocrits, and differential WBC's out of range.

Concentrations of norfloxacin in urine averaged 30 mcg/ml or higher during each dosing interval. Cumulative renal clearances ranged between 240 and 330 ml/min from one dosing interval to the next dosing interval. Mean peak plasma norfloxacin concentrations were 1.15, 1.18, 1.27, and 1.35 mcg/ml following the first dose given on Days 1, 2, 7, and 14, respectively. Peak plasma concentrations occurred between 1.5 and 2 hours after the dose while the mean trough concentration determined at 12 hours was 0.12 mcg/ml after the first drug dose. It fluctuated between 0.15 and 0.23 mcg/ml, thereafter. Steady-state conditions were established on a 12-hourly norfloxacin regimen between 2 and 7 days of drug administration.

"There were no norfloxacin crystals found in the urine at 1 to 2 hours post norfloxacin and placebo dosing."

Reviewer's Comment: The report does not say whether drug crystals or crystals of the metabolites were found in other specimens of urine sediment anytime during the study.

The applicant concludes that norfloxacin, when administered twice daily to subjects with normal renal function, produces serum levels 12 hours after dosing on Days 2, 7, and 14 that are similar. Steady state is attained between 2 and 7 days after the beginning of a 400 mg q 12 h schedule. This dose appears to be safe and well tolerated.

Medical Officer's Comment: The medical officer's summary of the positive entries in the 27 patient diaries in this study is shown below:

Norfloxacin

- #3 Sleepy - Day 2. Sluggish after second dose - Day 3. "Clog-noise" and sneezing - Days 5 & 8. Headache - Day 6. Cough - Day 10.
- #8 Headache 1 hr. after dosing for 2 hrs. - Day 1. Massive headache - Day 9.
- #10 Headache 1/2 hr. after first dose for 1 1/2 hrs. - Day 1. Cold - Days 3-4.
- #12 Headache - Day 7.
- #15 "I thought I felt something from the drug, could be psychosomatic, I think" - Day 1. Tired - Day 9, Sleepy - Day 10.
- #16 Tired - Day 5.
- #19 Headache - Day 1. Headache and tension - Day 13.
- #20 Sleepy - Day 1. Dizzy and sleepy - Day 4. Cold - Day 10. Lump in throat - Days 11 and 13-14.
- #21 "Not myself today" - Day 6. Headache - Day 7. Nausea - Day 10.
- #22 Diarrhea - Day 3. Tired - Day 7.
- #23 Headache - Days 4-5. Nausea, sleepy, lightheaded, and dizzy - Day 5. Lightheaded - Day 6. Head swirling - Day 10.
- #27 Cold - Day 6.

Placebo

- #10 Cold symptoms - Day 8
- #11 Headache after dosing for 2 hrs - Day 1. Headache for 30 minutes - Day 2. Headache for 15 minutes - Day 8.
- #21 Tired - Day 1. Headache - Day 6. Nausea & stomachache - Day 9.
- #22 Sour stomach - Day 12.
- #24 Chills and fever, draining sinuses, headache, and dizziness - Day 6. Sore throat - Days 7 & 11.
- #25 Metallic taste in mouth - Day 1. Fever and headache - Day 2. Depressed and suffering from needle withdrawal - Day 7. Headache - Day 9. "I have a strong need for some "coffee" - Day 14.
- #26 Drowsy - Day 1. Soreness in limbs and abdominal pain - Day 2.
- #27 Headache and itching - Day 1. Tired and itching - Day 2. Tired - Day 13. Headache - Day 14.

According to the patient diaries, twelve of 27 subjects (44%) reported one or more adverse reactions while on norfloxacin and 8 of 27 subjects (29.6%) reported one or more adverse reactions while on placebo. This difference is not statistically significant.

(2) Study No. 66 Miguel A. Zinny, M.D., above, conducted a second randomized, double-blind, multiple-dose, crossover pharmacokinetic study. In this study subjects received either placebo or 400 mg q 8 h for 5 days (instead of q 12 h for 14 days). Twenty-six healthy adult subjects participated, one was a female. Only four participated in the pharmacokinetic phase of the study. Subjects completed diary sheets.

The applicant reports that six volunteers experienced adverse clinical

effects: two while on norfloxacin, three while on placebo, and one while on both regimens. None were serious or drug related. One subject had an abnormal laboratory report. These reports followed placebo treatment and were elevations in SGOT and alkaline phosphatase.

Pharmacokinetic parameters are summarized as follows:

	Day 1 (Dose 1)	Day 2 (Dose 4)	Day 5 (Dose 13)
Mean C_{max} (mcg/ml)	1.50	1.73	1.49
Mean C_{min} (mcg/ml)	0.36	0.52	0.44
8-hr AUC (mcg/hr/ml)	6.34	7.79	7.04

Concentrations of norfloxacin in the urine averaged 30 mcg/ml or higher for the duration of each dosing interval. No drug crystals of norfloxacin were found in the urinalysis samples or in the 1-2 hour filtered voidings obtained from the four volunteers who participated in the pharmacokinetic arm of the study.

Neurological examinations were normal.

The applicant concludes that norfloxacin at a dose of 400 mg q 8 h is safe and well tolerated. Too few volunteers (4) participated in the pharmacokinetic phase of this study to demonstrate to what degree norfloxacin accumulation might occur on a 400 mg q 8 h regimen.

Medical Officer's Comment: There is a difference between the investigator's report of the presence of adverse reactions and the patient's report as recorded on the 26 patient diaries. A few of the differences are listed below:

Case No.	Investigator	Patient's Diary
<u>Norfloxacin</u>		
#102	None	Headache after dosing - Day 1. Headache continues, unable to concentrate on newsprint, lassitude, lightheaded and weak when standing. Impaired vision - Day 2. Same but greatly reduced - Day 3. Very mild residual symptomatic effects - Day 4. Moderate headaches - Day 5.
#103	None	Tired this morning - Day 1. Tired again today - Day 2.
#104	None	Feeling good with slight mild headache in back of head - Day 1. Same as yesterday with mild headache in back of head - Days 2-3. Feeling fine with small headache - Day 4. The effect of second week of study pills, effect was the same

as first but milder with headaches, tiredness and seemed to accept them better each day - Day 5.

- #105 Sclera ery-
thematosus rt
xl-2 days Sleepy - Day 1. Sleepy and coughing up phlegm - Day 2. Sick to my stomach this morning, sleepy, also, but after lunch felt fine - Day 3.
- #106 None Mild headache today from 1:00 PM to 8:00 PM - Day 4. Felt good today except mild upset stomach from 6:00 PM until 9:00 PM. Otherwise good and no side effects - Day 5.
- #107 None Slight stomachache this afternoon Day 5.
- #112 None Slight headache continuing until 3:00 PM. Slacked off at that time - Day 1. Sleepy most of the day but otherwise I felt well. Am still slightly drowsy at present time (10:00 AM) - Day 2. Drowsy, slight headache until noon. Left at that time, and felt better by 5:30 - Day 4. Very sleepy all day. Still drowsy now at 10:00. Otherwise, I felt in the best of health - Day 5.
- #116 None Lightheadedness - Days 1-5.
- #118 None Very tired and sleepy and very bad headache - Day 1. Very tired and sleepy and was very drowsy and had a small headache - Day 2. Tired, drowsy, headache - Day 3. Tired, drowsy, and very bad headache - Day 4. Tired, drowsy, and small headache - Day 5.
- #120 None Today I felt a little flush in the face with a monotonous headache - Day 1. Headache, a minor one - Day 2. Minor headache - Day 3. Had another one of these headaches but I felt that sleep would remedy the situation by sleeping it off and it really worked - Day 4. No headache but had a little upset stomach - Day 5.
- #122 None Tired - Days 1-2 and 4.
- #123 None Didn't feel any side effects, just dry lips - Day 1. Felt a little cramp in right side - Day 2. Felt a little numb in fingers and hands. A little tired but good - Day 3. A little pain in belly but not bad, outside of fever from cold that everyone has had - Day 4.
- #126 None I have been a little drowsy most of the day and evening but other than that I feel fine as usual - Day 1. I am not so tired or sleepy today and no other problems or side effects - Day 2.

Same as yesterday - Day 3. Same as last 2 days - Day 4..

Placebo

- #103 None Tired this morning - Day 1. Sleepy morning - Day 2. Tired all day, tired AM, all right PM - Day 5.
- #104 None Headache all day - Day 1. Milder headache - Day 2. Headache and very tired - Day 3. Headache gets less and less and still very tired within two hours of taking pills, headache seems to be in temple area- Day 4. Headache and tiredness - Day 5.
- #105 Sclera erythematous rt eye 1-2 days Sleepy and slight headache - Day 1. Right eye is sore and slightly red - Day 3.
- #112 None Tired and listless in the morning - Day 2. Have felt hyperactive all day - Day 3. Had a slight headache this afternoon but it quit bothering me after a little sleep - Day 4.
- #118 None Headache and very tired - Day 1. Headache and very tired - Day 2. I did not feel very good today because I had a headache and was very tired - Day 3. Very bad headache and not very tired - Day 4. Headache - Day 5.
- #120 None Slight headache. Subsided and felt very tired - Day 1. Slight headache but it subsided at a later time - Day 3.
- #122 None Slight headaches on & off, tired - Day 2. Slight headaches on & off, tired, weight gain - Day 3. Still a bit tired - Day 4. Still tired - Day 5.

The MO's tally shows that 13/26 (50%) of norfloxacin-treated subjects and that 7/26 (27%) of placebo-treated subjects reported one or more effects in their diaries. The difference in rates is not statistically significant but is suggestive of a difference ($p = 0.089$).

In the applicant's summary for these same cases, the applicant reports the following seven adverse events:

Case #108 (Norf.) - Night sweats	Case #102 (Placebo) - Frontal headache
Case #109 (Norf.) - Vomiting	Case #105 (Placebo) - Erythematous sclera with mild pruritis
Case #125 (Norf.) - Pediculosis	Case #109 (Placebo) - Headache
	Case #121 (Placebo) - Cold symptoms

These differences show underreporting of adverse reactions by the investigator and the applicant.

c. Bioavailability

(1) Study No. 13 Miguel A. Zinney's third study was a randomized, three-way crossover-type, single-dose bioavailability study to compare a 200-mg tablet and a 400-mg tablet with a solution containing 430 mg of norfloxacin. The solution was given by a nasogastric tube. Fifteen healthy adult male volunteers participated.

Relative bioavailability ratios were 0.89, 0.90, and 1.0 for the 200 mg-tablet/430 solution, 400-mg tablet/430 mg solution, and 200-mg tablet/400 mg tablet, respectively.

	430-mg sol.	200-mg tab.	400-mg tab.
Mean 48-hr Urinary Recovery % of Dose	121.9 mg 28.38%	52.15 mg 25.45%	105.14 mg 26.48%
Mean 8-hr AUC (mcg/hr/ml)	6.04	5.57	5.44
Mean cumulative renal clear- ance (ml/min)	276.37	263.39	299.26
Mean C _{max} (mcg/ml)	1.87	1.60	1.62
Mean T _{max} (hr)	0.70	1.03	1.03
Mean half-life (hr)	2.99	3.26	3.32

Peak fecal concentrations of norfloxacin-like antimicrobial activity ranged from 144 mcg to 2715 mcg of norfloxacin per gram of feces. While this was the range, most of the 13 volunteers who had bowel movements within 48 hours of drug administration had peak fecal norfloxacin-like antimicrobial activity levels of between 200-750 mcg/gm of feces.

The applicant reports that there was only one adverse clinical effect, soreness of the rectum in one subject. Neurologic examinations performed by a neurologist, and ophthalmologic examinations including tests for visual acuity, field defects, color vision and funduscopic examinations, showed no abnormalities or changes from baseline tests.

The applicant concludes that after the first half-hour after dosing, the tablets show similar bioavailability to each other and to the solution with serum levels and urinary recovery being directly proportional to the dose. All three formulations appear safe.

Medical Officer's Comments:

1. Although the medical officer asked for diaries in pharmacokinetic studies, diaries were not kept in this study. The report that there was only one adverse effect cannot be accepted to mean that other adverse reactions did not occur. It is accepted to mean that the investigator was only aware of one reaction. The differences between the diaries and this investigator's report in the study above (Study No. 66) confirm this

conclusion.

2. The presence or absence of crystals in urine sediment is not addressed in the applicant's narrative. However, Table 14 on pages I-00890-I-00896 shows that non-amorphous crystals per HPF were present as follows:

	Pre		Post		Sign. difr.
	No. cases	%	N. cases	%	
200 mg tablet	3/15	20.0%	3/15	26.7%	NS
400 mg tablet	1/15	6.7%	2/15	13.3%	NS
430 mg solution	4/15	26.7%	6/15	40.0%	NS

It is not known whether these were drug crystals.

(2) Study No. 55 Miguel A. Zinny, M.D. conducted a fourth study. This was a randomized, two-way crossover bioavailability study of single doses of the new 400-mg Merck Sharp & Dohme tablet and the old 400-mg Kyorin tablet. Twenty healthy adult male volunteers participated. There was a one week crossover interval.

Nineteen of the 20 subjects completed diary sheets. None of the comments noted on these diary sheets were assessed by the investigator as adverse experiences. There were no adverse experiences reported by the investigator.

The applicant summarized diary sheet data as follows:

Case #	Period 1 New MSD tab	Period 2 Old Ky. tab	Case #	Period 1 New MSD tab	Period 2 Old Ky. tab
51	Fine	Fine	52	Sleepy	Sleepy
53	Fine	All right	54	OK	Good
			56	OK	OK
58	Lightheaded	Lightheaded	57	No problems	Great
60	Very good	Good	59	Lack of energy	Fine
61	Fine	OK	62	Fine	Fine
63	Drowsy and tired then normal	Normal then tired	64	Normal	Fine
66	Fine	Fine	65	Normal, dry lips	Normal
68	Fine	Fine	67	Dry mouth	Fine
69	Fair	Fine	70	Foggy, tired headache	Fine

Two subjects had an elevated SGOT report.

No crystals of norfloxacin were found in any of the examined urine specimens collected from volunteers who participated in this study. The observation applies to all urine collected for screening before and after the study and to all urine collected through the 48 hours after the dose during the study.

	New MSD tab	Old Ky. tab
Mean Urinary Recovery % of Dose	117.43 mg 27.74%	106.55 mg 26.72%
Mean AUC mcg/hr/ml X hr	7.71	6.90
Mean cumulative renal clear- ance (ml/min)	266.10	269.98
Mean C _{max} (mcg/ml)	1.56	1.54
Mean T _{max} (hr)	1.35	1.07

The new norfloxacin formulation is 94% as bioavailable as the old formulation.

Stool specimens were collected for assay from 18 subjects. Norfloxacin activity was found in stool specimens after the first two hours. Peak concentrations occurred between 12 and 24 hours and ranged from 1,212.17 to 1,916.13.

The applicant concludes that norfloxacin is similarly bioavailable from both 400-mg tablets. Norfloxacin was absorbed faster following the ingestion of tablets manufactured by the new MSDRL process.

Medical Officer's Comments:

1. Diaries from this study cannot be included as part of the minimum 100 diaries that FDA requires for the quinolones because this was a single-dose study. We asked for at least 100 diaries following multiple doses from the longest recommended treatment period.

2. According to the diaries, six of 19 subjects (32%) reported side effects while on the new MSD tablet and three of 19 subjects (18%) reported side effects while on the Old Kyorin tablet.

d. Renal Function

Study No. 576 Prof. A. William Asscher, Welsh National School of Medicine, Renal Unit - Royal Infirmary, Cardiff, Wales, conducted a pharmacokinetic study of single 400-mg oral doses of norfloxacin in patients with varying degrees of renal dysfunction and in subjects with normal renal function. Twenty males and seven females were assigned to four groups based on glomerulo-filtration rate assessed by creatinine clearance as follows:

- Group I (normal renal function) - GFR greater than 100 ml/min/1.73 m²
- Group II (mild renal impairment) - GFR 31-60 ml/min/1.73 m²
- Group III (moderate impairment) - GFR 10-30 ml/min/1.73 m²
- Group IV (severe renal impairment) - GFR less than 10 ml/min/1.73 m²

Urinary recovery and renal clearance of norfloxacin were similar for Groups I and II, but were significantly decreased for Groups III and IV. Mean urinary

recoveries of norfloxacin were 27, 34, 5 and 2% of the dose administered for Groups I to IV, respectively, while mean renal clearances were 280, 254, 17, and 11 ml/min. Peak serum concentrations and time to peak were similar among the groups. Observed differences in total AUC appeared to arise from differences in serum concentrations beginning at about 4 hours after dosing. Mean total AUCs were 7, 9, 20, and 13 mcg/hr/ml for Groups I to IV, respectively. Groups I and II were significantly different from Group III, and Group I was different from Group IV ($p = 0.06$). Groups I and II had significantly shorter mean serum half-lives (3.5 hours) compared to Groups III and IV.

The applicant reports that there were no adverse experiences during this study.

The applicant concludes that a single 400 mg dose of norfloxacin appears to be safe in renally-impaired patients. Based on the renal elimination rate of norfloxacin, no change is needed in the dosing regimen for subjects whose GFR exceeds 30 ml/min/1.73 m². When the rate is 30 ml/min/1.73 m² or greater, the regular dose should be given once a day rather than twice a day.

2. Controlled Clinical Efficacy Studies

(a) Protocol No. 001 Domestic Multiclinic Study of Uncomplicated Urinary Tract Infections

A randomized, controlled, multiclinic trial to compare norfloxacin and trimethoprim-sulfamethoxazole (TMP-SMZ) in the treatment of uncomplicated urinary tract infections in adults was conducted at five clinical centers. The following investigators participated in this trial and treated the number of patients shown:

Study No. 3 Charles E. Cherubin, M.D., Chief, Microbiology Laboratories, Jewish Hospital of Brooklyn, 555 Prospect Place, Brooklyn, NY 11238. (Qualified for efficacy evaluation: 6/7 norfloxacin patients and 3/3 TMP-SMZ patients.)

Study No. 6 Clair E. Cox, M.D., College of Medicine, Dept. of Urology, University of Tennessee, 956 Court Avenue, Box 10, Memphis, TN 38163. (Qualified for efficacy evaluation: 22/23 norfloxacin patients and 22/22 TMP-SMZ patients.)

Study No. 7 Ellie J. C. Goldstein, M.D., 11980 San Vincente Blvd., Suite 103, Los Angeles, CA 90049. (Qualified for efficacy evaluation: 21/23 norfloxacin patients and 22/22 TMP-SMZ patients.)

Study No. 2 Anthony J. Schaeffer, M.D., Northwestern University, The Medical School, Ward Memorial Bldg., 303 E. Chicago Avenue, Chicago, IL 60611. (Qualified for efficacy evaluation: 21/25 norfloxacin courses and 20/25 TMP-SMZ patients.)

Study No. 5 Richard L. Sweet, M.D., Room 6J2, San Francisco General Hospital, 1001 Potrero Avenue, San Francisco, CA 94110. (Qualified for efficacy evaluation: 2/6 norfloxacin patients and 0/7 TMP-SMZ patients.)

(Jack L. LeFrock, M.D., Hahnemann Medical College, Hospital of Philadelphia, 230 N. Broad Street, Philadelphia, PA 19102. Dr. LeFrock did not admit any patients into the study and the study was suspended.)

Norfloxacin-treated patients in Studies Nos. 2, 3, and 5 received four 100-mg tablets twice daily for seven to ten days. Patients in Studies Nos. 6 and 7 received two 200-mg tablets twice daily. These studies were initiated at a time when the 100 mg tablets were no longer being produced.

Ambulatory patients with a diagnosis of uncomplicated urinary tract infection were selected. Clinical symptoms included dysuria, frequency, urgency, etc. of less than one week's duration prior to therapy. All patients were required to have a positive urine culture within 48 hours prior to initiation of therapy. A colony count by either the pour plate or streak method was obtained and uropathogens were speciated. Patients received a history and physical examination that included visual acuity tests, examination of the eye, and tests of neurological function. Ophthalmological and neurological tests were repeated when the patient returned at one week after treatment. Routine follow-up evaluations were made again at 4-6 weeks after the completion of therapy. Urine specimens for culture were obtained during the first 48-72 hours of therapy, 5-9 days after completion of therapy, and 4-6 weeks after completion of therapy. Vaginal-vestibular and anal cultures were optional. Laboratory studies included routine hematology, blood chemistry, and urinalyses which included microscopic examination of the urine sediment for the presence of crystals,

Exclusions included patients with a history of allergy to nalidixic acid, oxolinic acid, trimethoprim, or any sulfa drug; patients under 21 or over 75 years of age; patients with a temperature greater than 101°F, flank pain, chills or any other manifestation suggestive of upper urinary tract infection; patients with complicated UTI; comatose patients or those with a high probability of death; patients with impaired renal function; patients with serious concurrent infections; patients with resistant uropathogens; patients on or just completing other antimicrobial therapy; patients with indwelling urinary bladder catheters; and patient with a history of visual disturbance or psychiatric or CNS illness.

The clinical outcome categories were: cured, improved, did not improve, and other. The bacteriological outcome categories were eradication, suppression, and persistence. Suppression and persistence were considered to be bacteriological failures. The investigator also noted the presence of colonization, superinfection, and at 4-6 weeks, relapse and reinfection.

Guidelines for susceptibility or resistance in all studies are

	Disc Diffusion Zone Size	MIC
Susceptible	17 mm or greater	Greater than 16 mcg/ml
Intermediate	13-16 mm	
Resistant	12 mm or less	Under 16 mcg/ml

Intermediate zone sizes were considered as susceptible for urinary tract pathogens.

In this study, 160 patients received 163 courses, 81 patients received norfloxacin and 79 patients received TMP-SMZ. Only the first entries of the three patients who were treated more than once were counted in the analysis of data. Of the 160 patients, there were 136 evaluable cases, 69 norfloxacin cases and 67 TMP-SMZ cases.

Reasons for Efficacy Disqualification

	Norfloxacin	TMP-SMZ
Causative pathogen not proven	4 (33%)	7 (58%)
Other effective treatment	2 (17%)	0
Course too short	1 (8%)	1 (8%)
Inadequate cultures	5 (42%)	4 (33%)

Characteristics for evaluable patients are shown in the following table:

Age (yrs.)	Norfloxacin			TMP-SMZ		
	Males	Females	Total	Males	Females	Total
18-21	1	2	3		4	4
22-30	2	22	24		25	25
31-40		11	11	2	11	13
41-50	2	5	7	1	3	4
51-60	1	7	8		3	3
61-70	3	7	10	7	6	13
71-80	2	1	3	3	1	4
81-90	2	1	3		1	1
Total No.	13	56	69	13	54	67
Mean Age	56.5	39.3	42.6	61.3	36.5	41.2
Minimum	19	20	19	35	19	19
Maximum	82	81	82	75	82	82

The primary diagnosis was cystitis for about 95% of patients in each treatment group. Four patients had pyelonephritis, three had urinary tract infections not otherwise identified, two had vaginitis, and one had leukocyturia. There was a secondary diagnosis for 42% of norfloxacin-treated patients and for 46% of control patients. Other non-antimicrobial drugs were given to 23% in the norfloxacin group and 31% in the TMP-SMZ group. The mean length of therapy was 10.7 and 10.4 days for the norfloxacin and TMP-SMZ groups, respectively. Roughly, just over one-third of the number in each group were minority.

Of all pathogens tested, 100% (148/148) were susceptible to norfloxacin and 95% (140/148) were susceptible to TMP-SMZ. The eight pathogens which were not susceptible to both drugs were 3/123 E. coli strains and 5/5 P. aeruginosa strains.

Clinical outcome for evaluable patients is shown below:

Diagnosis	Norfloxacin				TMP-SMX			
	Cured	Impro- ved	Not Impro- ved	# Pts	Cured	ved	Not Impro- ved	# Pts
UTI Lower or Upper	65	1	2	68	63	1	1	65
UTI, NOS	1	0	0	1	2	0	0	2

The percentage of patients who were cured or improved was 97% (67/69) in the norfloxacin group and 99% (66/67) in the TMP-SMZ group.

Bacteriological outcome for evaluable patients is given below (number eradicated/number isolated):

Pathogen	Norfloxacin	TMP-SMZ
<u>Staphylococcus aureus</u>	2/2	0/0
<u>Staphylococcus saprophyticus</u>	1/1	0/0
<u>Citrobacter species</u>	0/0	1/1
<u>Citrobacter diversus</u>	1/1	0/0
<u>Enterobacter aerogenes</u>	0/1	2/2
<u>Enterobacter agglomerans</u>	1/1	0/0
<u>Enterobacter cloacae</u>	1/1	0/0
<u>Escherichia coli</u>	53/54	58/58
<u>Klebsiella pneumoniae</u>	2/2	3/3
<u>Proteus mirabilis</u>	3/3	1/1
<u>Pseudomonas aeruginosa</u>	4/5	0/0
<u>Pseudomonas fluorescens</u>	0/0	1/1
Total	67/69 (97%)	66/66 (100%)

Adverse clinical and laboratory experiences for all patients are shown below:

Adverse Reactions	Norfloxacin		TMP-SMZ	
	No.	No. Discon- tinued	No.	No. Discon- tinued
Drug Related				
Dyspepsia	1		0	
Nausea, headache, & insomnia	1	1	0	
Total	2 pts			
Not Drug Related				
Pain and insomnia	1	1	0	
Headache	1		3	1
Dyspepsia	1	1	0	
Nausea and anorexia	0		1	
Nausea	0		1	
Diarrhea	0		1	
Total	3 pts		6 pts	
No. pts with AR	5 pts		6 pts	
Total No. Patients	81		79	

Abnormal Laboratory Effects	Norfloxacin No.	TMP-SMZ No.
Drug Related	0	0
Not Drug Related		
WBC Count	0	1
Segmented neutrophils and elevated lymphocytes	1	0
Alanine transferase	0	1
Total	1	2
No. Patients	81	79

The applicant reports that there were no serious adverse reactions or laboratory abnormalities. No changes were found in ophthalmologic and neurologic examinations.

The applicant concludes that all 148 isolates were susceptible to norfloxacin and it was highly effective in the treatment of uncomplicated urinary tract infections. It was well tolerated and safe. The efficacy, safety and tolerance of norfloxacin and trimethoprim/sulfamethoxazole are similar.

Medical Officer's Comments:

1. Since the presence or absence of crystalluria was not addressed in the applicant's summary, the medical officer reviewed each case report form to observe the presence of crystals in the optional during therapy (48-72 hour) urine specimen. Nonamorphous crystals were reported for 0/38 specimens in the norfloxacin group and for 3/31 specimens in the TMP/SMZ group. Urine sediment was examined microscopically for an additional six norfloxacin and five TMP/SMZ specimens but no entry was made for the presence or absence of crystals. There was no laboratory sheet for one norfloxacin patient (Case No. 117). There was no during therapy laboratory report for the remaining patients in each group.

2. No conclusion can be drawn regarding adverse reactions since adverse reactions are best analyzed from patient diaries. No diaries were reported for this study.

(b) (1) Protocol No. 002 Domestic Multiclinic Study of Complicated and Uncomplicated Urinary Tract Infections

A randomized, controlled multiclinic trial of norfloxacin and trimethoprim-sulfamethoxazole (TMP-SMZ) in the treatment of uncomplicated and complicated urinary tract infections was conducted at five clinical centers. The following investigators participated in this trial and treated the number of patients shown:

Study No. 11 O. Thomas Bolding, M.D., Medical Director, Bolding Research Foundation, Inc., 2022 Brookwood Medical Ctr. Dr., Birmingham, Alabama. (Qualified for efficacy evaluation: 3/8 norfloxacin patients and 1/4 TMP-SMZ patients)

Study No. 8 R. H. K. Eng, M.D., Medical Service (111), V. A. Medical Center, East Orange, NJ. (Qualified for efficacy evaluation: 10/14 norfloxacin patients and 9/14 TMP-SMZ patients)

Study No. 10 Lloyd H. Harrison, M.D., Assistant Professor Dept of Urology, Bowman Gray School of Medicine, Winston-Salem, NC. (Qualified for efficacy evaluation: 24/29 norfloxacin patients and 21/28 TMP-SMZ patients)

Study No. 12 Ralph R. Landes, M.D., Danville Urology Clinic, Danville, VA. (Qualified for efficacy evaluation: 35/62 norfloxacin patients and 15/30 TMP-SMZ patients)

Study No. 9 J. L. Ryan, M.D., Ass't Professor Department of Internal Medicine, Yale University School of Medicine, New Haven, CT. (Qualified for efficacy evaluation: 7/13 norfloxacin patients and 8/11 TMP-SMZ patients)

Male or female patients 18 years of age or over with symptomatic uncomplicated or complicated urinary tract infections were selected. Women of childbearing potential were excluded at the beginning of the study but were allowed later in the study. Patients were required to have a positive urine culture within 48 hours prior to initiation of therapy. Exclusions were the same as those given in the previous study except that patients with symptoms suggestive of upper tract infections were included. FDA's guidelines for the study of urinary tract infections were followed. This study was similar to the one described above.

Patients received either two 200 mg tablets of norfloxacin two times a day orally or two tablets of trimethoprim-80 mg with sulfamethoxazole-400 mg twice a day orally. Treatment was to be 7 to 30 days. Drugs were dispensed in unit doses to hospitalized patients and, for outpatients, in pre-labeled bottles containing enough for a 14-day course. The investigator dispensed supplemental drug if therapy beyond 14 days was deemed clinically appropriate.

Drs. Bolding and Landes' studies were designed to admit twice as many norfloxacin as TMP-SMZ patients. There were 213 treatment courses for 210 patients, 124 of whom were treated with norfloxacin and 86 of whom were treated with TMP-SMZ. Where more than one course was given, only the first course is included in the efficacy analysis. A total of 133 patients were evaluated for efficacy, 79 in the norfloxacin group and 54 in the TMP-SMZ group.

Reasons for Efficacy Disqualification

	Norfloxacin	TMP-SMZ
Causative pathogen not proven	26	18
Course too short	2	4
Inadequate cultures	17	10
Total Disqualified	45 (34%)	32 (37%)
Qualified	79	54

Characteristics of evaluable patients are shown in the following table:

Age (yrs.)	Norfloxacin			TMP-SMZ		
	Males	Females	Total	Males	Females	Total
No data	1		1			
1-17	1	1	2		1	1
18-21	1	5	6		8	8
22-30	1	25	26		17	17
31-40	3	12	15	4	11	15
41-50	2	8	10	1	8	9
51-60	7	9	16	10	4	14
61-70	10	12	22	8	6	14
71-80	3	8	19	5	1	6
81-90	2	5	7	1	1	2
Total No.	39	85	124	29	57	86
Mean Age	59.8	45.0	49.6	59.2	37.5	44.8
Minimum	13	17	13	34	17	17
Maximum	86	87	87	83	81	83

Most patients in the two treatment groups had urinary tract infections which were uncomplicated, of moderate intensity, and were caused by a single pathogen. Seventy percent of the norfloxacin group and 64% of the TMP-SMZ group had some other disease, about half had had prior drug therapy, and 44% and 30%, respectively, had concomitant procedures. The mean duration of therapy was 12 days for norfloxacin and 10 days for TMP-SMZ.

The two treatment groups were significantly different with respect to several characteristics. There were more Caucasians, patients with complicated UTIs, patients with polymicrobial infections, patients with concomitant procedures, and patients with prior drug therapy in the norfloxacin group than in the TMP-SMZ group. Only one of these parameters, prior drug therapy, was related to the percentage of patients cured or improved, in that, regardless of treatment group, evaluable patients with prior drug therapy had a significantly lower response rate (80%) than those without prior drug therapy (94%).

Clinical outcome for evaluable patients is shown below:

Diagnosis	Norfloxacin				TMP-SMX			
	Cured	Not Impro- ved	Not Impro- ved	# Pts	Cured	Not Impro- ved	Not Impro- ved	# Pts
<u>Applicant</u>								
Upper UTI	13	1	3	17	4	1	2	7
Lower UTI	53	3	6	62	38	2	7	47
<u>Medical Officer</u>								
Upper UTI	13	1	3	17	4	1	2	7
Lower UTI	53	3	5	61	38	2	6	46

Bacteriological outcome or evaluable patients is given below (number eradicated/number isolated):

Pathogen	Applicant		Medical Officer	
	Norfloxacin	TMP-SMZ	Norfloxacin	TMP-SMZ
<u>Corynebacterium</u>	0/1		0/1	
<u>Staphylococcus</u>		1/1		1/1
<u>S. saprophyticus</u>		1/1		1/1
<u>Staphylococcus epidermidis</u>	3		3/3	
<u>Streptococci (Grp B)</u>	1/1	1/1	1/1	1/1
<u>Streptococci (Grp D)</u>	6/7	0/1	6/7	0/1
<u>Strep. (Grp D enterococci)</u>	3/3	0/1	3/3	0/1
<u>Strep., alpha hemolytic</u>		1/1		1/1
<u>Citrobacter species</u>	1/1		1/1	
<u>Citrobacter freundii</u>	2/3		2/3	
<u>Enterobacter</u>		1/1		1/1
<u>Enterobacter aerogenes</u>	1/1	1/2	1/1	1/1
<u>Escherichia coli</u>	38/38	27/32	37/37	27/32
<u>Klebsiella pneumoniae</u>	7/10	7/7	7/9	7/7
<u>Morganella morganii</u>	1/1	1/1	1/1	1/1
<u>Proteus vulgaris</u>	1/1		1/1	
<u>Proteus mirabilis</u>	7/7	5/6	7/7	5/6
<u>Providencia rettgeri</u>	2/2		2/2	
<u>Pseudomonas aeruginosa</u>	11/13		11/12	
<u>Lactobacillus</u>	1/1		1/1	
Total strains eradicated	85/93	46/55	84/90	46/54
Percent	(91.3%)	(83.6%)	(93.3%)	(85.1%)
Number Qualified Pts.	79	54	77	53

The differences between the two bacteriological outcome rates and the two clinical outcome rates are not statistically significant.

All 210 patients who received the study drugs were analyzed for safety. The duration of treatment ranged from one to 49 days for norfloxacin and one to 21 days for TMP-SMZ. The percentage of single entry patients with any adverse clinical experience was significantly greater in the TMP-SMZ group (10.5% or 9/86) than in the norfloxacin group (1.6% or 2/124), as was the percentage with any adverse laboratory experience (5.8% or 5/86, vs. 0.8% or 1/124), respectively). Significantly more patients in the TMP-SMZ group (5/86) than in the norfloxacin group (1/124) discontinued due to clinical adverse experiences.

For all characteristics measured in the ophthalmological and neurological examinations, there were no patients in either group who changed from normal at pretreatment to abnormal at post-treatment or from abnormal to normal.

There were no serious or drug related abnormal laboratory reports. In the norfloxacin group, there was one patient with a low WBC count, low segmented neutrophils, and high lymphocyte count. In the TMP-SMZ group, there were two abnormal WBC counts, one abnormal lymphocyte count, one elevated AST, one elevated ALT, and one elevated serum LDH.

Adverse experiences are shown below.

Adverse Reactions	Norfloxacin No.	TMP-SMZ No.
Drug Related		
Rash	0	3
Urticaria	0	2
Nausea	0	1
Insomnia, Depression	0	1
Total	0 pts	7 pts
Not Drug Related		
Nausea	1	0
Diarrhea	0	1
Nervousness	0	1
Dizziness and Dis-orientation	1	0
Total	2 pts	9 pts
Total No. Patients	122	86

Although patients were randomized to either norfloxacin or TMP-SMZ, patients receiving norfloxacin tended to have more complicated infections, more secondary diagnoses, more frequent prior therapies, concurrent procedures, severe infections, and polymicrobial infections. In general, patients who had a prior history of therapy did significantly worse than patients without such prior history. The cure rate for norfloxacin in prior therapy patients is equivalent to TMP-SMZ in patients without prior therapy (89% vs. 90%).

The applicant concludes that (1) norfloxacin showed a greater in vitro and in vivo spectrum of activity than TMP-SMZ, (2) the efficacy of norfloxacin is equivalent or superior to TMP-SMZ in patients with urinary tract infections, (3) no neurological or ophthalmological adverse experiences occurred in either treatment group, and (4) norfloxacin produced fewer adverse experiences than TMP-SMZ.

Medical Officer's Comments:

1. No conclusion can be drawn regarding adverse reactions since adverse reactions are best analyzed from patient diaries. No diaries were reported for this study.
2. No conclusion can be drawn regarding the presence of crystalluria. The applicant did not report the presence or absence of drug crystals.
3. The MO disqualifies three patients because they were under 18 years of age, norfloxacin cases #1498 (13-yr old male treated by Dr. Landes), and #908 (17-yr old female treated by Dr. Ryan), and TMP-SMZ case #916 (17-yr old female treated by Dr. Ryan). Corrected outcome rates are shown above. Case #908 had already be disqualified for another reason. The other two were qualified by the applicant.

(b) (2) Protocols #504-01 and #505-01 International Multiclinic Study of Complicated and Uncomplicated Urinary Tract Infections

Nineteen investigators in eleven countries participated in a randomized, controlled multiclinic trial of norfloxacin and trimethoprim-sulfamethoxazole in the treatment of urinary tract infections. The following investigators participated in this study:

- Study No. 514 J. B. J. Boerema, University Hospital St. Radboud, Nijmegen, The Netherlands. (Qualified for efficacy evaluation: 1/15 norfloxacin patients and 1/13 TMP-SMZ patients)
- Study No. 505 John Christodouloupolou, M.D., Diagnostic and Therapeutic Institute of Piraeus, Metaxas Memorial, Piraeus, Greece. (Qualified for efficacy evaluation: 4/6 norfloxacin patients and 3/4 TMP-SMZ patients)
- Study No. 543 A. De Greef, M.D., Tygerberg Hospital, Bellville, Cape Town, South Africa. (Qualified for efficacy evaluation: 10/10 norfloxacin patients and 10/10 TMP-SMZ patients)
- Study No. 521 Kevin Roy Forward, M.D., St. Clare's Mercy Hospital, St. John's, Newfoundland. (Qualified for efficacy evaluation: 1/5 norfloxacin patients and 2/5 TMP-SMZ patients)
- Study No. 515 Gerardo B. Gabilondo, M.D., National Institute of Nutrition, Mexico City, Mexico. (Qualified for efficacy evaluation: 7/9 norfloxacin patients and 7/8 TMP-SMZ patients)
- Study No. 502 Jorge Guerra, M.D., Infectious Disease Unit, Cayetano Heredia Hospital, Lima, Peru. (Qualified for efficacy evaluation: 20/20 norfloxacin patients and 19/20 TMP-SMZ patients)
- Study No. 547 Prof. Dr. med. A. Hofstetter, Head of Dept. of Urology, University of Munich. (Qualified for efficacy evaluation: 7/10 norfloxacin patients and 8/10 TMP-SMZ patients)
- Study No. 522 Primarius Dr. Kurt Jurkovic, Head of Urology Department, Hospital of Elisabethinen, Linz, Austria. (Qualified for efficacy evaluation: 7/9 norfloxacin patients and 4/9 TMP-SMZ patients)
- Study No. 562 Dr. M. C. Kelsey, Department of Pathology, Barnet General Hospital, Hertsford, U.K. (Qualified for efficacy evaluation: 0/6 norfloxacin patients and 1/5 TMP-SMZ patients)
- Study No. 526 S. L. Levin, M.D., Coronation Hospital, Johannesburg, South Africa. (Qualified for efficacy evaluation: 10/10 norfloxacin patients and 10/10 TMP-SMZ patients)
- Study No. 520 S. W. B. Newson, M.D., Consultant Microbiologist, Addenbrook Hospital, Cambridge, U.K. (Qualified for efficacy evaluation: 5/14 norfloxacin patients and 5/16 TMP-SMZ patients)

Study No. 506 Giovanni Panichi, Clinical Medical Department, University of Rome, Rome, Italy. (Qualified for efficacy evaluation: 10/20 norfloxacin patients and 20/20 TMP-SMZ patients)

Study No. 523 Allan R. Ronald, M.D., Head of the Department of Microbiology, University of Manitoba, Winnipeg, Manitoba, Canada. (Qualified for efficacy evaluation: 5/10 norfloxacin patients and 4/9 TMP-SMZ patients)

Study No. 517 S. Seiler, M.D., Stephenshorn Hospital, St. Gallen, Switzerland. (Qualified for efficacy evaluation: 2/3 norfloxacin patients and 1/2 TMP-SMZ patients)

Study No. 527 Vincenzo Speranza, M.D., Professor and Head, Surgical Clinic VI, University of Rome Medical School, Rome, Italy. (Qualified for efficacy evaluation: 5/6 norfloxacin patients and 5/5 TMP-SMZ patients)

Study No. 524 Prof. Dino Alessandro Subrizi, Department of Obstetrics and Gynecology, University of Rome, Rome, Italy. (Qualified for efficacy evaluation: 8/8 norfloxacin patients and 6/7 TMP-SMZ patients)

Study No. 529 Prof. Alessandro Tizzani, Head of Urology Department, University of Torino, Torino, Italy. (Qualified for efficacy evaluation: 10/10 norfloxacin patients and 10/10 TMP-SMZ patients)

Study No. 525 Enzo Usai, M.D., Head of Urology, University of Cagliari, Cagliari, Italy. (Qualified for efficacy evaluation: 10/10 norfloxacin patients and 10/10 TMP-SMZ patients)

Study No. 540 Brian Watt, M.D., Consultant Microbiologist, Western General Hospital, Edinburgh, Scotland. (Qualified for efficacy evaluation: 7/9 norfloxacin patients and 8/9 TMP-SMZ patients)

Drs. Guerra and Panichi (Study Nos. 502 and 506) followed Protocol No. 504-01 and treated 80 hospitalized patients while all other investigators followed Protocol No. 505-01 and treated 290 outpatients. Hospitalized patients were studied initially until it was determined that there were no safety problems, then, outpatients were selected.

Case reports are available for 370 patients who were treated for cystitis, asymptomatic bacteriuria, and pyelonephritis caused by susceptible uropathogens. Hospitalized patients (#504-01) received either four 100-mg tablets of norfloxacin bid (total 800 mg/day) or two 80/400-mg tablets of TMP-SMZ bid for ten days. Outpatients (#505-01) received either two 200-mg tablets of norfloxacin bid (total 800 mg/day) or two 80/400-mg tablets of TMP-SMZ bid for five days and sufficient drug for a second five-day period at the time of the during therapy evaluation.

FDA's guidelines for protocols for the study of urinary tract infections were followed. Bacteriologic documentation of infection was required in pretreatment cultures. Prior to treatment, urine specimens were obtained for gram stain and for the antibody-coated bacteria immunofluorescence test. Patients were excluded from the study if there was a history of allergy to the

drugs or to related drugs, if patients were pregnant, under 12 or greater than 75 years of age, if they had renal abnormalities, if the infection was caused by a resistant organism, if effective antimicrobial therapy had been given within 72 hours or if there would be concomitant antimicrobial therapy, and if the patient was in coma. Patients receiving cancer chemotherapy, patients with serious systemic infections, and patients with a high probability of death were excluded.

For the bacteriological evaluation of outcome, the applicant divided patients into two groups, evaluable and assessable. Evaluable patients were those with acceptable bacteriological data. Outcome was graded as eradicated, suppressed or persisted (failures), and undetermined. Assessable patients were those in whom either of the two follow-up cultures were not taken within the specified day ranges or those who had only one follow-up post-therapy urine culture. Clinical outcome was based on changes in clinical signs and symptoms and laboratory test results and was graded as cured, improved, not improved or other.

Ninety-four patients were disqualified for the following reasons:

	Norfloxacin	TMP-SMZ
Inadequate bacteriology	34	30
Initial pathogen not proven	15	9
Effective concomitant antimicrobial therapy	0	3
Inadequate length of therapy	1	2
Inadequate dosing	1	0
Second entry into study	1	2
Total	52	46

Characteristics of evaluable patients are shown in the following table:

Age (yrs.)	Norfloxacin			TMP-SMZ		
	Males	Females	Total	Males	Females	Total
5-19		8	8		12	12
20-29	4	19	23	2	22	24
30-39	5	22	27	6	20	26
40-49	3	12	15	4	18	22
50-59	6	18	24	7	13	20
60-69	14	12	26	5	15	20
70-79	5	10	15	4	5	9
80-89					1	1
Total No.	37	101	138	28	106	134
Mean Age	54.8	42.8	46.0	49.9	41.0	42.8
Minimum	21	17	17	21	15	15
Maximum	75	77	77	73	83	83

Symptoms for evaluable patients were

	Norfloxacin	TMP-SMZ
Dysuria	99	100
Frequency of urination	102	93
Malodorous urine	46	33
Suprapubic pain	73	67
Urgency of urination	72	64
Rigor	15	21
Flank pain and fever	21	19

The treatment groups were similar at baseline with respect to age, sex, incidence of secondary diagnoses, incidence of prior therapy, signs and symptoms of UTI and mean values of all laboratory safety variables. Associated diseases or secondary diagnoses at entry were diagnosed for 151 norfloxacin-treated patients (79.5%) and 131 TMP-SMZ-treated patients (72.3%).

Bacteriological outcome for evaluable patients is given below (number eradicated/number isolated):

Pathogen	Norfloxacin	TMP-SMZ
<u>Micrococcus</u>	1/1	1/1
<u>Staphylococcus aureus</u>		1/1
<u>Staphylococcus epidermidis</u>	1/1	2/2
<u>S. saprophyticus</u>	3/3	1/1
<u>Streptococcus faecalis</u>		1/1
<u>Strep. (Grp D enterococci)</u>	1/1	4/4
<u>Alcaligenes faecalis</u>		2/2
<u>Alcaligenes species</u>	1/1	
<u>Citrobacter species</u>	2/2	
<u>Citrobacter freundii</u>	1/1	
<u>Enterobacter</u>	2/2	4/4
<u>Enterobacter aerogenes</u>	0/1	1/1
<u>Enterobacter agglomerans</u>	1/1	
<u>Enterobacter cloacae</u>	5/6	1/1
<u>Escherichia coli</u>	82/82	85/94
<u>Klebsiella species</u>	1/2	1/1
<u>Klebsiella oxytoca</u>	2/2	
<u>Klebsiella pneumoniae</u>	5/9	6/7
<u>Morganella morganii</u>		0/1
<u>Proteus rettgeri</u>	2/2	
<u>Proteus vulgaris</u>	1/1	1/1
<u>Proteus mirabilis</u>	15/15	9/11
<u>Providencia species</u>	1/1	
<u>Pseudomonas aeruginosa</u>	8/8	0/1
<u>Pseudomonas species</u>		1/1
<u>Serratia liquefaciens</u>	1/1	
<u>Serratia marcescens</u>	1/1	1/2
Total strains eradicated	137/144 (95.1%)	122/137 (81.7%)
Eradication by patient	131/138 (95%)	119/134 (89%)

The three most frequently isolated pathogens were E. coli, Proteus mirabilis, and Klebsiella pneumoniae.

Clinical outcome is reported below.

	Norfloxacin	TMP-SMZ
Cured or improved	129 (93%)	126 (94%)
Not improved	9 (7%)	8 (6%)

Seven patients, three in the norfloxacin group and four in the TMP-SMZ group, experienced superinfection. Late post-therapy period cultures were obtained for 145 patient in the norfloxacin group and 132 patients in the TMP-SMZ group. Of these, 15 norfloxacin-treated patients (10%) and ten TMP-SMZ-treated patients (7.5%), experienced relapse. Most were due to E. coli. Seven norfloxacin-treated patients and four TMP-SMZ-treated patients experienced reinfection.

Adverse experience were reported for 26 norfloxacin-treated patients (13.7%) and for 32 TMP-SMZ-treated patients (17.8%). Only one norfloxacin-group adverse reaction was serious (acute myocardial infarction) and this was not thought to be drug related. It occurred in the follow-up period after termination of the drug.

Adverse reactions are summarized below.

	Norfloxacin	TMP-SMZ
Body as a Whole/Site unspec.	3 (1.6%)	5 (2.8%)
Abdominal pain	1	3
Abdominal swelling	1	
Fever	1	1
Malaise		2
Cardiovascular System	1 (0.5%)	0
Acute myocardial infarction	1	
Digestive System	14 (7.4%)	14 (7.8%)
Anorexia	1	1
Aphthous stomatitis	1	
Constipation	1	1
Dry mouth	1	
Dyspepsia		4
Flatulence	2	
Gastrointestinal cramps	2	
Heartburn	4	2
Mouth ulcer		1
Nausea	6	5
Vomiting		2
Musculoskeletal System	1 (0.5%)	
Back pain	1	

(Continued on next page)

	Norfloxacin	TMP-SMZ
Nervous System & Psychiatry	9 (4.7%)	8 (4.4%)
Depression	1	1
Dizziness	3	2
Headache	3	3
Nervousness		1
Paresthesia		1
Somnolence		1
Tremor		1
Skin & Skin Appendage	0	6 (3.3%)
Allergic dermatitis		1
Pruritus		2
Rash		3
Special Senses	1 (0.5%)	2 (1.1%)
Ear obstruction, NOS		1
Taste perversion	1	1
Visual disturbances		1
Urogenital System	1 (0.5%)	2 (1.1%)
Lactation suppressed		1
Vaginal candidiasis	1	1
No patients with reactions	26 (13.7%)	32 (17.8%)
Number of patients	190	180

One patient in the norfloxacin group and seven patients in the TMP-SMZ group were discontinued from the study because of clinical adverse experiences. The patient in the norfloxacin group had abdominal cramps. Patients in the control group had gastrointestinal experiences and rash.

Adverse laboratory values were reported for 75 patients, 36 in the norfloxacin group and 39 in the TMP-SMZ group. They were not summarized.

Drug crystalluria did not occur.

The applicant concludes that norfloxacin has antimicrobial activity which is superior to that of TMP-SMZ against bacteria encountered in urinary tract infections. It was well tolerated at oral doses of 400 mg bid for ten days. It was effective in the treatment of uncomplicated and complicated urinary tract infections. Norfloxacin is more efficacious than TMP-SMZ for the treatment of urinary tract infections.

Medical Officer's Comments:

1. The statement that norfloxacin is more efficacious than TMP-SMZ should be modified. This study shows that it is only more efficacious than TMP-SMZ for one uropathogen and the sentence should read, "For E. coli, the eradication rate was significantly greater ($p = 0.005$) in the norfloxacin group than in the TMP-SMZ group."
2. The applicant was requested to summarize adverse laboratory experiences.
3. Patients under 18 years of age should be disqualified.

(c) Bacterial Gastroenteritis

c.1 Protocol No. 005 (Study No. 14) David L. Cohn, M.D. Assistant Director, Disease Control Service, Denver, CO and L. Barth Reller, M.D., University of Colorado Health Science Center, Infectious Disease Section, Denver, CO, conducted a double-blind, randomized three-way comparison of norfloxacin, erythromycin, and placebo in the treatment of patients with bacterial gastroenteritis. The purpose of the study was to measure clinical efficacy, tolerance, and safety of norfloxacin when compared to placebo and erythromycin in the treatment of adults with acute gastroenteritis due to Campylobacter species and other susceptible micro-organisms.

Patients with diarrhea who met the criteria selection were enrolled.

1. Men and women 18 years of age or older who were diagnosed as having invasive gastroenteritis, on the basis of an appropriate clinical history and the finding of fecal leukocytes in a stool specimen, were eligible for the study.
2. A second group of patients, i.e., those with no fecal leukocytes but with a positive stool culture for a known bacterial pathogen, who had not already been entered into the study, were eligible.

The reason for separating these two groups was to ensure, via two distinct allocation groups, that by chance alone, patients with fecal leukocytes did not receive one therapy more than either of the other two. However, the separation was ignored in the analysis because of the small number of patients in the second stratum.

Exclusions included patients who were pregnant; those who were under 13 years of age; those who had a history of hypersensitivity to the drugs; those who had concomitant disease; those who received other antimicrobial agents within 72 hours of the onset of their gastro-intestinal symptoms; those who had renal abnormalities; those who had a history of visual disturbance, psychiatric or central nervous system disorders; and those who had a condition which in the judgement of the investigator should exclude them. Women of childbearing potential were excluded during the early months of the study.

Patients were randomized to receive either one 400 mg tablet of norfloxacin three times a day, or 333 mg of erythromycin three times a day, or placebo tablets three times a day. Treatment was to be stopped if the patient had a positive stool culture for Shigella species and still had abdominal cramps, fever, and diarrhea after two to three days of treatment. Other standard therapy was to be given.

Stools were collected for culture of enteric pathogens and for susceptibility testing before therapy, and two days and one month after completion of therapy. Patients received a physical examination including a neurological examination, a special ophthalmological examination, and laboratory studies before therapy and on the second day after completion of therapy.

Clinical outcome was graded as cured, improved, or did not improve. Bacteriological outcome was graded as eradication or persistence.

Adverse reactions as reported by the applicant are shown below.

	800 mg Nor.	1200 mg Nor.	TMP-SMZ
Serious/Not drug related			
Pneumonia	1		
Not Serious/Drug Related			
Eyelid edema, two rashes, and pruritus			1
Urticaria		2	
Not Serious Nor Drug Related			
Insomnia	1		
Flatulence		1	
Anxiety disorders and nervousness		1	
Headache		1	
Headache and somnolence			1
Somnolence			1
Dizziness and asthenia	1		
Vomiting & abdominal pain		1	
No. pts with AEs	3 (2%)	6 (4%)	3 (2%)
Number pts.	142	145	152

Adverse laboratory experiences were reported for 41 patients during the study: 16 (19%) in the 800-mg norfloxacin group, 12 (15%) in the 1200-mg norfloxacin group, and 13 (16%) in the TMP-SMZ group. The most common adverse laboratory experiences were elevated aspartate transferase and alanine transferase values. None of the adverse experiences were serious and all recovered without medical action.

	800 mg Nor.	1200 mg Nor.	TMP-SMZ
Low Hemoglobin	2	0	1
Low Hematocrit	3	2	1
Low WBCs	1	5	2
High Lymphocytes	0	0	1
High Eosinophils	1	1	3
High Platelet count	0	1	0
High P/N	1	0	0
High Serum creatinine	1	0	1
High ASAT	7	5	3
High ALAT	6	4	3
High Serum Alk. Phos.	3	2	0
High Serum sodium	0	0	1
Low Serum Potassium	1	0	1
High Serum chloride	0	0	2
High Urine RBCs	1	0	0
High Urine WBCs	1	0	0
Total pts with Adverse values	16	12	13
No. felt to be drug related	2	3	2
No. pts	86	79	79

The applicant concludes that norfloxacin in doses of 400 mg bid or tid is effective in the treatment of acute bacterial gastroenteritis. There were no significant differences between norfloxacin and TMP-SMZ. Norfloxacin is well tolerated and has a good safety profile for oral administration at these doses.

Medical Officer's Comments:

1. This study cannot be used for the evaluation of adverse reactions for two reasons.

a) No patient diaries were submitted and patients were not observed or questioned for the presence of adverse reactions during treatment. The only observation was a post-treatment observation. Diaries to record the number of stools and with check-off boxes are not acceptable as patient diaries with blank lines intended to record the presence of adverse reactions.

b) Symptoms of the infection were so similar to the gastrointestinal-type adverse reactions of norfloxacin that were to be assessed that no side effect information can be drawn from this study.

2. This study cannot be used for the evaluation of the presence of drug crystals. Urine was not examined during treatment. The post-treatment urine specimen was collected after the drug had been fully excreted at a time when crystals would not be expected to be present.

3. The following seven underage applicant-qualified patients should be disqualified from the efficacy evaluation and safety evaluation. The lower age limit for the use of the quinolones in humans has been set at 18 years because of the development of arthropathy in juvenile animals in all species that have been tested. This represents a serious protocol violation.

Carcelen #4022	15-yr old in 800 mg Nor.	- <u>V. parahaemolyticus</u>	-Eradicated
Carcelen #4056	15-yr old in 800 mg Nor.	- <u>S. flexneri</u>	- Eradicated
Salazar #4122	13-yr old in 800 mg Nor.	- <u>E. coli</u> , enterotox.	- Eradicated
Carcelen #4029	16-yr old in 1200 mg Nor.	- <u>V. parahaemolyticus</u>	-Eradicated
Carcelen #4109	17-yr old in TMP-SMZ	- <u>S. flexneri</u>	- Eradicated
De Godoy #4451	15 yr old in TMP-SMZ	- <u>Salmonella</u>	- Eradicated
Rodriguez #4641	17-yr old in TMP-SMZ	- <u>Shigella boydii</u>	- Eradicated

These disqualifications change the bacteriological cure rates slightly as shown in the table. Differences between group rates are not statistically significant.

d Suppression of aerobic flora of the oral cavity in patients with cancer

(1) Study of the effect of the antibiotic Moxifloxacin (Bayer AG, Medical Oncology Fellow, Baltimore Cancer Research Center, University of Maryland School of Medicine, Baltimore, MD) on the oral flora of patients with cancer. Comparison of a regimen of norfloxacin plus amphotericin B with a regimen of TMP-SMZ with amphotericin B in the prevention of infections related to the oral cavity and the gastrointestinal tract during neutropenia.

Patients selected for the study were hospitalized men and women 18 years of age or older. Pregnant women were excluded. Other exclusions were patients with a temperature of 38°C or higher, patients receiving or who had received other antibiotic therapy within the preceding 36 hours, allergic patients, patients who were to be treated with thymidine or methotrexate, comatose patients and those with a high probability of death; patients with renal abnormalities, visual disturbances, psychiatric or CNS disorders, and patients with acute leukemia involving the central nervous system.

Before treatment, patients were examined and complete histories were obtained. Examinations included visual acuity tests, and tests of neurologic function. All patients had surveillance cultures of their nose, throat, perirectal areas and urine. Isolates were tested for susceptibility. Specimens were obtained for hematology, blood chemistry and urinalysis including microscopic examination for the presence of drug crystals. These studies were repeated during treatment approximately three times a week, and, again, post-therapy. Subjects were observed for the presence of adverse reactions.

Patients enrolled in this study received either one 400-mg tablet of norfloxacin tid or one tablet containing 160 mg of trimethoprim and 800 mg of sulfamethoxazole (TMP-SMZ) tid. In addition, the protocol provided that all patients were to "swish (preferably for one minute) and swallow the equivalent of 12.5 mg of amphotericin B" tid. Drugs were to be administered while the patient's neutrophil count remained below $1000/\text{mm}^3$. When neutropenia persisted for more than two months, treatment was continued if the benefit outweighed the potential risk of continued therapy. Treatment was stopped if the neutrophil count increased above 1,000 cells per cm^3 , if the patient developed an allergic reaction or a serious side effect, and if the prophylactic drug was incompatible with cancer chemotherapeutic drugs.

Clinical outcome was assessed on the basis of the occurrence of infections and/or febrile episodes. Febrile episodes were classified as either microbiologically documented, clinically documented, equivocal, or noninfectious episodes. A clinical outcome of "effective" prophylaxis was ascribed to patients when no microbiologically and/or clinically documented episodes occurred. Patients with one or more microbiologically or clinically documented infectious episodes were considered prophylactic failures. Bacterial and fungal organisms identified in infectious episodes were further defined as gastrointestinal-related pathogens or not-GI-related pathogens. Organisms monitored from gastrointestinal sites during surveillance cultures which subsequently initiated an infectious process were considered GI related. Oral cavity, perirectal, and perineal surveillance sites were

considered gastrointestinal in origin. Cultures from the nose were not considered gastrointestinal in origin.

There were 72 treatment courses given to 66 patients, 34 received norfloxacin and 32 received TMP-SMZ. Only the first entry of the six patients with multiple entries was included in the analysis. A total of 66 patients were available for efficacy, 21 in the norfloxacin group and 25 in the TMP-SMZ group.

Characteristics of evaluable patients are shown in the following table:

	Norfloxacin & Amphotericin B			TMP-SMZ & Amphotericin B		
	Males	Females	Total	Males	Females	Total
Age (yrs.)						
17-19	1		1			
20-29		1	1	2		2
30-39	2		2	4	3	7
40-49	2	1	3	4	1	5
50-59	4	1	5	2	3	5
60-69	6	2	8	2	3	5
70-79	1		1		1	1
Total No.	16	5	21	14	11	25
Mean Age	53.7	50.8	52.0	44.1	52.5	47.8
Minimum	18	23	18	20	30	20
Maximum	73	67	73	69	75	75
Mean Duration (Days)			49.0			38.5
Primary Diagnoses (%)						
Leukemia, Acute			47.6%			48%
Lung Neoplasm, Malignant			23.8%			4%
Lymphoid leukemia, Acute			14.3%			12%
Myeloid leukemia, acute			14.3%			16%
Myeloid Leukemia, chronic			0			12%
Other			0			8%

A majority of patients had secondary diagnoses of other diseases. About one-third had prior therapy with other antibiotics within 72 hours prior to the start of the study. However, approximately 88% of the patients had antibiotic therapy for the treatment of possible infections which developed during the course of the study. Most patients entered the study with a granulocyte count greater than 1000 mm^3 . In general, the evaluable patient population was similar to the population of all patients.

Twenty of the 66 patients (30%) were disqualified from the efficacy analysis for the following reasons:

<u>Reason for Disqualification</u>	<u>Norflox/Amp B</u>	<u>TMP-SMZ/Amp B</u>
Inadequate length of neutropenia	4	5
Infection before prophylaxis	9	2
Total Disqualified	13	7
Total Qualified	21	25

The applicant judged prophylactic response by measuring the percentage of patients who were prophylactic failures, that is, those with at least one microbiologically documented or one clinically documented infectious episode. Prophylactic successes were patients who were free of microbiologically documented or clinically documented episodes. Prophylactic response was reported by the applicant as follows:

	<u>Norflox/Amp B</u>	<u>TMP-SMZ/Amp B</u>
Microbiologically Documented Cases	8 (38.1%)	14 (56%)
Only Clinically Documented Cases	5 (23.8%)	4 (16%)
Non-infectious or Equivocal Cases	6 (28.6%)	3 (12%)
Cases with No Episodes	2 (9.5%)	4 (16%)
Total Cases	21 (100%)	25 (100%)

Since the proportion of patients receiving norfloxacin for more than 35 days was significantly greater than that proportion for TMP-SMZ, results were analyzed according to length of treatment as follows:

<u>Duration/Outcome</u>	<u>Norflox/Amp B</u>	<u>TMP-SMZ/Amp B</u>
5 Days or less		
Success	2 (50%)	5 (36%)
Failure	2	9
Over 35 Days		
Success	6 (54%)	2 (18%)
Failure	11	9
Total	21	25

The applicant reports that those receiving therapy for 35 days or less had a greater success rate if they were receiving norfloxacin (50%) than if they were receiving TMP-SMZ (36%). Three norfloxacin-treated patients and five TMP-SMZ-treated patients had GI-related septicemias. These data were also analyzed according to granulocyte count, according to the presence of GI-related septicemia, according to the percentage of febrile-free and infection-free days, and for all patients both qualified and disqualified.

A similar proportion of patients in each treatment group had at least one clinical adverse experience, 14/34 (41%) in the norfloxacin group and 14/32 (44%) in the TMP-SMZ group. Treatment was discontinued because of adverse reactions in 2/34 patients in the norfloxacin group and in 5/32 patients in the TMP-SMZ group.

adverse experiences are listed below.

	No. of Amp B	IMP-GMZ/Amp B
Serious and Drug Related	0	0
Serious and Not Drug Related		
Death		6
Fever	0	1
Fungal Infection		1
Fungal Infection		1
Candida Aspergillus		0
Congestive Heart Failure		0
Intraocular Hemorrhage		
Diarrhea	1	1
Dysphagia	1	1
Gastrointestinal Cramps	0	0
Gastrointestinal Hemorrhage	1	1
Hepatic Failure		1
Vomiting		0
Ataxia		0
Parosmia	0	1
Brain Compression	0	1
Cerebellar Ataxia	1	0
Fungal Pneumonia	1	1
Hemoptysis	1	0
Pulmonary Insufficiency	1	0
Rash	0	1
Nystagmus	1	0
Renal Failure	2	1
Abdominal Pain	0	0
Dehydration	0	0
Not Serious but Drug Related		
Vomiting	1	0
Rash	0	2
Not Serious and Not Drug Related		
Diarrhea	1	0
Gastrointestinal Cramps	1	0
Nausea	1	0
Bone Marrow Depression	0	1
Rash	2	4
Fever	0	0
Number of pts. with one or more AEs	14 (41.2%)	14 (43.8%)
Number of pts. without AEs	20	18
Total No of Single entry pts.	34	32

Laboratory adverse experiences in these 66 patients are shown in the next table.

	Norflox/amp B	TMP-SMZ amp B
Drug Related	0	0
Serious		
Elevated Serum Creatinine	2	1
Not Serious		
Elevated Serum Creatinine	1	3
Elevated Total Serum Bilirubin	20	15
Elevated AST	14	13
Elevated ALT	14	17
Elevated Serum Phosphatase	15	12
Elevated Serum LDH	11	10
Elevated Serum uric Acid	1	0
Elevated Urine Protein	0	1
No. Pts. with one or more Laboratory AEs	26 (76.5%)	23 (78.1%)
No. Pts. without Laboratory AEs	8	7

Results of ophthalmological examinations were reported for most patients. Eye morbidity was abnormal post-treatment for 2/27 norfloxacin-treated patients and 1/22 TMP-SMZ-treated patients. One norfloxacin patient's retina changed from abnormal before treatment to normal after treatment. No data were recorded for visual acuity or for color vision (except for one TMP-SMZ patient). Other ophthalmological parameters that were normal before treatment were normal after treatment.

Results of neurological examinations were reported for most patients. Romberg's sign was positive for 2/10 norfloxacin-treated patients and for 1/16 TMP-SMZ-treated patients. The straight-line walk test was improperly performed by 1/14 norfloxacin-treated patients and by 2/15 TMP-SMZ-treated patients. Deep tendon reflexes were abnormal for 2/26 norfloxacin-treated patients and for 1/20 TMP-SMZ-treated patients.

The applicant concludes that norfloxacin is at least as effective as TMP-SMZ in the following aspects:

1. Decreasing the occurrence of microbiologically documented infections.
2. Preventing the development of infections of any type
3. Preventing gram-negative aerobic bacteremias and fungemias.
4. Preventing septicemias emanating from the GI tract.

The applicant also concludes that Norfloxacin, TMP-SMZ are safe and tolerable when given to neutropenic patients for up to two months or more.

✓ / Medical Officer's Comments: The medical officer does not agree with any of the applicant's conclusions.

1. The route of administration of amphotericin B in this study, swishing it in the mouth for one minute then swallowing it, is an investigational route for the use of intravenous vials. Amphotericin B was provided in 50 mg intravenous vials and efficacy and safety by the oral route have not been established. Oral amphotericin B, however, is available as a fixed

Of the 69 patients who were entered into the study, 43 patients were evaluable: 14/24 in the norfloxacin group, 16/23 in the erythromycin group, and 13/13 in the placebo group.

Reasons for Efficacy Disqualification

	Norfloxacin	Erythromycin	Placebo
Bacteriology not proven	8	6	6
Other effective therapy	0	1	0
Inadequate cultures	2	0	3
Total	10	7	9

The average length of therapy was five days. A secondary diagnosis of some other disease was present in 36% of evaluable patients in the norfloxacin group, 25% in the erythromycin group and 15% in the placebo group.

There were eleven patients who did not complete treatment, three in the norfloxacin group (lost to follow-up), two in the erythromycin group (one resistant organism and one lack of therapeutic response), and six in the placebo group (one protocol deviation, three lacked therapeutic response, and two were uncooperative)

Characteristics of evaluable patients are shown in the following table:

Age (yrs.)	Norfloxacin			Erythromycin			Placebo		
	Males	Females	Total	Males	Females	Total	Males	Females	Total
18-21	3		3	1	1	2	1	1	2
22-30	3	3	6	8		8	9	1	10
31-40	3	1	4	3	1	4	1		1
41-50		1	1						
51-60				1	1	2			
Total No.	9	5	14	13	3	16	11	2	13
Mean Age	26.3	29.6	27.5	28.3	37.3	30.0	25.8	24.5	25.6
Minimum	20	22	20	21	20	20	21	20	20
Maximum	38	43	43	52	60	60	31	29	31

The bacteriological response is shown below (number of strains eradicated/number of strains susceptible). The difference in rates is not statistically significant.

Pathogen	Norfloxacin	Erythromycin	Placebo	Unknown
<u>Aeromonas hydrophilia</u>	1/1			
<u>Campylobacter jejuni</u>	6/9	12/13	4/12	
<u>Salmonella enteritidis</u>	1/1			
<u>Shigella species</u>				1/1
<u>Shigella flexneri</u>	2/2			
<u>Shigella sonnei</u>	1/1	1/1		
Total	11/14	13/14	4/12	1/1
Percent	78.6%	92.9%	33.3%	

combination with tetracycline (Mystecilin-F^R (Squibb): NAS/NERC rated as ineffective). It is labeled as being "extremely well tolerated and is virtually nontoxic in prophylactic doses." Adverse reactions which are reported in this labeling are those due to tetracycline rather than to amphotericin B. This study should be disregarded because two investigational drugs should not be studied at the same time.

No comparison can be made regarding fungemias since amphotericin B was given to all patients in each group.

2. No decision regarding prophylactic efficacy can be made on the basis of this study because of the use of another investigational drug and because of the small size of the treatment groups. The conclusion regarding the superiority of norfloxacin in patients treated 35 days or less is based upon success in two of only four patients. This does not represent substantial evidence and this difference is surely due to chance alone. One cannot even conclude that there is a suggestion of superiority. There are too few qualified patients for which to adjust efficacy rates.

3. Since patients randomized to receive norfloxacin and graded as evaluable were five times more likely to be profoundly neutropenic at the time of randomization as were the patients in the control group, there must have been a randomization bias. There must also have been a duration-of-treatment bias in that the norfloxacin group was treated longer than the control group, 49 days versus 38 days.

4. No decision regarding the safety of norfloxacin can be made from this study.

- a) There was no evaluation of adverse reactions during treatment by the investigator.
- b) No adverse reaction diaries were kept as requested in order to ascertain the patient's concept of how he felt.
- c) No data were recorded for visual acuity or for changes in color perception as requested.
- d) The adverse reaction rate for TMP-SMZ (43.8%) is twice as high as would be expected.
- e) The rate of abnormal laboratory values of 78.1% for TMP-SMZ is four times higher than would be expected.
- f) No report of the presence or absence of crystalluria is included. However, the computerized printout in the appendix revealed that four patient had nonamorphous crystals, one norfloxacin-treated patient and three TMP-SMZ-treated patients.

Clinical outcome for evaluable patient: is shown below.

	Cured or Improved		Not Improved No. pts.
	No. pts.	%	
Norfloxacin	7/9	(77.8%)	2
Erythromycin	11/12	(100.0%)	0
Placebo	6/11	(54.5%)	5

Cumulative counts of evaluable patients who were free of symptoms of gastroenteritis by day of treatment.

	Number symptom-free by						
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 7	
Norfloxacin	1	1	3	7	10	10	(71.4%)
Erythromycin	0	1	2	7	12	16	(100.0%)
Placebo	0	0	3	4	5	7	(53.8%)

Two patients in each treatment group had had a recurrence of gastroenteritis when contacted one month after withdrawing therapy..

	Norfloxacin	Erythromycin	Placebo
<u>Adverse Reactions</u>			
Serious/Drug related			
Dizziness and Mydriasis		1	
Not Serious/Not Drug Related			
Diarrhea and Pruritis			1
Dizziness		1	
Dizziness and Nausea			1
Dizziness and Asthenia			1
GI Cramps and Nausea		1	
Nausea		1	
Headache			1
Photosensitivity		1	
Back Pain and Paresthesia		1	
Discontinued because of AR			1
Number Pts. with AR	0	6	4
<u>Abnormal Laboratory Reports</u>			
Not Serious/Drug Related			
Serum bilirubin, AST and alkaline phosphatase	1		
Elevated AST and LDH		1	
Elevated AST		1	
Urine WBC			1
No. Pts. with Adverse Lab.	0	6	4
Number of Patients	24	23	22

(2) Study No. 17 D. J. Winston, M.D., Assistant Professor of Medicine, UCLA Center for Health Sciences, Los Angeles, conducted a randomized, controlled comparison of a regimen of norfloxacin plus nystatin with a regimen of polymyxin plus vancomycin, plus nystatin in the prevention of infections derived from the gastrointestinal tract during neutropenia. Except for the different treatment regimens, this study was the same as Study No. 16, described above.

Patients enrolled in this study received either one 400 mg tablet of norfloxacin tid or two 50 mg capsules of polymyxin B plus two 250 mg capsules of vancomycin tid. In addition, all patients received 10 mg of nystatin oral suspension, 100,000 units per ml, tid. The investigator was furnished with norfloxacin and nystatin. Polymyxin B, 50/mg/capsule and vancomycin, 250 mg/capsule were supplied to the investigator by the institution's own pharmacy.

There were 82 treatment courses given to 62 patients, 35 received norfloxacin/nystatin and 32 received polymyxin/vancomycin/nystatin. Only the first entry of the 35 patients with multiple entries was included in the analysis. A total of 40 patients were evaluable for efficacy, 25 in the norfloxacin/nystatin group and 15 in the control group.

Characteristics of evaluable patients are shown in the following table:

	Norfloxacin & Nystatin			Polym./Vanco./Nystatin		
	Males	Females	Total	Males	Females	Total
<u>Age (yrs.)</u>						
18-19		1	1	2		2
20-29	1	5	6	3		3
30-39	3	1	4	1	2	3
40-49	2	2	4	2		2
50-59	3	1	4			
60-69	2	3	5	3	1	4
70-79		1	1	1		1
Total No.	11	14	25	12	3	15
Mean Age	44.3	42.1	43.1	42.0	42.3	42.0
Minimum	21	19	19	18	30	18
Maximum	62	70	70	73	63	73
Mean Duration (Days)			31.3	22.2		
<u>Primary Diagnoses (%)</u>						
Myeloid Leukemia, Acute	72.0%			73.3%		
Lymphoid Leukemia, Acute	16.0%			20.0%		
Myeloid Leukemia, Chronic	12.0%			6.7%		
Lymphoid Leukemia, Chronic	0.0			0.0%		

All 69 patients were included in the analysis for safety. Adverse reactions and abnormal laboratory reports as summarized by the applicant are shown above. It should be noted that patient diaries were not kept in this study.

The applicant concludes that norfloxacin and erythromycin are more effective at eradicating Campylobacter jejuni from the gastrointestinal tract than placebo is, and that norfloxacin produces fewer adverse experiences than either erythromycin or placebo. Norfloxacin eradicates other pathogens including Shigella, Salmonella, and Aeromonas species.

Medical Officer's Comments:

1. Although six of nine C. jejuni infections were eradicated by norfloxacin, no efficacy conclusion can be drawn from this study because of the small numbers. There is only a suggestion of norfloxacin efficacy. Erythromycin appears to be superior.
2. This study should not be considered in the evaluation of adverse effects due to norfloxacin because the very adverse effects that one would watch for are symptoms of the disease. Symptoms of gastroenteritis, besides diarrhea that were used in the evaluation of outcome, were abdominal cramps, nausea, vomiting, anorexia, etc. Gastrointestinal-type adverse effects that would be anticipated with norfloxacin are gastrointestinal cramps, nausea, vomiting, heartburn, flatulence, anorexia, abdominal pain, dyspepsia, etc.
3. The presence or absence of crystalluria cannot be evaluated because urine sediment was only examined before treatment and again two days after treatment was discontinued. Urine sediment should have been examined for the presence of drug crystals during treatment at the height of the drug excretion period.

There is a discrepancy between the printout and several case report forms regarding the presence of nonamorphous crystals.

Case #302 - Printout shows 50 nonamorphous crystals/HPF on Day 7. The case report shows "Many" nonamorphous crystals two days after treatment.

Case #308 - Printout shows 4/HPF before treatment. The case report shows 4+ before treatment.

Case #113 - Printout shows 1/HPF on Day 8. The case report shows 1+ calcium oxalate two days after treatment.

Over 86% of patients had secondary diagnoses of other diseases. Sixteen percent of the norfloxacin group and none of the control group had had prior therapy with other antibiotics within 72 hours before the start of the study. However, 96% in the norfloxacin group and 100% of the control had antibiotic therapy for the treatment of possible infections which developed during the course of the study. Most patients entered the study with a granulocyte count greater than 1000 mm³. In general, the evaluable patient population was similar to the population of all patients.

Twenty-two of the 62 patients (35%) were disqualified from the efficacy analysis for the following reasons:

<u>Reason for Disqualification</u>	<u>Norflox/Nyst</u>	<u>Poly/Van/Nyst</u>
Inadequate length of neutropenia	9	6
Infection before prophylaxis	1	4
Effective concomitant prophylaxis	0	2
Total Disqualified	10	12
Total Qualified	25	15

The applicant judged prophylactic response by measuring the percentage of patients who were prophylactic failures, that is, those with at least one microbiologically documented or one clinically documented infectious episode. Prophylactic successes were patients who were free of microbiologically documented or clinically documented episodes. Prophylactic response was reported by the applicant as follows:

	<u>Norflox/Nyst</u>	<u>Polym/Van/Nyst</u>
Microbiologically Documented Cases	11 (44.0%)	12 (80.0%)
Only Clinically Documented Cases	3 (12.0%)	1 (6.7%)
Non-Infectious or Equivocal Cases	10 (40.0%)	2 (13.3%)
Cases with No Episodes	1 (4.0%)	0 (0.0%)
Total Cases	25 (100%)	15 (100%)

Results were analyzed according to length of treatment as follows:

<u>Duration/Outcome</u>	<u>Norflox/Amp B</u>	<u>TMP-SMZ/Amp B</u>
28 Days or less		
Success	8 (57.1%)	1 (8.3%)
Failure	6	11
Over 28 Days		
Success	3 (27%)	1 (33%)
Failure	8	2
Total	25	15

The applicant reports that the percentage of evaluable patients who were prophylactic successes was significantly greater in the norfloxacin group than in the control, 44% vs. 13%, respectively, regardless of duration of therapy.

(c) (2) Protocol #519-01 Seven investigators in seven countries conducted a randomized, controlled, trial of two doses of norfloxacin and trimethoprim-sulfamethoxazole, orally administered, in the treatment of acute bacterial gastroenteritis caused by susceptible pathogens. The following investigators participated in this study:

Study No. 588 Amador Carcelen, M.D., Honorio Delgado High Altitude Institute, Unit of Neumology, San Martin, Lima Peru. (Qualified for efficacy evaluation: 19/36 800-mg norfloxacin patients, 13/38 1200-mg norfloxacin patients, and 14/36 TMP-SMZ patients)

Study No. 591 Cid Vieira Franco de Godoy, M.D., Associate Professor and Head Department of Microbiology and Immunology, University of Sao Paulo, Sao Paulo, Brazil. (Qualified for efficacy evaluation: 6/33 800-mg norfloxacin patients, 10/35 1200-mg norfloxacin patients, and 13/43 TMP-SMZ patients)

Study No. 595 Dr. Pablo Pagliano, Chief of the Pediatrics Department, Luis A. Maspero Hospital, Buenos Aires, Argentina. (Qualified for efficacy evaluation: 2/13 800-mg norfloxacin patients, 0/11 1200-mg norfloxacin patients, and 1/13 TMP-SMZ patients)

Study No. 609 Guillermo G. Rodriguez, M.D., Intensive Care Unit, Hospital Mexico, San Jose, Costa Rica. (Qualified for efficacy evaluation: 7/18 800-mg norfloxacin patients, 5/17 1200-mg norfloxacin patients, and 7/15 TMP-SMZ patients)

Study No. 590 Guillermo Ruiz-Palacios, M.D., Chief of the Department of Infectious Diseases, Instituto Nacional de la Nutricion, Tlalpan, Mexico. (Qualified for efficacy evaluation: 8/21 800-mg norfloxacin patients, 8/22 1200-mg norfloxacin patients, and 11/24 TMP-SMZ patients)

Study No. 589 Augusto S. Salazar, M.D., Chief of the Department of Gastroenterology of the Colombianna Association of Diabetes, Bogota, Colombia. (Qualified for efficacy evaluation: 11/18 800-mg norfloxacin patients, 9/19 1200-mg norfloxacin patients, and 7/19 TMP-SMZ patients)

Study No. 634 Vincenzo Vagni, M.D., Department of Surgery, General Hospital (Ospedale Generale S. Giovanni Decollato Andosilla), Civita Castellana, Italy. (Qualified for efficacy evaluation: 3/3 800-mg norfloxacin patients, 3/3 1200-mg norfloxacin patients, and 2/2 TMP-SMZ patients)

Patients selected for the study were inpatients or outpatients with clinical diagnoses of acute gastroenteritis. Bacteriological documentation of infection in pretreatment cultures (specimens taken within the three-day period before initiation of treatment) was required for evaluation of bacteriological outcome.

Exclusions included those with a history of allergy to nalidixic acid, oxolinic acid, norfloxacin, sulfonamides or trimethoprim; those who were pregnant, less than 12 years of age, or over 75 years of age; renal, visual, psychiatric or CNS abnormalities, other effective antimicrobial therapy; and

sex, or granulocyte count range. Seven norfloxacin-treated patients and seven control patients had GI-related septicemias. These data were also analyzed according to granulocyte count, according to the presence of GI-related septicemia, according to the percentage of febrile-free and infection-free days, and for all patients both qualified and if qualified.

The percentage of single entry patients with both a clinical and a laboratory adverse experience in the norfloxacin group (23/35, 66%) was greater than that in the polymyxin/vancomycin group (14/27, 52%). A similar proportion of patients in each treatment group (28/35, 80%, for norfloxacin and 21/27, 78%, for polymyxin/vancomycin) had at least one clinical adverse experience. No serious and drug-related adverse experiences were reported. Two patients in the norfloxacin group (6%) and no patients in the polymyxin/vancomycin group discontinued the study due to a clinical adverse experience. A greater proportion of patients in the norfloxacin group (25/35, 71%) than in the polymyxin/vancomycin group (15/27, 56%) had at least one laboratory value that was considered adverse by the investigator but this difference was not significant.

Adverse Clinical and/or Laboratory Experiences
Regardless of Drug Relationship

	Norfloxacin	Polym/Vanco.
Adverse Clinical Experience Only	5 (14.3%)	7 (25.9%)
Adverse Laboratory Experience Only	2 (5.7%)	1 (3.7%)
Adverse Clin. and Lab. Experiences	23 (65.7%)	14 (51.9%)
Patients with Adverse Experiences	30 (85.7%)	22 (81.5%)
Patients without Adverse Experiences	5 (14.3%)	5 (18.5%)
Total Single Entry Patients	35	27

concomitant disease contraindicating the use of the study drugs.

Each patient received either one 400-mg tablet of norfloxacin bid, one 400-mg tablet of norfloxacin tid, or two 80/400-mg tablets of TMP-SMZ. The usual length of treatment was five days. Patients who were treated at least three days were considered to be evaluable. Patients were numbered consecutively in the order of acceptance into the study and were assigned to treatment according to a randomized allocation schedule.

Patients were examined before treatment, between the second and fifth post-treatment days, and one month after therapy. The pretreatment examination included a complete history, physical examination, laboratory studies, and evaluation of the characteristics of the diarrheal disease (length of illness, number of stools, presence of blood, fecal leukocytes, or mucus, history of fever and GI symptoms). Stools were cultured for enteric pathogens. E. coli was regarded as a pathogen only when enterotoxin production was demonstrated. Three investigators performed these assays. Stool cultures and laboratory studies were repeated at the two follow-up evaluations.

Tolerability to the study drug was monitored throughout the study (well, moderately well, and poorly tolerated). Patients of two investigators, Drs. Carcelen and Ruiz-Palacios, kept diaries on the number of stools per day after the initiation of treatment.

Adverse experiences volunteered by the patient were recorded and evaluated at each post-therapy visit. Adverse laboratory experiences were evaluated by the investigator.

Bacteriological outcome was graded as eradicated, persisted, or reinfection. Clinical outcome was graded as cured, improved, not improved, or other (lost to follow-up).

Characteristics of evaluable patients are shown in the following table:

Age (yrs.)	Norfloxacin 800-mg			Norfloxacin 1200-mg			TMP-SMZ 160/800		
	Males	Females	Total	Males	Females	Total	Males	Females	Total
13-17	1	2	3	1		1	3		3
18-21	8	2	10	1	1	2	5	2	7
22-30	6	9	15	9	10	19	12	4	16
31-40	5	4	9	8	3	11	10	3	13
41-50	2	7	9	2	5	7	4	8	12
51-60	3	2	5	3	2	5	2		2
61-70		5	5	1	2	3	2		2
Total No.	9	31	56	25	23	48	38	17	55
Mean Age	26.3	38.2	34.3	35.8	37.2	36.5	32.8	35.1	33.5
Minimum	20	13	13	16	18	16	15	18	15
Maximum	38	65	65	62	68	68	67	49	67

Adverse experiences are listed below.

	Norflox/Amp. B	IMP-5Hz/Amp. B
Serious and Drug Related	0	0
Serious and Not Drug Related		
Death	5	7
Fungemia	1	1
Fungus Infection	1	2
Cardiac Arrest	1	0
Heart Failure	1	0
Intracranial Hemorrhage	1	0
Diarrhea	2	0
Gastrointestinal Hemorrhage	1	0
Vomiting	1	0
Leukemia	1	1
Respiratory Failure	1	2
Hematuria	0	0
Renal Failure	2	1
Abdominal Pain	0	1
Bacterial Septicemia	0	1
Septic Shock	0	1
Acute Cerebrovascular Disease	0	1
Hepatorenal Syndrome	0	1
Acute Myeloid Leukemia	0	2
Rhabdomyolysis	0	1
Oliguria and Anuria	0	1
Dysarthria	0	0
Asthma	0	0
Not Serious but Drug Related		
Diarrhea	0	3
Vomiting	0	1
Not Serious and Not Drug Related		
Abdominal Pain	0	2
Syncope	1	0
Bowel Sound Abnormalities	1	0
Diarrhea	20	15
Dyspepsia	1	0
Nausea	2	1
Vomiting	14	8
Muscle Cramps	1	0
Headache	2	0
Rash	8	6
Conjunctivitis	3	0
Constipation	0	1
Erythematous Condition	0	0
Arthostatic Effects	0	0
Dysuria	0	0
Tachycardia	0	0
Number of pts. with one or more AEs	28 (80.0%)	21 (77.8%)
Number of pts. without AEs	7	6
Total No of Single entry pts.	35	27

Of the 439 patients in the study, 159 were evaluable (36%), 56 in the 800 mg group, 48 in the 1200 mg group and 55 in the TMP-SMZ group.

Reasons for Efficacy Disqualification

	800 mg Nor.	1200 mg Nor.	TMP-SMZ
No initial pathogen isolated	80	93	91
Effective concomitant antimicrobial therapy	0	0	1
Inadequate cultures	6	4	5
Total	86	97	97

Common signs and symptoms of gastroenteritis before treatment for evaluable patients are listed below:

	800 mg Nor.	1200 mg Nor.	TMP-SMZ
Abdominal cramps	53	42	49
Nausea	33	23	34
Vomiting	18	12	23
Rash	3	0	1
Fever	32	20	32
Anorexia	27	24	23
Tenesmus	22	17	12
Chills	24	21	24

Bacteriological outcome for evaluable patients is shown in the following table.

Pathogen	Number eradicated/Number Qualified					
	800 mg Nor.		1200 mg Nor.		TMP-SMZ	
	Merck	MO	Merck	MO	Merck	MO
<u>Aeromonas hydrophila</u>	6/6	6/6			4/4	4/4
<u>Campylobacter</u> species					1/1	1/1
<u>Campylobacter fetus</u> ss. <u>jejuni</u>					1/2	1/2
<u>E. coli</u> (invasive)			1/1	1/1		
<u>E. coli</u> , enterotoxigenic	15/16	14/15	19/19	19/19	9/10	9/10
<u>Plesiomonas shigelloides</u>	2/2	2/2	1/1	1/1	3/3	3/3
<u>Salmonella</u> species	4/4	4/4	2/2	2/2	7	6/7
<u>Salmonella enteritidis</u>					2/2	2/2
<u>Shigella</u> species					1/1	1/1
<u>Shigella boydii</u>	1/1	1/1			4/4	3/3
<u>Shigella dysenteriae</u>	1/1	1/1	3/3	3/3	2/2	2/2
<u>Shigella flexneri</u>	9/9	18/18	15/15	15/15	16/16	15/15
<u>Shigella sonnei</u>	5/5	5/5	4/4	4/4		
<u>Vibrio cholerae</u>	1/1	1/1				
<u>Vibrio parahaemolyticus</u>	3/3	2/2	3/3	2/2	2/2	2/2
Total strains	56/57	52/63	49/49	48/48	52/55	49/52
Number patients	52/56	53/54	48/48	47/47	52/55	49/52
	98%	98.1%	100%	100%	95%	94.2%

Two patients had polymicrobial infections, one in each of the norfloxacin groups. Shigella flexneri and enterotoxigenic E. coli were the most commonly isolated organisms. The only one of the failures to develop resistance was

Laboratory adverse experiences in these 66 patients are shown in the next table.

	Norflox/Amp B	TMP-SMZ/Amp E
Drug Related	0	0
Serious and Not Drug Related		
Elevated Serum Creatinine	2	6
Elevated Total Serum Bilirubin	1	4
Elevated ALT	0	1
Elevated Ser. Alk. Phosphatase	0	1
Elevated Serum LDH	0	2
Elevated BUN	1	5
Elevated Urine RBC's	2	1
Not Serious and Not Drug Related		
Elevated Serum Creatinine	7	3
Elevated Total Serum Bilirubin	11	3
Elevated AST	15	8
Elevated ALT	19	9
Elevated Serum Alk. Phosphatase	8	6
Elevated Serum LDH	1	1
Elevated Serum Uric Acid	0	1
Elevated Urine Protein	6	4
Elevated BUN	6	2
Elevated Urine Glucose	1	1
Elevated Urine RBC's	2	1
Elevated Granular Casts	0	0
No. Pts. with one or more Laboratory AEs	25 (71.4%)	15 (55.6%)
No. Pts. without Laboratory AEs	10	12

Results of ophthalmological examinations were reported for most patients. For all but one of the parameters measured, there were no patients who changed from normal at pretreatment to abnormal at post-treatment or from abnormal to normal. One patient's deep tendon reflex (polymyxin/vancomycin group) changed from normal at pretreatment to abnormal at post-treatment.

The applicant concludes that norfloxacin is superior to polymyxin plus vancomycin in preventing infectious complications during neutropenia and may be less likely to produce drug-related adverse clinical experiences.

Medical Officer's Comments: The medical officer does not agree with the applicant's conclusions.

1. The routes of administration of polymyxin and vancomycin in this study are investigational routes for these products.

2. This study must be regarded as an uncontrolled trial because the control was not approved for this indication. Two investigational regimens should not be studied at the same time.

the Campylobacter fetus subspecies jejuni strain and the resistance was to TMP-SMZ.

In the evaluation of clinical outcome, all of the evaluable patients were rated as either cured or improved.

Clinical Outcome for Evaluable Patients			
	800 mg Nor.	1200 mg Nor.	TMP-SMZ
Cured	55 (98%)	47 (98%)	48 (27%)
Improved	1	1	7
Total	56	48	55

Approximately 35% of the patients in each treatment group had diarrhea eliminated after one day of therapy. After two days, the percentages increased to 50%. The three treatment groups were similar regarding the number of days required for the elimination of diarrhea. Information on the usual number of stools per day before the development of gastroenteritis and daily diaries on the number of stools per day after the initiation of treatment was available for 43 evaluable patients.

Time Required for the Elimination of Diarrhea			
Days	800 mg Nor.	1200 mg Nor.	TMP-SMZ
1	5	5	5
2	4	3	3
3	2	3	1
4	1	1	1
5 or more	3	1	5
Total	15	13	15

Late post-therapy stool cultures which were performed for 142 of the 155 patients with a bacteriological outcome of eradication revealed that two patients had reinfections after the post-therapy visit.

Adverse reactions were reported by the applicant for twelve patients. Most of the adverse reactions were related to the nervous system (anxiety, dizziness, drowsiness, headache, insomnia, and nervousness). The second most common body system was hypersensitivity manifested as skin reactions (pruritus, rash, and urticaria).

The study drug was discontinued in one patient in each group because of adverse clinical effects. The norfloxacin patient had pneumonia and the TMP-SMZ patient had pruritus, rash, and edema.

3. No decision regarding the safety of norfloxacin can be made from this study. The adverse reaction rate for norfloxacin is four times higher than would be expected. The rate of abnormal laboratory values is four times higher than would be expected. No report of the presence or absence of crystalluria is included. No adverse reaction diaries were kept in this study.

(e) Gonorrheal Infection

(1) Protocol No. 010 (Study No. 30) Samuel William Berg II, M.D., Head of the Infectious Disease Branch, Naval Regional Medical Center, San Diego, California conducted a controlled study of orally administered norfloxacin and intramuscularly administered spectinomycin in the treatment of symptomatic uncomplicated gonorrheal urethritis in 130 men at Subic Bay Naval Base in the Philippines. A random design was not followed. Each patient received either 1200 mg of norfloxacin given orally as three 200 mg tablets and followed in four hours by three additional 200 mg tablets, or spectinomycin 2 grams IM in one dose.

Patients were men 18 years of age or older who were "presumptively diagnosed if they had a history of recent sexual exposure and/or signs or symptoms of urethritis or cervicitis, and a urethral or cervical gram stain showing polymorphonuclear neutrophils and intracellular gram-negative diplococci."

✓ Medical Officer's Comment: Obviously, reference to cervicitis and cervical smears in men is an error.

Exclusions were patients unlikely to return for test-of-cure cultures, those requiring concurrent antibacterial therapy, those with hypersensitivities to the two drugs or related compounds, those with conditions which precluded evaluation, those having successful antimicrobial therapy within the three-day period preceding the pretreatment examination, those with syphilis, and those with other varieties of gonococcal infection.

All patients had a pretreatment urethral swab for gram stain, a gonococcal culture (urethral, pharyngeal, or rectal specimens), and a serological test for syphilis. Before treatment, a history was taken and patients received a physical examination. These findings were compared to repeat examinations at the completion of the study. The test-of-cure visit was 3-7 days after treatment. Smears and cultures were repeated 3-7 days after treatment. In addition, laboratory studies which were obtained before and after treatment were hematocrit, hemoglobin, WBC with differential, platelet estimate, BUN & creatinine, ASAT (SGOT), ALAT (SGPT), total bilirubin, LDH, alkaline phosphatase, and urinalysis with observation for non-amorphous crystals.

Clinical outcome was graded as cured, improved, recurrence, no improvement, or unable to evaluate. Bacteriological outcome was graded as eradication or persistence. Patients whose beta-lactemase status changed during the study were presumed to be re-infected and were deleted from analysis.

There were 131 treatment courses given to 130 patients. Seventy-four of the 107 norfloxacin patients and 16 of the 23 spectinomycin patients were evaluable for efficacy.

APPL #: 019384

FIRM: MSD RES LABS

2 OF 4

TRADE NAME: NOROXIN (NORFLOXACIN) 400MG TABLET

GENERIC NAME: NORFLOXACIN

Characteristics of evaluable patients are shown in the following table:

	Norfloxacin Males	Spectinomycin Males
<u>Age (yrs.)</u>		
18-21	28 (37.8%)	9 (56.3%)
22-39	38 (51.4%)	6 (37.5%)
31-40	6 (8.1%)	1 (6.3%)
41-42	2 (2.7%)	
Total No.	74	16
Mean Age	24.3	22.6
Minimum	18	19
Maximum	42	31
<u>Strain</u>		
<u>N. gonorrhoeae</u>	5 (7.0%)	0
<u>N. gonorrhoeae</u> pcnase +	32 (43.2%)	3 (18.8%)
<u>N. gonorrhoeae</u> pcnase -	37 (50.0%)	13 (81.2%)

The imbalance in distribution of patients occurred because the investigator did not follow the allocation schedule. The medical personnel at Subic Bay Naval Base were notified that they were to be moved from the site in six weeks. They felt that it was imperative to obtain as much information on norfloxacin as possible. Of the 74 evaluable norfloxacin patients, five were diagnosed by gram stain. The remaining 69 patients were diagnosed by gram stain and positive culture. All 16 evaluable spectinomycin patients were diagnosed by gram stain and positive culture.

Forty patients were disqualified from the efficacy evaluation because the diagnosis was not microbiologically confirmed for one norfloxacin patient and because cultures were inadequate for 32 norfloxacin patients and seven spectinomycin patients.

Only 28 of the 90 evaluable patients had in vitro susceptibility tests performed. Of these, 26 were susceptible to both drugs. Two were susceptible to norfloxacin and resistant to spectinomycin.

All evaluable patients regardless of susceptibility or with unknown susceptibility had a bacteriological response of eradicated. All evaluable patients regardless of susceptibility or with unknown susceptibility were graded as clinical cures. In addition, two patients in the norfloxacin group had gonococcal pharyngitis and these were cured.

The applicant reports that all 90 evaluable patients were clinically cured. Yet, three norfloxacin-treated patients had signs and symptoms present at the follow-up evaluation. Case #1851 had nonspecific urethritis on Day 6, case #1899 had dysuria, and case # 2009 had dysuria and a mucoid urethral discharge at the first post-therapy visit.

Two patients treated with norfloxacin and none of the patients treated with spectinomycin reported adverse clinical experiences. None were considered serious or drug related.

Adverse Reactions

	Norfloxacin	Spectinomycin
Nausea and headache	1	0
Insomnia, nervousness and anorexia	1	0
Total with adverse reactions	2	0
Total without adverse reactions	105	23

The applicant concludes that norfloxacin and spectinomycin are effective in the treatment of gonococcal urethritis. Both drugs are safe in this treatment. Norfloxacin in extraurethral gonorrheal infection merits further study. Both drugs are active in vitro against penicillin-resistant N. gonorrhoeae.

Medical Officer's Comments: (1) Failure to randomize lessens the value of this study and removes it from the list of controlled trials. (2) In spite of the 100% cures in each group, the medical officer can only accept 27 of the 90 patients that the applicant found qualified because only these 27 cases had susceptibility testing, 22 in the norfloxacin group and 5 in the spectinomycin group. (One cannot be accounted for.) Cases for which there was no susceptibility testing should be disqualified. (3) Post therapy cultures should have been obtained 4-7 days after therapy instead of 3-7 days after therapy. (4) The presence or absence of drug crystals is not reported. No diaries were used in this study.

(2) Protocol No. 015 Lisa Kaplowitz, M.D., Assistant Professor, Department of Medicine, Medical College of Virginia, Richmond, Virginia (Study No. 49), and Margaret Simpson, M.D., Acting Director, Section of Infectious Disease, Hennepin County Medical Center, Minneapolis, Minnesota (Study No. 48), conducted a randomized, controlled, multiclinic study to compare norfloxacin and a regimen of ampicillin plus probenecid in the treatment of gonorrheal infection in men and women.

Fifty-seven patients 18 years of age or over with symptomatic urethritis or cervicitis were enrolled to receive either 1200 mg of norfloxacin given as three 200-mg tablets orally, then followed in four hours by three additional 200-mg tablets, or 3.5 grams of ampicillin given as seven 500-mg tablets plus two 500-mg tablets of probenecid. Twenty-eight patients received norfloxacin and 29 received the control regimen.

Exclusions were similar to those given above for Study #30. Laboratory observations were similar. Microbiological outcome criteria were the same.

Of the 57 patients treated, there were 48 that were considered by the applicant to be evaluable, 26 in the norfloxacin group and 22 in the ampicillin/probenecid group.

Characteristics of evaluable patients are shown in the following table:

	Norfloxacin			Ampicillin/Probenecid		
	Males	Females	Total	Males	Females	Total
Age (yrs.)						
18-21	6		6	5	3	8
22-30	14	1	15	9	2	11
31-40	3	1	4	2		2
41-50				1		1
51-60						
61-70	1		1			
Total No.	24	2	26	17	5	22
Mean Age	26.2	31.0	26.6	24.9	21.4	24.1
Minimum	19	25	19	18	20	18
Maximum	69	37	69	41	23	41

At enrollment, the two treatment groups were comparable except that twice as many patients in the ampicillin/probenecid group received other anti-infective therapy before the 72-hour prestudy interval than did those in the norfloxacin group (48.3% vs 21.4%, $p =$ less than 0.05). Most of these anti-infective agents had been taken for a previous episode of gonorrheal infection.

Nearly all evaluable patients in each treatment group had a diagnosis of gonococcal urethritis (males) or gonococcal cervicitis (females). Only one patient in the ampicillin/probenecid group was classified with a different diagnosis, gonococcal proctitis. One norfloxacin patient also had herpes, one ampicillin/probenecid patient had gonococcal proctitis and two ampicillin/probenecid patients had gonococcal pharyngitis. No patient had concomitant antimicrobial therapy.

Susceptibilities were determined by the disk method or by measuring MICs. For norfloxacin, 46 of 46 (100%) pathogens were susceptible. For ampicillin/probenecid, 33 of 33 (100%) pathogens were susceptible. For 13 patients, susceptibility was tested for norfloxacin but not for ampicillin. Data were incomplete for 22 patients.

Two norfloxacin patients and four ampicillin/probenecid patients were not evaluable because of inadequate cultures. In addition, three ampicillin/probenecid patients were unevaluable because bacteriology was not proven (2) and because the clinical diagnosis was not clear (1).

Pathogens from all evaluable patients were eradicated. The microbiological outcome is shown in the following table:

N. gonorrhoeae	Norfloxacin		Ampicillin/Probenecid	
	Eradicated	Persisted	Eradicated	Persisted
Norfloxacin susceptible (Pcnase negative)	20 (100%)	0	14 (100%)	0
Susceptibility not tested	6	0	8	0
Total	26 (100%)	0	22 (100%)	0

The symptomatic outcome for evaluable patients is shown below:

	Norfloxacin	Ampicillin/Probenecid
Symptom-Free	22 (88%)	18 (82%)
At Least One Symptom Present	3 (12%)	4 (18%)
Total	25	22

There was no significant difference between rates. One norfloxacin-treated patient who did not have signs or symptoms is excluded.

In the norfloxacin group, one patient continued to have a urethral discharge. One patient had a urethral discharge before therapy but the discharge had changed to mucoid at the post-therapy visit. One patient continued to have a vaginal discharge. In the ampicillin/probenecid group, two patients had a urethral discharge before therapy but the discharge was mucoid after treatment. One patient continued to have dysuria and had a purulent urethral discharge before therapy but the discharge was mucoid after therapy. One patient continued to have a vaginal discharge and developed dysuria at the post-therapy visit.

Adverse experiences and adverse laboratory effects are summarized below:

	Norfloxacin	Ampicillin/Probenecid
<u>Adverse Experiences</u>		
Not Serious but Drug-Related		
Dizziness	1	0
Headache and Nausea	1	0
Nausea alone	0	1
No. Pts. with Adverse Reactions	2 (7.1%)	1 (3.4%)
No. Pts.	28	29
<u>Adverse Laboratory Effects</u>		
Dec. WBC, elevated Lymphocytes, Alk. phos. and LDH		1
Band Neutrophils	1	
Lymphocytes	3	1
Eosinophils	1	
Elevated AST and ALT		1
Urine Glucose	1	
Nonamorphous crystals	1	
No. Pts with Adverse Lab	7 (25%)	3 (10.3%)
No. Pts	28	29

The applicant concludes that norfloxacin is active in vitro against N. gonorrhoeae. It is effective in treating gonococcal urethritis and cervicitis. Norfloxacin is as safe as ampicillin when used to treat

gonorrhoeal infection.

Reviewer's Comments:

1. Although norfloxacin is probably effective, data from this study are inadequate to show that norfloxacin is effective in treating gonococcal urethritis and cervicitis. There were only two evaluable females in the norfloxacin group and only five in the control group. Susceptibility was not tested for one of the two norfloxacin females and for four of the five control female cases. For a common infection like gonorrhoeal infection, at least 75 or 100 cases would be needed. The same is true for males: in this study, there were only 24 evaluable males in the norfloxacin group and only 17 in the control group. These low numbers might be acceptable for a rare infection but they do not represent the substantial data needed for a common infection like gonorrhoeal infection.
2. The applicant's clinical outcome criteria which mistakenly included microbiological outcomes were disregarded. The medical officer graded clinical outcome on the presence or absence of signs and symptoms.
3. The fact that one norfloxacin-treated patient had nonamorphous crystals after only two 600-mg doses four hours apart may be significant.
4. Post-therapy cultures should have been obtained 4-7 days after therapy instead of 3-7 days after therapy.
5. No diaries were used in this study.
6. The applicant has mistakenly classified isolates for which there was no susceptibility testing with evaluable cases. These cases should be disqualified. Strains from only 19 of the 24 males in the norfloxacin group, 13 of 17 males in the control, and for only two females were tested for susceptibility.

3. Uncontrolled Clinical Studies

a) Acute Bacterial Gastroenteritis

Study No. 31 Mark J. Kunkel, M.D., Director of Diagnostic Virology Laboratory and Consultant in Infectious Disease, Danbury Hospital, Danbury, CT, studied norfloxacin in doses of 400 mg tid in the treatment of acute bacterial gastroenteritis. Of 14 patients, nine were evaluable. Campylobacter jejuni had been eradicated from eight of the nine patients (89%) five days after norfloxacin was stopped. One patient experienced taste perversion, irritability, and euphoria. One patient had paresthesia and headache. One patient had dizziness and headache. One had joint pain.

Medical Officer's Comment: This diarrhea study had been placed "on hold" status pending evaluation of a report of a Phase I tolerance study of norfloxacin in doses as high as 1200 mg/day. This study had already been in progress. The applicant mistakenly classified this report with controlled trials. The reviewer put it with uncontrolled trials.

(b) Urinary Tract Infections - Two multiclinic studies were conducted.

(b) (1) Protocols No. 011 and 017 - Domestic Studies A multiclinic uncontrolled study of norfloxacin in the treatment of complicated and uncomplicated urinary tract infections in men and women over 18 years of age was conducted at eight clinical centers. The following investigators participated in this trial and treated the number of patients shown:

Study No. 37 Ellie J.C. Goldstein, M.D., R. M. Alden Research Laboratory and Associate Clinical Professor of Medicine, U.C.L.A. School of Medicine, Los Angeles, California. (Qualified for efficacy evaluation: 11/14 patients)

Study No. 38 Lloyd Harritage Harrison, M.D., Professor of Surgery, Department of Surgery, Division of Urology, Bowman Gray School of Medicine, Winston-Salem, North Carolina. (Qualified for efficacy evaluation: 14/19)

Study No. 27 Mark J. Kunkel, M.D., Director Virology Laboratory, Consultant in Infectious Disease, Danbury Hospital, Danbury, CT. (Qualified for efficacy evaluation: 14/16)

Study No. 25 Ralph R. Landes, M.D., Danville Urology Clinic, Danville, Virginia. (Qualified for efficacy evaluation: 28/36)

Study No. 36 Anthony Joseph Schaeffer, M.D., Associate Professor, Department of Urology, Northwestern University Medical School. (Qualified for efficacy evaluation: 15/19)

Study No. 40 Rodney M. Snow, M.D., Norwood Clinic, Inc., Birmingham, Alabama. (Qualified for efficacy evaluation: 5/11)

Study No. 35 Frank E. Thomas, M.D., Assistant Professor of Medicine, Meharry Medical College, Nashville, TN. (Qualified for efficacy evaluation: 0/1)

Study No. 28 W. Glen Wells, Jr., M.D., Brookwood Medical Center, Birmingham, Alabama. (Qualified for efficacy evaluation: 11/21)

Male or female patients with symptomatic urinary tract infections were selected to receive one 400-mg tablet of norfloxacin twice daily. The treatment period was at least seven days for lower urinary tract infections and at least ten to fourteen days for upper urinary tract infections. Exclusions were similar to those given above for controlled trials. Urine specimens were obtained for culture within 48 hours of the initiation of treatment, during the first 2-4 days of therapy, 5-9 days after completion of therapy, and 4-6 weeks after completion of therapy. The 4-6 week culture was optional. Appropriate physical examinations and laboratory studies were conducted. Ophthalmological and neurological tests were conducted before treatment and again at the one-week follow-up visit.

In studies of Drs. Goldstein, Harrison, Schaeffer, Snow, and Thomas, patients were to complete diary cards on which they described how they felt each day of

the study. The investigator was to review each diary card and comment on any adverse clinical experiences noted by the patient. In other studies, adverse reactions were to be recorded by the investigator.

There were 137 treatment courses given to 136 patients. Patients were mostly female (72%) and most infections were uncomplicated infections (61%) caused by a single pathogen (79%). Of these, 97 patients (courses) were evaluable for efficacy. The mean duration of therapy was 13 days. The mean duration for evaluable patients was 14.9 days and 90.8% of infections in evaluable patients were due to single pathogens.

Characteristics of evaluable patients are shown in the following table:

<u>Age (yrs.)</u>	<u>Males</u>	<u>Females</u>	<u>Total</u>
18-21	2	2	4
22-30	1	20	21
31-40	3	9	12
41-50	1	7	8
51-60	6	2	8
61-70	5	10	15
71-80	7	13	20
81-90	5	5	10
Total No.	30	68	98
Mean Age	61.3	49.4	53.0
Minimum	20	19	19
Maximum	87	90	90

The microbiological outcome for evaluable patients is given below:

	<u># Eradicated</u>	<u># Susceptible</u>	
Gram-positive			
<u>Staphylococcus</u> sp.	1/1		
<u>S. aureus</u>	2/3		
<u>S. epidermidis</u>	3/3		
<u>Staphylococcus</u> , coag.-	1/1		
<u>Streptococci</u> Group D	1/1		
Strep. Grp D enterococci	2/4		
Strep. beta-hemolytic	1/1		
Total Gram-positive	11/14	(79%)	
Gram-negative			
<u>Acinetobacter</u> sp.	0/1	(One developed resistance)	
<u>Citrobacter freundii</u>	3/3		
<u>E. aerogenes</u>	2/3		
<u>E. agglomerans</u>	1/1		
<u>Escherichia coli</u>	43/44		
<u>K. pneumoniae</u>	8/8		
<u>Proteus</u> species	1/1		
<u>P. vulgaris</u>	1/1		
<u>Pseudomonas aeruginosa</u>	13/14	(One developed resistance)	
Total Gram-negative	81/86	(94%)	
All	92/100	(92%)	6 persisted 2 acquired resistance

In regard to signs and symptoms, 76 of 89 patients (85%) who were symptomatic before therapy were symptom free at their post-therapy visit. Thirteen patients had at least one symptom at the follow-up.

Adverse reactions were experienced by 14 of 136 patients (10.3%) and adverse laboratory events were reported for 5 of 136 patients (3.7%).-

	<u>No. patients</u>
Adverse Reactions	
Nausea and headache	1
Nausea	2
Dizziness	1
Dizziness, nausea, tinnitus	1
Taste perversion	1
Dream abnormalities	1
Flatulence	1
Musculoskeletal disorders	1
Insomnia	1
Vaginal discharge	1
Headache	1
Dry skin	1
Constipation	1
Total	14 (10.3%)
Adverse Laboratory Reports	
Elevated Alk. Phosphatase	3
Elev. ALT/Dec. Seg. Neutrophils	1
Elevated BUN	1
Total	5 (3.7%)

The applicant concludes that norfloxacin is active in-vitro against uropathogens, that it is effective in treating urinary infections due to both gram positive and negative bacteria, that it is effective in treating complicated and uncomplicated infections whether polymicrobial or monomicrobial in nature, and that norfloxacin is safe in the treatment of these infections.

Medical Officer's Comment:

1. The applicant reports that patient diaries were kept in five of these eight studies, yet, completed diaries cannot be located. At least 100 patient diaries were requested. Patient diaries should be handwritten by the patient and should not be transcribed or altered in any way. Original unaltered diaries should have been filed as part of the case report forms. During the norfloxacin IND period, we talked about patient diaries as follows: Conference with Merck 8-1-82, TC 12-13-82, MOR 8-19-82, Letter to Merck 9-10-82, Letter from Merck 11-10-82, TC 3-11-83, MOR 12-19-83, and End of Phase II Conference 12-8-83.

2. The applicant's clinical outcome criteria which mistakenly included microbiological outcomes were disregarded. Clinical outcome was graded on the presence or absence of signs and symptoms.

b) (2) International Studies (Protocols No. 506-01 and No. 508-01) A multiclinic uncontrolled study of norfloxacin in the treatment of complicated and uncomplicated urinary tract infections in men and women over 18 years of age was conducted at 19 clinical centers in twelve countries. The protocols were essentially the same as the one for the domestic study of urinary tract infections described above (Section 3.b.1.) except for tablet strength. In Protocol No. 506-01, patients received two 200-mg tablets twice daily (five investigators), and in Protocol No. 508-01, patients received one 400-mg tablet twice daily (24 investigators).

The following investigators participated in this trial and treated the number of patients shown:

- Study No. 554 Pr. J. L. Albarede, Hospital Purpan, Toulouse, France. (Qualified for efficacy evaluation: 4/8)
- Study No. 545 Dr. Carlo P. Baccarani, Primario Divisione Urologica, Ospedale degli Infermi, Rimini, Italy. (Qualified for efficacy evaluation: 11/15)
- Study No. 535 Prof. Alberto Baglioni, Primario Chirurgo, Ospedale Generale Provinciale "SS. Trinita", Sora (Fr), Italy (Protocol #506-01). (Qualified for efficacy evaluation: 14/15)
- Study No. 539 Ross Raymond Bailey, M.D., Department of Nephrology, Christchurch Hospital, Christchurch, New Zealand. (Qualified for efficacy evaluation: 7/10)
- Study No. 549 Dr. Michael John Bendali, Senior Lecturer/Consultant Physician, Department of Health Care of the Elderly, University of Nottingham, Sherwood Hospital, Nottingham, UK. (Qualified for efficacy evaluation: 3/3)
- Study No. 538 Prof. Dr. med. P. Bruehl, Department of Urology, University of Bonn, Venusberg, West Germany. (Qualified for efficacy evaluation: 10/15)
- Study No. 565 Prof. W. Brumfitt, Head of the Department of Medical Microbiology, Royal Free Hospital, Hampstead, London, UK. (Qualified for efficacy evaluation: 4/5)
- Study No. 542 Dr. Franco Clara, Ospedale civico, Lugano, Switzerland. (Qualified for efficacy evaluation: 1/16)
- Study No. 564 N. Desplaces, M.D., Hospital St. Joseph, Paris, France. (Qualified for efficacy evaluation: 0/3)
- Study No. 530 Prof. C. Dimopoulos, Department of Urology, University of Athens Medical School, Athens, Greece. (Qualified for efficacy evaluation: 12/15)
- Study No. 518 Dr. Roberto Esguerra, Hospital Militar Central, Bogota, Colombia, So. America. (Qualified for efficacy evaluation: 11/15)

- Study No. 551 Prof. D. Fries, Hospital Paul Brousse, Villejuif, France. (Qualified for efficacy evaluation: 3/13)
- Study No. 534 Prof. Antonio Furbetta, Direttore della Cattedra di Urologia Ginecologica, University of Rome, Rome, Italy (Protocol #506-01). (Qualified for efficacy evaluation: 9/15)
- Study No. 533 Prof. Carlo Grassi, Clinica Tisiologica e Malattie dell'Apparato Respiratorio, University of Pavia, Pavia, Italy (Protocol #506-01). (Qualified for efficacy evaluation: 9/15)
- Study No. 541 W. D. Heinrich, Urologist, Essen, West Germany. (Qualified for efficacy evaluation: 12/15)
- Study No. 528 PD Dr. K. Hell, Kantonsspital, Liestal, Switzerland. (Qualified for efficacy evaluation: 2/6)
- Study No. 537 Dr. med. J. Jost, Urologist, Furstenfeldbruck, West Germany. (Qualified for efficacy evaluation: 9/15)
- Study No. 532 E. Kloek, Private Practice, Heenskerk, The Netherlands. (Qualified for efficacy evaluation: 4/12)
- Study No. 519 Louis Laplante, M.D., Assistant Professor, School of Medicine, University of Montreal, Hospital Maisonneuve-Rosemont, Montreal, Quebec, Canada. (Qualified for efficacy evaluation: 5/12)
- Study No. 555 Donald Albert Leigh, M.D., Consultant Bacteriologist, Wycombe and Amersham District General Hospitals, High Wycombe, Buckinghamshire, England. (Qualified for efficacy evaluation: 1/6)
- Study No. 548 John Rees Morgan, Senior Lecturer, Department of Medical Microbiology, Welsh National School of Medicine, Cardiff, Wales, United Kingdom. (Qualified for efficacy evaluation: 3/9)
- Study No. 544 Prof. Aldo Pauselli, Clinica Urologica, Ospedale Provinciale "S. Maria," Terni, Italy (Protocol #506-01). (Qualified for efficacy evaluation: 15/15)
- Study No. 531 Dr. J. Pretorius, Sandton Clinic, Peter Place, Lyme Park, Sandton, South Africa. (Qualified for efficacy evaluation: 10/13)
- Study No. 504 Nelson Rodrigues Netto Junior, Faculdade de Ciencias Medicas-UNICAMP, Campinas, Brazil. (Qualified for efficacy evaluation: 13/18)
- Study No. 546 J. P. Schepers, Gynecology Department, R. C. Hospital, Sittard, The Netherlands. (Qualified for efficacy evaluation: 9/21)
- Study No. 536 Albrecht Schilling, M.D., University Hospital for Urology, University of Munich, Munich, West Germany. (Qualified for efficacy evaluation: 13/15)

Study No. 516 Prof. Andrea Trenti, "Primario Chirurgo," Gubbio Hospital, Gubbio (Perugia), Italy (Protocol #506-01). (Qualified for evaluation: 14/15)

Study No. 559 Dr. P. Vialatte, Department Head, Visceral Surgery, Hospital St. Michel, Paris, France. (Qualified for efficacy evaluation: 0/1)

Study No. 552 Dr. D. White, Public Health Laboratory, Royal United Hospital, Combe Park, Bath, 'X. (Qualified for efficacy evaluation: 1/4)

For analysis, the applicant divided patients into two groups: evaluable and assessable. Evaluable patients were those who contributed bacteriological data. Assessable patients were those in whom follow-up cultures were not taken within the specified day ranges or those who had only one follow-up post-therapy urine culture. However, having met all other criteria for evaluability, a bacteriological outcome could be determined in these patients. The applicant reports that for these patients a single post-therapy urine culture obtained within 20 days after drug discontinuation determined bacteriological outcome.

Another change was that a pretherapy culture obtained within 12 days before initiation of the study was acceptable.

Patients with bacteriological outcomes of "suppressed" (during therapy culture equal to or less than 10^4 but post-therapy culture greater than 10^4) and "persisted" were treatment failures.

The five Italian investigators who gave two 200-mg tablets twice daily treated 75 patients and other investigators treated 265 patients, a total of 340 patients. One investigator, Dr. Rodriguez-Netto, conducted neurological examinations before and after therapy on 18 patients.

Of the 340 patients, the applicant found 209 evaluable patients. The distribution by age and sex is shown below:

<u>Age (yrs.)</u>	<u>Males</u>	<u>Females</u>	<u>Total</u>
No data		1	1
5-19	1	7	8
20-29	4	27	31
30-39	4	21	25
40-49	10	21	31
50-59	14	25	39
60-69	14	17	31
70-79	20	17	37
80-89	1	4	5
90-99		1	1
Total No.	68	141	209
Mean Age	57.5	47.0	50.4
Minimum	13	9	9
Maximum	81	90	90

The applicant reports microbiological outcome (number eradicated/number of patients) for evaluable patients as follows:

	Upper UTI	Lower UTI	Total
Complicated UTI	12/14	50/57	62/71
Uncomplicated UTI	22/29	103/109	125/138
Total	34/43	153/166	187/209

Forty-three clinical adverse experiences were reported in 27 patients. Some of them are listed below.

	No. patients
Serious and definitely drug related	
Anxiety, dry mouth, tachycardia, rash, tongue enlargement, euphoria, accommodation disorder (Day 1)	1 Recovered
Serious and probably not drug related	
Fever, purpura, knee pain (Day 2)	1 Recovered
Serious and not drug related or other	
Severe convulsive disorder (Day 1)	1 Recovered
Congestive heart failure (Day 18)	1 Died
Cerebrovascular accident (Day 41)	1 Died
Shock, hypovolemia (Day 6)	1 Died
Acute myocardial infarction (Day 6)	1 Died
Hypovolemic shock (Day 31)	1 Died
Other	
Cutaneous rash	1
Nausea	3
Nausea and vomiting	1
Heartburn	1

Only 14 of the 43 adverse reactions are summarized. (The above table is the medical officer's combination of two summary tables.)

Forty patients (12%) had laboratory adverse experiences. None were reported to be serious, definitely or probably drug related. None were statistically significant. Drug crystalluria which was reported for one patient during therapy disappeared in the post-therapy urinalysis. There is no summary table of abnormal laboratory values. Summary tables compare pretherapy mean values with post-therapy mean values but do not list the 40 adverse laboratory experiences.

The applicant concludes that norfloxacin has excellent in vitro antimicrobial activity against bacteria encountered in upper and lower UTI. It is effective in women and men in the treatment of upper and lower UTI caused by susceptible bacteria. It is effective in UTIs caused by P. aeruginosa in patients without severe structural or functional abnormalities of the urinary tract. It is effective in the treatment of acute pyelonephritis and complicated UTIs caused by susceptible bacteria. Norfloxacin is well tolerated at oral doses of 400 mg twice daily for ten days. Norfloxacin has a good safety profile for oral

administration at these doses.

Medical Officer's Comments: This study has not been analyzed in such a manner that one can come to these conclusions. The applicant should re-analyze this study so that the following deficiencies are corrected:

1. The clinical outcome criteria which contain microbiological assessments should be disregarded. The clinical outcome should be based upon a comparison of the presence or absence of signs and symptoms before and after therapy.
2. "Assessable" patients should be regarded as unevaluable patients.
3. Patients with pretherapy urine cultures obtained earlier than 48 hours before the initiation of treatment should be considered unevaluable. In this study pretherapy cultures were considered if they were obtained within 12 days of the initiation of treatment.
4. Culture timing requirements are not acceptable and should be revised to be in keeping with FDA guidelines for the treatment of urinary tract infections. In this study, they were changed from those specified in FDA's guidelines that were used in other studies to read as follows:

Relative-Day Ranges (page I-6157, Vol 2.17)

Protocol	Actual	Nomenclature Used in Text
Day 3 or 4 during therapy	Days 2 to 5 during therapy	During therapy
5 to 9 days post-therapy	5 to 20 days post-therapy	Post-therapy
4 to 6 weeks post-therapy	25 to 48 days post-therapy	Late post-therapy

5. Patients under 18 years of age should be disqualified. There are approximately eight, the youngest was 9 years old.
6. No effort should be made to separate upper and lower urinary tract infections because of the impreciseness of the diagnostic technique.
7. The report lacks a summary table which gives the microbiological outcome according to uropathogens.
8. Adverse reactions are tallied in the appendix but the report lacks a summary table to show all 43 adverse reactions. Unfortunately, no patient diaries were used in this study.
9. Summary tables compare pretherapy mean values with post-therapy mean values but do not list the 40 adverse laboratory experiences.

c) Compassionate Treatments

(c) (1) Treatment of Salmonellosis

Studies No. 61, 62, 63, 67, and 71 Two investigators used norfloxacin on a compassionate basis to treat six patients for salmonellosis. Investigators were

Robert Lyons, M.D., St. Francis Hospital, Hartford, CT. (Qualified for efficacy evaluation: 4/5)

Howard A Nadworny, M.D., St. Mary's Hospital, Waterbury, CT. (Qualified for efficacy evaluation: 1/1)

Norfloxacin was given in doses of 400 mg twice daily (4 patients) and three times daily (1 patient) for 8-22 days. One patient who was treated twice was treated for 43 days. There were three females and two males. Three patients were 83 years of age, one was 88 and the other was 62. Salmonella species isolated from each patients were susceptible to norfloxacin. The organism was eradicated after norfloxacin treatment in three of the five patients. One patient developed eosinophilia.

The applicant concludes that norfloxacin is effective in the eradication of salmonellosis in patients with active infection or chronic carrier states. The applicant concludes that norfloxacin is safe when given as 400 mg bid for up to 43 days to treat salmonellosis.

Reviewer's Comments: Data from this study are inadequate to draw these conclusions.

(c) (2) Treatment of Multiple Antibiotic Resistant Infections

Studies No. 68, 23, 33, 20, 22, 69, 42, 43, 44, 52, 47 Seven investigators in United States treated thirteen patients compassionately for infections due to organisms resistant to multiple antimicrobial agents. The investigators are listed below.

Study No. 23 Myles Gombert, M.D., SUNY Downstate Medical Center, Brooklyn, NY. (Qualified for efficacy evaluation: 1/1)

Studies No. 20 and 22 Ralph Landes, M.D., Danville Urologic Clinic, Danville, VA. (Qualified for efficacy evaluation: 2/2)

Studies No. 42, 43, 44, and 52 John Ryan, M.D., West Haven V.A. Hospital, West Haven, CT. (Qualified for efficacy evaluation: 4/4)

Study No. 47 James Tan, M.D., Professional Center, Akron, OH. (Qualified for efficacy evaluation: 1/1)

Study No. 33 H. Bradford Hawley, M.D., Good Samaritan Hospital, Dayton, OH. (Qualified for efficacy evaluation: 1/1)

Study No. 68 S. Fikrig, M.D., SUNY Downstate Medical Center, Brooklyn, NY. (Qualified for efficacy evaluation: 1/1)

Study No. 69 Wick Many, M.D., 3439 Prytania, Suite 508, New Orleans, LA. (Qualified for efficacy evaluation: 1/1)

Ten patients were treated for complicated urinary tract infections. One seven-year old boy with chronic granulomatous disease of childhood and who was treated for salmonellosis was a special entry patient. Doses varied from 100 mg tid to 400 mg bid. Repeat courses for two of these patients are not included in the analysis.

Microbiological outcome is summarized as follows

	<u>Eradicated</u>	<u>Persisted/Suppressed</u>
<u>P. aeruginosa</u>	3/8	5/8
<u>E. coli</u>	0/1	1/1
<u>S. epidermidis</u>	0/1	1/1
<u>Salmonella species</u>	0/1	1/1

Eight of eleven treatments were failures, three were successes.

One patient had an adverse experience, insomnia. The seven-year old boy had close neurological and ophthalmological supervision during therapy. A line walk and observation for joint pain and limp were performed. No such adverse experiences occurred.

The applicant does not draw conclusions from these studies.

✓ Medical Officer's Comment: The applicant did not include these data in the total data on efficacy in this NDA. They should have been included.

d) Suppression of Aerobic Bowel Flora in Patients With Granulocytopenia

d) (1) Studies No. 19 and 15 Two investigators participated in a double-blind, randomized controlled trial of norfloxacin plus nystatin and placebo plus nystatin in the prevention of infections in patients with neutropenia. Investigators were

Study No. 19 Robert Harold Rubin, M.D., Associate Professor of Medicine, Massachusetts General Hospital, Boston, MA. (Qualified for efficacy evaluation: 0/4. Qualified for safety evaluation: 4/4.)

Study No. 15 George Harrison Talbot, M.D., Hospital Epidemiologist, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania. (Qualified for efficacy evaluation: 0/19. Qualified for safety evaluation: 19/19.)

Patients enrolled in this study received either one 400-mg tablet of norfloxacin tid or one tablet of placebo tid. In addition, all patients received 1.0 mg of nystatin, 100,000 units per ml. qid.

There were 27 treatment courses given in these two studies to 23 patients. Twelve were treated with norfloxacin/nystatin and eleven with placebo/nystatin. Only the first entry of multiple-entry patients was included in the safety analysis.

Nine patients (75%) treated with norfloxacin and seven patients (64%) treated with placebo reported one or more adverse effects. None was considered by the investigator to be drug related. The applicant reports them as follows:

Clinical Adverse Experiences (Table S1 - Vol. 2.20, p. I-07158)

	Placebo (n=11)		NOROXIN™ (n=12)	
<u>Drug Related</u>	0		0	
<u>Serious</u>	3	(1)	3	
Peripheral Nervous System Disorder	1		0	
Fungus Infection	1		2	
Blood Stream Infection	1		0	
Intra-abdominal Abscess	1		0	
Death	2	(1)	3	
Intra-cerebral hemorrhage	0	(1)	0	
Pneumonia	0		1	
<u>Not Serious</u>	7 ^a	(1)	9 ^a	(1)
Nausea	1		3	
Diarrhea	5	(1)	6	
Visual Disturbances	0		1	
Rash	4		5	(1)
Flatulence	1		0	
Vomiting	3	(1)	0	
Jaundice	0		1	
Anorexia	1		2	
Fever	3		2	
Pharyngeal Pain	0		1	
Melena	0		1	
Headache	0		1	
Epistaxis	0		1	
Abdominal Pain	1		1	
Gingivitis	0		1	
Cough	1		0	
Nasal Congestion	1		0	
Dysphagia	1		0	
Mouth Ulcer	1		0	
Pneumothorax	1		0	
Dysuria	1		0	
Anal and Rectal Pain	1		0	
Total Single Entry Patients with at Least One Adverse Experience	7	(64%)	9	(75%)
Total Single Entry Patients without Adverse Experience	4	(36%)	3	(25%)
Total Single Entry Patients	11		12	

(#) number of multiple entry patients with AE.

(a) Three patients had both serious and not serious adverse experiences.

Five patients treated with norfloxacin and one patient treated with placebo had laboratory values that were considered adverse by the investigator. This difference was not significant.

<u>Adverse Laboratory Experiences</u>	<u>Placebo/N</u>	<u>Norfloxacin/N</u>	
Drug Related	0	0	
Not Drug Related			
Elevated AST and Urine Glucose	0	1	
Elevated Total Serum Bilirubin	0	3	
Elevated Alk. Phos. and/or Serum LDH	0 (1)		
Elevated Urine RBC	0	1	
Elevated Urine WBC	1	0	
Elevated Urine Protein, WBC, RBC	0	1	
Total Number of Patients with Laboratory Adverse Experience	1 (9.1%)	5 (41.7%)	
Total Number of Patients without Laboratory Adverse Experience	10 (90.9%)	7 (58.3%)	
Total	11	12	

() Number of multiple-entry patients with adverse laboratory experience.

The applicant concludes that there appear to be no differences between the number of adverse experiences with norfloxacin and placebo. The types of adverse experiences are similar. Norfloxacin appears to be as safe as placebo when given to patients who are neutropenic.

Medical Officer's Comments:

1. The applicant failed to analyze these data for efficacy or to explain why this was not done. The medical officer's review of the data reveals that cases cannot be evaluated for efficacy because all patients received one or more other highly active antibiotics that interfered with the evaluation of outcome due to the test regimens. One patient received thirteen antibiotics, one received ten, seven received between 7 and 9, and the rest received one or more other antibiotics.
2. Unfortunately, no diaries were kept in this study. Diaries from patients receiving this high dose, 1200 mg/day, would have been important for the evaluation of daily side effects.
3. A norfloxacin adverse reaction rate as high as 75% seems to be unacceptable. At the same time, an adverse reaction rate in the placebo group of 64% is not to be consistent with what might be expected with placebo. (Oral nystatin is considered to be well tolerated. Large oral doses have occasionally produced GI reactions but these were not large doses.) The applicant's summary of adverse reactions is difficult to interpret. Adverse reactions as summarized by the reviewer are shown below.

Case #		Norfloxacin/ Nystatin	Placebo/ Nystatin
#403	Nausea, Diarrhea, Anorexia, Fever	1	
#404	Diarrhea	1	
#406	Nausea, Rash, Visual Disturbances	1	Disc.
#408	Rash (Re-entry of #402)	1	Disc.
#411	Fungus Infection, Pharyngeal Pain, Melena, Rash, Death*	1	
#414	Anorexia, Headache, Diarrhea, Jaundice	1	
#418	Diarrhea, Pneumonia, Death*	1	
#419	Diarrhea, Rash	1	
#477	Fungus Infection, Diarrhea, Rash Death*	1	
#480	Epistaxis, Fever, Abdominal Pain, Rash, Gingivitis, Nausea	1	Disc.
#401	Fever, Diarrhea, Flatulence (See #409 & #416)		1
#402	Fever Cough, Nasal Congestion, Vomiting, Dysphagia, Mouth Ulcer, Diarrhea, Rash (See #408)		1
#405	Anorexia, Nausea, Rash, Diarrhea, Fungus Infection, Death*		1
#407	Peripheral Nervous System Disorder Rash		1 Disc.
#409	Diarrhea, Vomiting (Re-entry #401)		1 Disc.
#410	Vomiting		1 Disc.
#413	Diarrhea, Vomiting, Rash, Blood- stream Infection, Intra-Abdom. Abscess, Death*		1
#416	Death*, Intracerebral Hemorrhage (3rd Entry for #401)		1
#479	Pneumothorax, Dysuria, Abdominal Pain, Diarrhea, Anal & Rectal Pain		1
	No. pts. with one or more adverse reactions	9 (75%)	7 (64%)
	No. pts. without adverse reactions	3	4
	Total	12	11

* Death not drug related.

d) (2) Study No. 24 Jack L. LeFrock, M.D., Chief, Division of Infectious Diseases and Clinical Microbiology, Hahnemann Medical College and Hospital of Philadelphia, initiated a randomized controlled study to compare a regimen of norfloxacin plus nystatin with a regimen of trimethoprim/sulfamethoxazole (TMP-SMZ) with nystatin in the prophylaxis of infections in patients with neutropenia. At the time this application was filed, two TMP-SMZ patients had been treated. Both patients experienced rashes which were considered possibly drug related.

4. Controlled Urinary Tract Infection Studies Filed for the Evaluation of Safety Only

a) Studies No. 507, 508, 512, 509, 510, and 511 Six investigators in two countries followed Protocol No. 503-01 to conduct a randomized, controlled, nonblinded comparison of norfloxacin and trimethoprin/sulfamethoxazole (TMP-SMZ) in the treatment of acute uncomplicated urinary tract infections. The following investigators participated in this study:

Study No. 507 Prof. Alberto Albertazzi, Chief of Urology Department, University of Chieti, Italy. (Qualified for efficacy evaluation: 10/10 norfloxacin patients and 10/10 TMP-SMZ patients)

Study No. 508 Prof. George K. Daikos, Head of the Department of Medicine, Athens University Medical School, Athens, Greece. (Qualified for efficacy evaluation: 8/10 norfloxacin patients and 10/10 TMP-SMZ patients)

Study No. 512 Prof. Rullio Lotti, Director of Urology Department, University of Naples, Italy. (Qualified for efficacy evaluation: 10/10 norfloxacin patients and 10/10 TMP-SMZ patients)

Study No. 509 Prof. Ettore Martini, Head of Urology, S. Salvatore Hospital L'Aquila, Italy. (Qualified for efficacy evaluation: 10/10 norfloxacin patients and 9/10 TMP-SMZ patients)

Study No. 510 Prof. Lucio Miano, Head of Urology Department, University of Rome, Italy. (Qualified for efficacy evaluation: 10/10 norfloxacin patients and 10/10 TMP-SMZ patients)

Study No. 511 Prof. Fabio Prosperi, Head of Urology Department, S. Camillo Hospital, Rome, Italy. (Qualified for efficacy evaluation: 8/10 norfloxacin patients and 6/10 TMP-SMZ patients)

Characteristics of evaluable patients are shown in the following table:

Age (yrs.)	Norfloxacin			TMP-SMZ		
	Males	Females	Total	Males	Females	Total
11-12	1	1	2			
13-17		1	1		1	1
18-21		3	3		2	2
22-30		7	7		11	11
31-40	1	10	11		7	7
41-50	3	8	11	1	6	7
51-60	4	4	8	2	8	10
61-70	5	2	7	7	3	10
71-80	4	2	6	6	1	7
Total No.	18	38	56	16	39	55
Mean Age	56.9	49.3	45.0	66.8	40.2	47.9
Minimum	12	11	11	44	16	16
Maximum	73	73	73	74	74	74

Patients selected for the study were ambulatory outpatients with urinary tract infections caused by bacteria proven susceptible to both norfloxacin and TMP-SMZ. Urine specimens were obtained for gram stain and ACB testing. Patients with positive ACB test results were withdrawn from the study and received appropriate alternate therapy. Exclusions were similar to those given for other UTI studies.

In this study, 115 patients received either 200 mg of norfloxacin bid or 80/400 mg of TMP-SMZ bid. The duration of treatment was ten days.

Although clinical visits were scheduled on Day 3 or 4 during therapy, five to nine days after therapy, and four to six weeks after therapy, some patients did not have their visits exactly at these times. A broader range for the collection of urine specimens for culture similar to the one that was used in the uncontrolled international UTI study, above, was used in this study as follows:

Visit	Urine Specimen for Culture
Day 3 or 4 during therapy	Days 3 to 7 during therapy
5 to 9 days after therapy	5 to 14 days after therapy
4 to 6 weeks after therapy	20 to 88 days after therapy

Four patients in the norfloxacin group and five in the TMP-SMZ group were considered to be nonevaluable and were excluded from the analysis of efficacy because of inadequate bacteriological data.

Treatment groups differed markedly ($p = \text{less than } 0.0001$) with respect to baseline susceptibility patterns of causative pathogens. Twenty pathogens from 20 patients were susceptible to one study drug and not to the other and all received the drug to which the pathogen was susceptible. Eighteen of these patients were in the norfloxacin group. This strongly suggests that randomization was not strictly followed and is a source of bias.

The applicant reports microbiological outcome and clinical outcome for evaluable patients as follows:

	Norfloxacin	TMP-SMZ
Microbiological Outcome		
Eradicated	51 (94%)	45 (87%)
Suppressed/Persisted	3 (6%)	7 (13%)
Clinical Outcome		
Cured/Improved	52 (96%)	45 (87%)
Not Improved	2 (4%)	7 (13%)

E. coli, Proteus mirabilis, and K. pneumoniae were the most frequently isolated uropathogens. All others were isolated four times or less.

Only one patient reported a clinical adverse experience in this study. She experienced gastric fullness on the eighth day of treatment with TMP-SMZ. Three patients had adverse laboratory experiences and all occurred 5-9 days after treatment. One norfloxacin-treated patient had an increased bilirubin,

and two TMP-SMZ-treated patients experienced increased LDH and increased potassium, respectively.

The applicant concludes that norfloxacin has in vitro antimicrobial activity superior to that of TMP-SMZ against bacteria encountered in UTI, that it is at least as effective in the treatment of UTI, and that it is well tolerated and safe at oral doses of 200 mg twice daily for ten days.

After the cut-off date, five additional case reports were received. Three patients were treated with TMP-SMZ and two were treated with norfloxacin. There were no clinical or laboratory adverse effects.

Medical Officer's Comments: No conclusion can be drawn from this study.

1. This study cannot be used in the evaluation of efficacy for the following reasons:

- a) Removal of patients with positive tests for ACB after randomization and after treatment had begun biased results as does the assignment based upon the susceptibility of the pathogen.
- b) The change in the recommended times for the collection of urine specimens for culture is not acceptable as mentioned above on page 68 in the review of uncontrolled international studies.
- c) The medical officer agrees with the applicant's observation that there may be a randomization allocation bias because treatment groups differed significantly in regard to susceptibility patterns of uropathogens ($p = \text{less than } 0.0001$).
- d) The clinical outcome based upon a change in clinical signs and symptoms plus laboratory test results is not acceptable. Clinical outcome should be based upon signs and symptoms alone.

2. No diaries were reported for this study and there is no evidence that any special effort to observe the presence or adverse reactions was made.

3. There is no report of the presence or absence of drug crystallization in the urine.

4 (b) Studies No. 568, 567, 693, 573, 694, 574, and 692 Seven investigators in the United Kingdom participated in a multiclinic, randomized, controlled trial to compare a three-day course of norfloxacin with a three-day course of nalidixic acid/sodium citrate in patients twelve years of age or older in the treatment of uncomplicated urinary tract infections. Investigators were

Study No. 568 Adrian John Bint, M.B., Ch.B., Consultant Microbiologist, Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom. (Qualified for safety evaluation: norfloxacin 17/17 patients and 17/17 nalidixic acid patients)

Study No. 567 R. W. Lacey, M.D., District General Hospital, Kings Lynn, Norfolk, United Kingdom. (Qualified for safety evaluation: norfloxacin 43/43 patients and 16/16 nalidixic acid patients)

Study No. 693 Meena Mahendra, M.B.B.S, Department of Microbiology, West Middlesex Hospital - Isleworth, Middlesex, U.K. (Qualified for safety evaluation: norfloxacin 11/11 patients and 11/11 nalidixic acid patients)

Study No. 573 Dr. R. V. Mummery, Consultant Microbiologist, Enfield District Hospital, Enfield, Middlesex, UK. (Qualified for safety evaluation: norfloxacin 17/17 patients and 21/21 nalidixic acid patients)

Study No. 694 S. W. B. Newson, M.D., Consultant Microbiologist, Addenbrooke's Hospital, Cambridge, U.K. (Qualified for safety evaluation: norfloxacin 5/5 patients and 5/5 nalidixic acid patients)

Study No. 574 David Sims Reeves, M.R.C.Path, Consultant Medical Microbiologist, Southmead Hospital Group, South Western Regional Hospital Board, Bristol, U.K. (Qualified for safety evaluation: norfloxacin 28/28 patients and 28/28 nalidixic acid patients)

Study No. 692 M. O. Unadkat, M.D., St. Johns Health Center, Twickenham, London, U.K. (Qualified for safety evaluation: norfloxacin 5/5 patients and 4/4 nalidixic acid patients)

Nonpregnant females and males 12 years and older with symptoms of uncomplicated urinary tract infections and with positive urine cultures were selected. There were 126 patients in the norfloxacin group and 102 in the nalidixic acid/Na citrate group. Patients received either one 400 mg tablet of norfloxacin twice daily or one sachet containing 0.66 g nalidixic acid and 3.75 g of sodium citrate (MICTRAL) three times daily for three days.

Clinical efficacy was judged by the investigator and specimens were obtained for the microbiological evaluation one week after the initiation of the three-day course. Another culture was obtained 4-6 weeks after therapy. There was no during-therapy culture.

The investigator monitored and recorded adverse experiences volunteered by the patient. There were no serious adverse reactions. No laboratory adverse experiences were reported in these studies. Some patients had more than one adverse experience. Also, some patients had both drug related and non-drug related adverse experiences. Eleven patients had vaginal pruritis, irritation and discharge, and vaginitis monilial: these reactions were not considered adverse experiences.

Adverse reactions are summarized in the following table.

Adverse Reactions	Total		Drug-Related		Not-Related		Relationship Unknown	
	Norflx	Nal/Cit	Norflx	Nal/Cit	Norflx	Nal/Cit	Nor.	Nal/Cit
Abdominal Pain	1	1	0	0	1	0	0	1
Asthenia	1	1	0	1	1	0	0	0
Fatigue	3	3	0	1	3	1	0	1
Constipation	1	1	0	0	1	1	0	0
Diarrhea	3	7	1	0	2	7	0	0
Flatulence	0	1	0	0	0	1	0	0
Dry Mouth	0	1	0	1	0	0	0	0
Dyspepsia	1	1	1	1	0	0	0	0
Tongue Pain	0	1	0	0	0	1	0	0
Heart Burn	1	0	0	0	1	0	0	0
Mouth Ulcer	2	0	0	0	1	0	1	0
Nausea	11	20	4	10	6	10	0	0
Vomiting	0	3	0	1	0	2	0	0
Leg Pain	1	0	0	0	1	0	0	0
Depression	2	3	0	1	2	0	0	0
Weakness, local	1	1	0	0	1	1	0	0
Dizziness	5	7	2	1	3	5	0	1
Hallucinations	1	0	1	0	0	0	0	0
Explosive Personality Disorders	1	0	0	0	1	0	0	0
Headache	12	12	1	2	11	9	0	1
Somnolence	5	2	1	1	4	1	0	0
Rash	3	1	1	0	2	1	0	0
Flashing Lights	0	1	0	1	0	0	0	0
Dysmenorrhea	1	0	0	0	1	0	0	0
Vaginal Swelling	1	0	1	0	0	0	0	0
Breast Pain	0	1	0	0	1	0	0	0
Renal Colic	1	0	0	0	1	0	0	0
No. pts. with one or more ARs	38	44						
Percent (p = less than 0.05)	30.2%	43.1%						
Total Patients	126	102						

The applicant concludes that regardless of drug relationship, fewer clinical adverse experiences occurred with norfloxacin than with nalidixic acid even when nalidixic acid is given at two grams daily, one-half the recommended dose in United States.

Medical Officer's Comments: (The reviewer redesigned the applicant's adverse reaction table to put drug-related, not-drug-related, and relationship-unknown adverse reactions side by side together with a total for each type of reaction.)

1. The reviewer agrees with the applicant in considering this study for safety only. A three-day course of nalidixic acid for the treatment of UTIs is not recommended in the labeling. Therefore, what was used as a control regimen is an investigational regimen. Also, FDA guidelines were

not followed in this study.

2. Patients between 12 and 17 years of age should be disqualified from any type of evaluation

3. Some adverse reactions which the investigator labeled not-drug-related reactions are very likely drug related and are typical of the type of adverse reactions that occur with the quinolones.

4 (c) Study No. 53 Allan Ross Ronald, M.D., Head, Section of Infectious Diseases, Department of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada, is conducting a randomized controlled study to compare norfloxacin and nalidixic acid in the treatment of patients with urinary tract infections. The study is ongoing. At the time the application was filed, 25 patients had been selected for the study, 12 in the norfloxacin group and 13 in the nalidixic acid group. Patients received either one 400-mg tablet of norfloxacin twice daily or one one-gram tablet of nalidixic acid qid for 7 to 14 days. All patients are completing diaries.

In these 25 reports, there were six patients with adverse reactions, three in each group as follows:

Norfloxacin

#2113 Dry mouth, suprapubic pain, vaginal pain	Drug discontinued
#2132 Scratchy eyes	Drug discontinued
#2135 Headache, abdominal pain	Drug discontinued

Nalidixic Acid

#2106 Nausea	Not discontinued
#2128 Emotional lability	Discontinued
#2131 Nausea	Not discontinued

Efficacy is not summarized or discussed. The applicant makes no attempt to draw conclusions from this study.

Medical Officer's Comments: There is clearly a difference between the way the applicant summarizes adverse reactions and the way the medical officer summarizes the same adverse reactions.

The medical officer reviewed the diaries in this study and found thirteen patients instead of six with adverse reactions to the two quinolones. Most of these reactions are typical of those which have been found with other quinolones. Diary entries which appear to be symptoms of the urinary tract infections were not included. Adverse reactions according to the MO's review of the diaries are listed as follows:

Norfloxacin

#2101 Diarrhea, headache (8-day course)

#2108 Slept poorly (6-day course)

#2111 Very tired, no energy, bloated, chills (8-day course)

#2113 Tired, thirsty, sweaty, uncomfortable, don't feel like walking, nausea, dry mouth, sick feeling in stomach

Disc. Day 3

#2132 Right hand tingles, eyes sore and sandy, burning eyes, eyes tired, sore and irritable, hands swollen, chills, nausea

Disc. Day 13

#2134 Nausea, backache (14-day course)

#2135 Headache, wavy lights in right eye

Disc. Day 2Nalidixic Acid

#2105 Aching legs, arms, and back (8-day course)

#2106 Upset stomach (7-day course)

#2114 Dizziness, cramps (5-day course)

#2128 Tired, tense, edgy, bad nerves, real sick

Disc. Day 7

#2129 Tired, dizzy, weak (14-day course)

#2131 Hard time getting to sleep, headache, sore stomach, dizzy

Disc. Day 4, Refused to return.AMENDMENTS:

April 2, 1985 In response to my request, the applicant files the interim summary of the dose-escalation, placebo-controlled study conducted by Dr. Roger Ferguson, Study No. . . . The report had been filed in the companion IND, instead of the NDA. As stated on pages 9 and 10 of this MOR, the report of this study in the NDA was incomplete. It lacked a report of the presence or absence of drug crystals. Urine was to be examined for crystals in the fractions collected 0-1, 1-2, 2-3, 3-4, and 4-6 hours after administration of norfloxacin. Urine volume and pH were to be measured, an aliquot was to be maintained in a 37° bath before being spun, and the sediment examined for the presence of crystals. There were 14 subjects in six treatment groups and 13 subjects in the highest dose treatment group.

The applicant reports that the review of the microscopic findings in the urine

regarding the presence of crystals shows that no morphological specificity was present since the type of crystals found in the urine after norfloxacin treatments were also present after treatment with placebo. Three types of crystals were identified, amorphous granular material, irregular spheres with multiplane and spiky edges, and spicule or needlelike crystals found individually or in small aggregations. The amorphous type material was extensively present following both placebo and norfloxacin treatments. No particular significance can be ascribed to it. Both the incidence and frequency of spherical and needle-like material do not support a drug-related increased potential for significant crystalluria. It should be noted that urinalysis did not show findings of mechanical irritation or other noxious effects on the urinary tract, i.e. increased urine content of red blood cells, white blood cells, renal tract epithelial cells, or protein in the norfloxacin-treated subjects. The number of urine samples with microscopic findings is shown below:

Treatment	No. Urine Samples Examined	Amorphous Granular Material	Spheres	Needle-like
Placebo	68	15	0	1
Placebo	67	24	2	1
Norfloxacin				
200 mg	69	9	1	0
400 mg	68	13	5	0
800 mg	70	27	3	0
1200 mg	69	34	5	3
1600 mg	64	19	3	6

The applicant concludes that, qualitatively, the crystals present in the urine could not be identified as being morphologically characteristic of the drug and their frequency did not suggest a potential for crystalluria, at least in the proposed therapeutic dose range of the drug.

Medical Officer's Comment: Unfortunately, crystals have not been identified. It is not known if these are crystals of norfloxacin or the metabolites of norfloxacin or crystals of something else. Similar data should be provided following multiple dosing and the crystals should be identified. Item #3 in FDA's letter to the applicant on June 17, 1981 about the IND reads, "Urine sediment should be examined for the presence of drug crystals in subsequent pharmacokinetic studies until it is established that drug crystallization is not a problem." The request following multiple dosing was specifically requested again in FDA's letter to Merck Sept. 10, 1982.

July 23, 1985 At the Swedish Microbiology Society Meeting, Professor Arne Forsgren reported his observation that stimulated T and B lymphocytes exhibited an increase in DNA synthesis (30-40%) as measured by incorporation of tritiated thymidine when ciprofloxacin, norfloxacin, and ofloxacin were added to the culture. He also found doubling of DNA synthesis when these quinolones are added to cultures of stimulated lymphocytes with hydroxyurea added to block S phase DNA synthesis. These were interpreted as induced repair synthesis. The number of DNA strand breaks studied in Epstein-Barr transformed lymphoblasts were also found to be increased when exposed to quinolones. The applicant gives six reasons why these observations of an apparent increase in induced DNA repair synthesis is of little significance as to human risk.

August 1, 1985 The applicant responds to a request from Dr. K-Y Lo of the Division of Biopharmaceutics for additional information.

September 13, 1985 In response to a telephone conversation with Mr. John Davitt, pharmacologist, the applicant files a copy of a published article by Dr. David Levin which provides the results of an Ames test using the Salmonella strain TA102.

Medical Officer's Comment: The applicant filed a 42-page computer printout instead of a simple half-page summary table. Adverse laboratory experiences are tallied from this printout by the MO as follows:

	Norfloxacin TMP-SMZ		Norfloxacin TMP-SMZ	
Hemoglobin dec.	4/184	9/174	ALT inc.	8/168 9/154
Hematocrit dec.	2/163	8/152	Alk. Phos inc.	4/166 10/156
WBC dec.	4/184	7/173	Serum LDH inc	2/128 3/120
inc.	1/184	0/173	Ser. Na inc.	1/178 1/169
Neutrophil dec.	2/171	2/159	Ser. K dec.	2/178 2/169
Lymphocytes inc.	1/171	0/159	inc.	1/169
Eosinophils inc.	12/170	7/158	Ser. Cl inc.	3/132 5/126
Platelets inc.	2/176	4/153	dec.	4/132 1/126
dec.	1/176	1/153	Urine	
Blood urea inc.	1/34	1/36	Protein inc.	2/176 0/166
BUN inc.	3/149	3/132	Glucose inc.	2/176 0/164
Ser. creat. inc.	1/182	4/171	WBCs inc.	1/185 2/171
Tot S. Bilir. inc.	3/179	0/167	RBCs inc	2/175 1/166
AST	10/182	11/168	Hyaline casts	0/2 1/4

October 10, 1985 In response to my request, the applicant files copies of curricula vitae for clinical investigators.

October 18, 1985 In response to my request, the applicant indicates that 94 (83 norfloxacin and 11 nalidixic acid) patient diaries had been filed in the original application from four studies, #45, #59, #66, and #53.

Medical Officer's Comments:

1. The MO's reviews of these diaries will be found on pages 12-13, 17, and 79-80.

2. Diaries from Dr. Zinny's study #59 cannot be included as part of the minimum 100 diaries that FDA required because this study was a single-dose study. We asked for as many diaries as possible but we required a minimum of 100 patient diaries, diaries which were prepared by patients who were receiving full doses for the longest recommended treatment period.

In my telephone conversation with the director of regulatory affairs, I reminded him that patient diaries have been specifically requested with all of the quinolones to address drug safety. Therefore, the MO disqualifies diaries from Dr. Zinny's Study #59 in this regard. That leaves 63 norfloxacin diaries instead of 83 in the original submission. Dr. Zinny's single-dose study diaries show that 18% and 32% of subjects report adverse reactions after a single 400-mg tablet.

Under the norfloxacin IND, we talked about patient diaries as follows:

Conference with Merck 8-18-82
Telephone Call 12-13-82
MOR 8-19-82
Letter to Merck 9-10-82
Letter from Merck 11-10-82

Telephone Call 3-11-83 (Design of
the diary card)
MOR 12-19-83
End of Phase II Conference 12-8-83

The failure to submit diaries is a major deficiency of the application. I would not consider the application completely filed until all patient diaries have been filed.

Undated Amendment Received October 30, 1985 In response to my request, the applicant rechecked its patient diaries and learned that diaries from 50 norfloxacin patients and 17 TMP-SMZ patients (total 67) from five other studies were available from investigators. These have never been submitted and are submitted now. The applicant, however, failed to summarize these diaries.

Medical Officer's Comment: These new diaries have been reviewed by the MO. Positive symptoms that are not related to the urinary tract infection are summarized by the medical officer as follows:

1. From the Phase III uncontrolled domestic urinary tract infection study (See 3 b (1), above.)

Study No. 40 Dr. Snow Five of six diaries are acceptable. Four of five patients had one or more effects.

- #2003 Slight headache all afternoon - Days 1-2. Slight headache all day - Day 8.
- #2006 Nauseated - Day 2.
- #2007 Felt bad - Day 2. Weak - Day 3.
- #2012 "First tablet vomited up" - Day 1. No vomiting - Day 2. Backache - Day 3.
- #2014 - Very weak all day and nervous - Day 1. Took two Urised tablets - Days 3, 4, 8, 13, and 17. Should be disqualified because of concomitant therapy.

Study No. 38 Dr. Harrison Nine of eleven patients reported one or more effects.

- #1804 Felt fine but did not sleep well - Day 1.
- #1812 A little tired and sleepy during the day - Day 5. Sleepless night - Day 6.
- #1807 Very drowsy and not very responsive - Day 3. Alert and very good - Day 4.
- #1805 Seemed quite tired but usually have this feeling when taking Septra also - Days 2, 3, and 4. Still extremely tired - Days 5 and 6. Some vision problem and experiencing tiredness - Days 7, 8 and 9. Back pains and extremely tired - Days 10-15.
- #1804 Recovering from previous stomach upset - Days 1-3. Washed out feeling - Day 4. Better but do not feel up to par - Day 5. Nervousness, sore tongue - Day 12.
- #1803 Stomach hurts - Day 4. Headache - Days 5-12. Hospitalized Day 8. "I never have headaches and I am still having them."
- #1802 Constipation - Day 5.
- #1806 Legs ached and went to bed after supper - Day 1. Dizzy - Day 2.
- #1815 Nausea and tense - Day 1. Not steady on feet, tired, vertigo-type sensation - Day 2. Dizzy, could not stand at first, tired, unsteady, headache in frontal area - Day 3. Tense, loss of equilibrium, very tired and wobbly - Day 4. Impossible to stand on first arising this AM for an hour, all day some rocky feeling - Day 5. Headache especially if I bend head downward, unsteady, very tired - Day 6. Pain top of head, face and upper body, wet with sweat, nausea, very tired - Day 7. Pain top of head, very tired, nausea - Day 8. Headache, nausea, balance unsteady, very tired - Day 9. Tired, nausea, "embalance," eyes hurt - Day 10. Slept 9 hours, unusual to sleep so long, awake with severe ache in forehead and eyes, lack of balance upon arising briefly, unsteady (No pills today) - Day 10. Resumed pills, dizziness - Day 12. Headache, very tense, eyes hurt, head swimming, nausea - Day 13. Eyes hurt - Day 14. Dizzy when held head up, unsteady - Day 16. (Some symptoms continued after treatment.)

Study No. 37 Dr. Goldstein Four of seven patients reported one or more effects.

- #1702 Headache and nausea - Day 1. Get very nauseous about 1 hour after taking pills - Day 2. Headache and nausea - Days 3-10.
- #1704 Headache approximately 1 hour after taking pill - Day 1.
- #1706 Tired and headachy, probably not related of medicine - Day 12.

#1707 Difficult to fall asleep - Day 1. Tired probably due to overwork - Day 4. Very tired but did double shift yesterday - Day 8. Itching of left eye - Day 9.

2. From the controlled domestic trial of norfloxacin and TMP-SMZ in UTI. (See section 2 a, above.)

Study No. 7 Dr. Ellie J. C. Goldstein Sixteen norfloxacin sheets and 17 TMP-SMZ sheets are filed.

None of the 33 check-off sheets are acceptable because they are not designed according to our agreement with the applicant about the design of patient diaries. It was agreed that there would be one question, "How do you feel?," with a blank space or blank lines for the patients to fill in his response to the question each day. Dr. Goldstein's diaries have five symptoms printed on the sheet for each treatment day with a check of block for a yes or no answer. This format does not give the patient the freedom to answer the question in his own words.

3. From the uncontrolled study of bacterial gastroenteritis (See section 3 a, above.)

Study No. 31 Dr. Mark J. Kunkel Ten norfloxacin sheets are filed.

None of these ten check-off sheets are acceptable, first, because of the same reason given for Dr. Goldstein's study, No. 7, above. One of the main purposes of these sheets was to determine the number of stools/day. Sheets also have four printed symptoms each with a yes or no to be circled daily in response to the question "Did you feel well today?"

They are also not acceptable because concomitant medications which were taken interfere with the evaluation of adverse effects. Concomitant medications taken by six of the ten patients were Bufferin, Aspirin, Aldactazide, Tylenol, and Ascriptin.

In summary,

1. Diaries reported to have been kept by the patients in the following studies are still missing:

Study No. 36 Dr. Anthony Joseph Schaeffer - The applicant reported in a telephone conversation 10-25-85 that Dr. Schaeffer threw his diaries away. Nineteen patients were treated.

Study No. 35 Dr. Frank E. Thomas - Only one patient was treated.

2. This October 30 amendment adds 23 acceptable norfloxacin diaries (27 are not acceptable). If these 23 are included with the 63 acceptable diaries filed in the original submission, a total of 86 acceptable norfloxacin diaries have been filed. This number falls short of the 100 norfloxacin diaries that were originally requested for the characterization of drug-induced adverse reactions.

3. The applicant failed to summarize diary information.

Also filed in the October 30 amendment is a table showing the microbiological outcome for evaluable patients in the 19-investigator, multiclinic, uncontrolled international urinary tract infection study (See section 3 b (2), above for Protocols No. 506-01 and 508-01).

<u>Gram Negative</u>	<u>Eradicated/ Total Isolated</u>	<u>Gram Positive</u>	<u>Eradicated/ Total Isolated</u>
<u>Citrobacter diversus</u>	2/2	<u>S. aureus</u>	5/5
<u>Citrobacter freundii</u>	3/4	<u>S. epidermidis</u>	3/4
<u>Enterobacter species</u>	1/1	<u>S. saprofiticus</u>	3/3
<u>Enterobacter cloacae</u>	1/2	<u>Enterococcus</u>	4/5
<u>E. agglomerans</u>	2/4	<u>S. faecalis</u>	4/4
<u>E. coli</u>	109/118	<u>Streptococcus</u>	1/1
<u>Klebsiella species</u>	1/1	nonhemolytic	
<u>Klebsiella oxytoca</u>	2/2		
<u>Klebsiella pneumoniae</u>	11/14		
<u>Morganella morganii</u>	1/1		
<u>Proteus species</u>	2/2		
(non-mirabilis)			
<u>Proteus indole positive</u>	3/3		
<u>Proteus mirabilis</u>	26/27		
<u>Proteus vulgaris</u>	3/3		
<u>Pseudomonas aeruginosa</u>	11/13		
<u>Pseudomonas cepacia</u>	1/1		
<u>Providencia stuartii</u>	1/1		
<u>Subtotals</u>	<u>180/199</u>		<u>20/22</u>
Total eradicated		200/221 (90.5%)	

Applicant's Efficacy Summary: The applicant summarized efficacy data for the four indications for evaluable patients in this application as follows. (Favorable Responses.* Protocol numbers are in parentheses.)

Indication & Claim No.	Organism	Controlled Trials			Uncontrolled Trials - Proto-	
		Norflor- acin	Control	Protocol #	#E/#I	col #
Urinary Tract Infections						
1.1	<u>E. coli</u>	53/54	58/59	(#001)	15/15	(#011)
		37/38	28/33	(#002)	29/30	(#017)
		78/82	84/94	(#504/505)	107/117	(#506/508)
	Total	168/174 (96.5%)	170/186 (91.4%)		151/162 (93.2%)	
1.2	<u>Klebsiella sp.</u> including <u>K.</u> <u>pneumoniae</u>	2/2	3/3	(#001)	4/6	(#011)
		7/11	7/7	(#002)	3/3	(#017)
		8/13	6/8	(#504/505)	13/17	(#506/508)
	Total	17/26 (65%)	16/18 (88.9%)		20/26 (76.9%)	
1.3	<u>Enterobacter sp.</u> including <u>E.</u> <u>aerogenes, cloacae,</u> <u>glomerans</u>	2/2	2/2	(#001)	3/4	(#011)
		1/1	2/3	(#002)	4/7	(#506/508)
		7/10	6/6	(#504/506)		
	Total	10/13 (76.9%)	10/11 (90.9%)		7/11 (63.6%)	
1.4	<u>Proteus mirabilis</u>	3/3	1/1	(#001)	5/5	(#011)
		7/7	5/6	(#002)	5/5	(#017)
		15/15	9/11	(#504/505)	25/26	(#506/508)
	Total	25/25 (100%)	15/18 (83%)		36/36 (100%)	
1.5	<u>Proteus, indole</u> <u>positive</u>	0/0	0/0	(#001)	1/1	(#011)
		2/2	0/1	(#002)	7/7	(#506/508)
		3/3	1/2	(#504/505)		
	Total	5/5	1/3		8/8 (100%)	
1.6	<u>Pseudomonas sp.</u> including <u>P.</u> <u>aeruginosa</u>	4/5	1/1	(#001)	11/14	(#011)
		8/14	2/2	(#002)	2/3	(#017)
		7/8	1/2	(#504/505)	13/15	(#506/508)
	Total	19/27 (70.4%)	4/5 (80%)		26/32 (81%)	
1.7	<u>Serratia sp.</u> including <u>S.</u> <u>marcescens</u>	2/2	1/2	(#504/505)		
1.8	<u>Providencia sp.</u>	2/2	0/0	(#002)		
		2/2	0/0	(#504/505)		

Indication & Claim No.	Organism	Controlled Trials			Uncontrolled Trials - Proto-	
		Norflor- acin	Control	Protocol #	#E/#I	col #
UTI - Con't						
1.9	<u>Citrobacter</u> sp.	1/1 3/4 3/3	1/1 0/0 0/0	(#001) (#002) (#504/505)	1/1 2/2 5/7	(#011) (#017) (#506/508)
	Total	7/8 (87.5%)	1/1		8/10 (80%)	
1.10	<u>Staphylococcus</u> sp. including <u>S.</u> <u>saprophyticus,</u> <u>aureus, epidermidis</u>	2/2 3/3 3/4	0/0 2/2 4/4	(#001) (#002) (#504/505)	4/5 3/3 9/11	(#011) (#017) (#506/508)
	Total	8/9 (88.9%)	6/6 (100%)		16/19 (84.2%)	
1.11	Enterococcus in- cluding <u>S. faecalis</u>	3/3 1/1	1/2 4/4	(#002) (#504/505)	1/2 1/2 8/9	(#011) (#017) (#506/508)
	Total	4/4	5/6		10/13 (76.9%)	
1.12	Other Grp D Streptococci	7/8 0/0	0/1 1/1	(#002) (#504/505)	4/4	(#011)
	Total	7/8 (87.5%)	1/2		4/4	
1.13	Other Streptococci including Grp B	3/3	1/1	(#002)	1/1 1/1	(#001) (#506/508)
Gonococcal Urethritis Uncomplicated						
2.1	<u>Neisseria gonor-</u> <u>rheae, PCNase</u> positive & neg.	74/74 26/26	16/16 21/21	(#010) (#015)		
	Total	100/100 (100%)	37/37 (100%)			
Gastroenteritis						
3.1	Enterotoxigenic <u>E. coli</u>	34/35	8/10	(#519)		
	Total	(97.1%)	(80%)			
3.2	<u>Shigella</u> species	3/3 47/48	1/1 23/23	(#005) (#519)		
	Total	50/51 (98%)	24/24 (100%)			

Indication & Claim No.	Organism	Controlled Trials			Uncontrolled Trials - Proto-	
		Norflox- acin	Control	Protocol #	#E/#I	col #
Gastroenter- itis Con't						
3.3	<u>Salmonella</u> sp.	1/1	0/2	(#005)	3/5	(#009)
		6/6	9/10	(#519)		
	Total	7/7	9/12			
		(100%)	(75%)			
3.4	<u>Aeromonas</u> sp.	1/1	0/0	(#005)		
		6/6	4/4	(#519)		
	Total	7/7	4/4			
		(100%)				
3.5	<u>Vibrio</u> species	7/7	2/2	(#519)		
		(100%)				
3.6	<u>Campylobacter</u> sp.	6/9	12/13	(#005)	8/9	(#012)
		0/0	2/3	(#519)		
	Total	6/9	14/16			
		(66.6%)	(87.5%)		(88.9%)	

*Favorable response = Cured or improved with bacteriological eradication.

Medical Officer's Comments

1. Percents were added by the medical officer.

2. This summary table is inaccurate as a summary table of microbiological outcome for evaluable patients and will be revised. The denominators do not include those cases which developed superinfections and it contains symptomatic outcome as well as microbiological outcome. The applicant is preparing a table summarizing microbiological outcome for evaluable patients.

3. The applicant's summary table, above, has been revised by the medical officer as follows in order to take the medical officer's disqualifications and comments into consideration. This is a preliminary summary only.

MEDICAL OFFICER'S PRELIMINARY SUMMARY OF EFFICACY

Indication & Claim No.	Organism	Controlled Trials			Uncontrolled Trials - Proto-	
		Norflor- acin	Control	Protocol #	#E/#I	col #
Urinary Tract Infections						
1.1	<u>E. coli</u>	53/54	58/59	(#001)	15/15	(#011)
		37/38	28/33	(#002)	29/30	(#017)
		78/82	84/94	(#504/505)		
	Total	168/174 (96.5%)	170/186 (91.4%)		44/45 (97.8%)	
1.2	<u>Klebsiella sp.</u> including <u>K.</u> <u>pneumoniae</u>	2/2	3/3	(#001)	4/6	(#011)
		7/11	7/7	(#002)	3/3	(#017)
		8/13	6/8	(#504/505)		
	Total	17/26 (65%)	16/18 (88.9%)		7/9 (77.8%)	
1.3	<u>Enterobacter sp.</u> including <u>E.</u> <u>aerogenes, cloacae,</u> <u>glomerans</u>	2/2	2/2	(#001)	3/4	(#011)
		1/1	2/3	(#002)		
		7/10	6/6	(#504/506)		
	Total	10/13 (76.9%)	10/11 (90.9%)		3/4 (75%)	
1.4	<u>Proteus mirabilis</u>	3/3	1/1	(#001)	5/5	(#011)
		7/7	5/6	(#002)	5/5	(#017)
		15/15	9/11	(#504/505)		
	Total	25/25 (100%)	15/18 (83%)		10/10 (100%)	
1.5	<u>Pseudomonas sp.</u> including <u>P.</u> <u>aeruginosa</u>	4/5	1/1	(#001)	11/14	(#011)
		8/14	2/2	(#002)	2/3	(#017)
		7/8	1/2	(#504/505)		
	Total	19/27 (70.4%)	4/5 (80%)		13/17 (76.5%)	
1.6	<u>Citrobacter sp.</u>	1/1	1/1	(#001)	1/1	(#011)
		3/4	0/0	(#002)	2/2	(#017)
		3/3	0/0	(#504/505)		
	Total	7/8 (87.5%)	1/1		3/3	
1.7	<u>Staphylococcus sp.</u> including <u>S.</u> <u>saprophyticus,</u> <u>ureus, epidermidis</u>	2/2	0/0	(#001)	4/5	(#011)
		3/3	2/2	(#002)	3/3	(#017)
		3/4	4/4	(#504/505)		
	Total	8/9 (88.9%)	6/6 (100%)		7/9 (77.8%)	

Indication & Claim No.	Organism	Controlled Trials			Uncontrolled Trials - Proto-	
		Norfloxac- acin	Control	Protocol #	#E/#I	col #
UTI - Con't						
1.8	Other Grp D	7/8	0/1	(#002)	4/4	(#011)
	Streptococci	0/0	1/1	(#504/505)		
	Total	7/8 (87.5%)	1/2		4/4	
Gastroenteritis						
2.1	Enterotoxigenic <u>E. coli</u>	34/35	8/10	(#519)		
	Total	(97.1%)	(80%)			
2.2	<u>Shigella</u> species	3/3	1/1	(#005)		
		47/48	23/23	(#519)		
	Total	50/51 (98%)	24/24 (100%)			
2.3	<u>Salmonella</u> sp.	1/1	0/2	(#005)	3/5	(#009)
		6/6	9/10	(#519)		
	Total	7/7 (100%)	9/12 (75%)			
2.4	<u>Campylobacter</u> sp.	6/9	12/13	(#005)	8/9	(#012)
		0/0	2/3	(#519)		
	Total	6/9 (66.6%)	14/16 (87.5%)		8/9 (88.9%)	

*Favorable response = Cured or improved with bacteriological eradication.

The medical officer's preliminary summary table will be further revised. Disqualified underage patients must be deleted. There will be other deletions.

4. The following organisms should be re-tallied to give a count for each individual species:

Klebsiella species
Pseudomonas species

Enterobacter species
Staphylococcus species

One species in each will probably account for practically all of the isolates reported.

Applicant's Safety Summary: The applicant's summary of adverse reactions and their frequencies by dosage and body system is shown below:

Adverse Experiences Body Site	Non-Neutropenics				Neutropenics 400 mg tid
	400 mg bid	200 mg bid	600 mg q 4 h x 2	400 mg tid	
Number of patients	1159	60	135	138	81
No. of adverse reactions	172	0	5	16	129
No. drug related	57		3	5	2
<u>Body as a whole/ site unspecified</u>					
Abdominal swelling	1				
Asthenia	2				
Death (not drug related)					15
Fatigue	3				
Fever	2				2
Pain	1				
Syncope					1
Total	9				
<u>Vascular System</u>					
Cardiac arrest					3
Cerebrovascular disease	1				
Congestive heart failure	1				2
Hemorrhagic shock	1				
Intracerebral hemorrhage					2
Myocardial infarction	2				
Shock	1				
Tachycardia	1 (1)				
Total	7				
<u>Digestive System</u>					
Abdominal pain	4 (2)			1	
Bowel sound abnormality					1
Anorexia	1 (1)		1		2
Aphthous stomatitis	1				
Constipation	4				
Diarrhea	3 (1)				30
Digestive System Disorder	1 (1)				
Dry mouth	3 (2)				
Dyspepsia	5 (4)				1
Dysphagia	1 (1)				
Flatulence	3			1	
Gastrointestinal cramps	2 (1)				
GI Hemorrhage/Melena					4
Gastrointestinal pain	1				
Gingivitis					1
Heartburn	4				
Jaundice					1

Adverse Reactions Body Site	Non-Neutropenics				Neutropenics
	400 mg bid	200 mg bid	600 mg q 4 h x 2	400 mg tid	400 mg tid
Mouth ulcer	2				
Nausea	28 (13)		2 (1)		6
Tongue enlargement	1 (1)				
Vomiting	2			1	16 (1)
Total	<u>66 (27)</u>				
<u>Hemic and Lymphatic</u>					
Purpura	1				
Hypovolemia	1				
Hemolysis					1
Epistaxis					1
<u>Musculoskeletal</u>					
Back pain	1				
Knee or leg pain	1				
Joint pain				1	
Musculoskeletal disorders	1				
Muscle cramp					1
Weakness, local	1				
Total	<u>5</u>				
<u>Nervous and Psychiatric</u>					
Anxiety	1 (1)			1	
Cerebellar ataxia					1
Convulsive disorder	1				
Depression	4 (1)				
Disorientation	1				
Dizziness	17 (6)		1 (1)	1	
Dream abnormalities	1				
Euphoria	1 (1)			1 (1)	
Explosive personality	1				
Hallucinations	1 (1)				
Headache	22 (4)		2 (1)	3	3
Insomnia	5 (2)		1		
Irritability				1 (1)	
Nervousness			1		
Paresthesia				1	
Somnolence	5 (1)				
Total	<u>60 (17)</u>				
<u>Respiratory System</u>					
Hemoptysis					1
Pharyngeal pain					1
Respiratory Insufficiency					1
Respiratory Failure					1

Adverse Experiences Body Site	Non-Neutropenics			Neutropenics
	400 mg bid	200 mg bid	600 mg q 4 h x 2	400 mg tid
Skin and Appendages				
Dry skin	1			
Erythema	3 (2)			
Pruritis	2 (2)			
Pruritis ani	1			
Rash	6 (3)			21
Urticaria				2 (2)
Total	13 (7)			
Special Senses				
Conjunctivitis				3
Epiphora	1 (1)			
Nystagmus				1
Taste perversion	2 (2)			1 (1)
Tinnitus	1 (1)			
"Scratchy eyes"	1			
Visual disturbances				1
Total	5 (4)			
Urogenital				
Dysmenorrhea	1			
Hematuria				1
Renal colic	1			
Renal failure				4
Vaginal swelling	1 (1)			
Vaginal pain	1			
Suprapubic pain	1			
Total	5 (1)			

Numbers in parentheses are the number of drug-related adverse effects.

Adverse Laboratory Events Body Site	Non-Neutropenics			Neutropenics
	400 mg bid	200 mg bid	600 mg q 4 h x 2	400 mg tid
Hematology				
Hemoglobin increase	6			
decrease	1			
Hematocrit decrease	5			2
WBC Count increase	3			
decrease	7 (3)			5 (3)
Neutrophil decrease	7 (3)			
increase			1	
Lymphocytes rel. increase	3 (1)		3	
Monocyte increase	2			

Adverse Laboratory Events Body Site	Non-Neutropenics				Neutropenics
	400 mg bid	200 mg bid	600 mg q 4 h x 2	400 mg tid	400 mg tid
Eosinophil increase (5 not drug related)	21 (2)		1	1	
Platelet Count increase	4			2	
decrease				1	
ESR (increase)	1				
Total	<u>60 (9)</u>				
<u>Renal Function (Blood Chem.)</u>					
BUN increase	12				7
Serum creatinine increase	6				12
Total	<u>18</u>				
<u>Liver Function (Blood Chem.)</u>					
Tot. Sr. Bilirubin increase	3	1		1	35
AST, ALT increase	27 (1)			13 (2)	63
Alk. Phosphatase increase (1/19 with no drug relation)	19 (1)			3	24
LDH increase	7				13
Total	<u>56 (2)</u>				
<u>Metabolic (Blood Chem.)</u>					
Ser. Uric Acid increase					1
<u>Electrolytes (Blood Chem.)</u>					
Serum sodium increase	2				
Serum potassium decrease	3				
increase	1				
Serum chloride decrease	4				
increase	3				
Total	<u>13</u>				
<u>Urinalysis</u>					
Urine protein increase	3				7
Urine glucose increase	2		1		2
Urine WBC increase (1/3 with no drug relation)	3				1
Urine RBC increase (2/4 with no drug relation)	4				5
Urine crystals	1				
Non-amorphous crystals			1		
Total	<u>13</u>				
Overall Total	160 (11)		7	28	171

Many patients had multiple adverse experiences so that the number of patients with adverse experiences was always fewer than the number of adverse experiences. The same was true for adverse laboratory events. Most adverse experiences at the 400 mg bid dose were in the digestive tract (38%) or the nervous/psychiatric systems (35%). Forty-seven percent of all drug-related adverse experiences were gastrointestinal compared to 30% for neuropsychiatric. The single most commonly described drug-related adverse experience was nausea. The next most commonly described were dizziness, dyspepsia, and headache. No single adverse laboratory experience approached a frequency of 1%. No single drug related adverse experience except nausea (2.0%), dizziness (1.2%), and headache (1.6%) occurred with a frequency of 1% or more.

The overall adverse reaction rate for 1528 non-neutropenic patients was 8.4% (129/1528)

The applicant's table comparing the frequency of adverse experiences of norfloxacin with those of the six control products is reproduced on the next four pages exactly as filed.

Overall Safety Analysis

The following tables compare the adverse experiences by drug (NOROXIN and all comparative regimens). The table is divided by drug and includes the total number of patients treated for each drug.

Clinical Adverse Experience

Nonneutropenic Studies: All adverse experiences/drug related adverse experiences

<u>Adverse Experiences</u>	<u>NFX</u> <u>N=1540*</u>	<u>SXT</u> <u>N=554</u>	<u>Nal. Acid</u> <u>N=102</u>	<u>Spec.</u> <u>N=23</u>	<u>Asp</u> <u>N=29</u>	<u>Ery</u> <u>N=23</u>	<u>Plac</u> <u>N=22</u>
<u>Body as Whole/Incl.</u>							
Abdominal Swelling	1/-	—	—	—	—	—	—
Fever	1/-	1/1	—	—	—	—	—
Malaise	—	2/1	—	—	—	—	—
Pain	1/-	—	—	—	—	—	—
Asthenia	2/-	—	1/-	—	—	—	1/-
Fatigue	3/-	—	3/1	—	—	—	—
TOTALS	8/-	3/2	4/1	—	—	—	—
<u>Cardiovascular</u>							
Myocardial infarction	2/-	—	—	—	—	—	—
Cerebrovascular accident	1/-	—	—	—	—	—	—
Congestive heart failure	1/-	—	—	—	—	—	—
Hemorrhagic shock	1/-	—	—	—	—	—	—
Shock, unspc.	1/-	—	—	—	—	—	—
Tachycardia	1/-	—	—	—	—	—	—
TOTALS	7/-	—	—	—	—	—	—

N = Number of patients receiving that therapy
 NFX = Norfloxacin
 Nal. Acid = nalidixic acid
 SXT = Sulfamethoxazole/trimethoprim

Spec. = spectinomycin
 Asp = Ampicillin
 Ery = Erythromycin
 Plac = Placebo

**Clinical Adverse Experience
(Cont'd)**

<u>Nonnutritional Studies:</u>							
	ALL adverse experiences/drug related adverse experiences						
<u>Adverse Experiences</u>	<u>IFX</u> <u>N=1540*</u>	<u>SXT</u> <u>N=554</u>	<u>Nal. Acid</u> <u>N=102</u>	<u>Spec.</u> <u>N=23</u>	<u>Am</u> <u>N=22</u>	<u>Ery</u> <u>N=23</u>	<u>Plac</u> <u>N=22</u>
<u>Digestive system</u>							
Abdominal Pain	4/2	3/2	1/-	-	-	-	-
Anorexia	2/1	2/-	-	-	-	-	-
Aphous stomatitis	1/-	-	-	-	-	-	-
Constipation	4/-	1/-	1/-	-	-	-	-
Diarrhea	3/1	2/-	1/-	-	-	-	1/-
Dry mouth	2/2	-	1/1	-	-	-	-
Dyspepsia	5/4	4/1	1/1	-	-	-	-
Flatulence	4/-	1/-	1/-	-	-	-	-
Gastrointestinal Cramps	2/1	-	-	-	-	1/-	-
Heartburn	4/-	2/1	-	-	-	-	-
Nausea	30/14	8/3	20/10	-	1/1	2/1	1/-
Digestive system disease	1/1	-	-	-	-	-	-
Dysphagia	1/1	-	-	-	-	-	-
Gastrointestinal pain	1/-	-	-	-	-	-	-
Vomiting	3/-	2/2	3/1	-	-	-	-
Mouth ulcer	2/-	1/-	-	-	-	-	-
Glossodynia	-	-	1/-	-	-	-	-
TOTALS	70/27	26/9	36/13	-	1/1	3/-	2/-
<u>Hemic</u>							
Purpura	1/-	-	-	-	-	-	-
<u>Metabolic</u>							
Hypovolemia	1/-	-	-	-	-	-	-

N = Number of patients receiving that therapy
 IFX = Norfloxacin
 Nal. Acid = nalidixic acid
 SXT = Sulfamethoxazole/trimethoprim

Spec. = spectinomycin
 /ap = Ampicillin
 Ery = Erythromycin
 Plac = Placebo

Nonneutropenic Studies: All adverse experiences/drug related adverse experiences

<u>Adverse Experiences</u>	<u>NFX</u> <u>N=1540*</u>	<u>SXT</u> <u>N=554</u>	<u>NaI. Acid</u> <u>N=102</u>	<u>Spec.</u> <u>N=23</u>	<u>Am</u> <u>N=29</u>	<u>Ery</u> <u>N=29</u>	<u>Plac</u> <u>N=22</u>
<u>Musculoskeletal</u>							
Back pain	1/-	--	--	--	--	1/-	--
Joint pain	1/-	--	--	--	--	--	--
Knee pain	1/-	--	--	--	--	--	--
Musculoskeletal disease	1/-	--	--	--	--	--	--
Leg pain	1/-	--	--	--	--	--	--
Weakness, local	1/-	--	1/-	--	--	--	--
TOTALS	6/-	--	1/-	--	--	1/-	--
<u>Neuro/psychiatric</u>							
Depression	4/1	2/1	1/1	--	--	--	--
Disorientation	1/-	--	--	--	--	--	--
Dizziness	19/7	2/-	7/1	--	--	2/1	2/-
Headache	26/5	8/-	12/2	--	--	--	1/-
Insomnia	4/1	1/1	--	--	--	--	--
Anxiety	2/-	--	--	--	--	--	--
Convulsive disorder	1/-	--	--	--	--	--	--
Dream abnormalities	1/-	--	--	--	--	--	--
Euphoria	2/2	--	--	--	--	--	--
Irritability	1/1	--	--	--	--	--	--
Insomnia	2/1	2/-	--	--	--	--	--
Nervousness	1/-	2/-	--	--	--	--	--
Explosive personality disorder	1/-	--	--	--	--	--	--
Hallucinations	1/1	--	--	--	--	--	--
Somnolence	5/1	2/-	2/1	--	--	--	--
Paresthesia	1/-	1/-	--	--	--	--	--
Tremor	--	1/-	--	--	--	1/-	--
TOTALS	73/20	19/2	22/3	--	--	3/1	2/-

N = Number of patients receiving that therapy
 NFX = Norfloxacin
 NaI. Acid = nalidixic acid
 SXT = Sulfamethoxazole/trimethoprim

Spec. = spectinomycin
 Am = Ampicillin
 Ery = Erythromycin
 Plac = Placebo

Clinical Adverse Experience
(Cont'd)

Nonneutropenic Studies: #All adverse experiences/drug related adverse experiences

<u>Adverse Experiences</u>	<u>NFX</u> <u>N=1540*</u>	<u>SXT</u> <u>N=554</u>	<u>NaI. Acid</u> <u>N=102</u>	<u>Spec.</u> <u>N=28</u>	<u>Amp</u> <u>N=29</u>	<u>Ery</u> <u>N=28</u>	<u>Plac</u> <u>N=22</u>

Skin & Allergies

Tongue enlargement	1/1	—	—	—	—	—	—
Drug skin	1/-	—	—	—	—	—	—
Erythema	3/2	—	—	—	—	—	—
Pruritis	2/2	3/1	—	—	—	—	—
Pruritis ani	1/-	—	—	—	—	—	—
Rash	6/3	1/1	1/-	—	—	—	1/-
Urticaria	2/2	2/2	—	—	—	—	—
Allergic dermatitis	—	1/1	—	—	—	—	—
Photosensitivity	—	—	—	—	—	1/-	—
TOTALS	16/10	13/11	1/-	—	—	1/-	1/-

Special senses

Taste perversion (bitter taste)	3/3	—	—	—	—	—	—
Epiphora	1/1	—	—	—	—	—	—
Tinnitus	1/1	—	—	—	—	—	—
Ear obstruction	—	1/-	—	—	—	—	—
Photopsia (flashing lights)	—	—	1/1	—	—	—	—
Mydriasis	—	—	—	—	—	1/1	—
Eyelid edema	—	1/1	—	—	—	—	—
Visual disturbances	—	1/1	—	—	—	—	—
TOTALS	5/5	3/2	1/1	—	—	1/1	—

Urogenital

Dysmenorrhea	1/-	—	—	—	—	—	—
Renal colic	1/-	—	—	—	—	—	—
Vaginal swelling	1/1	—	—	—	—	—	—
Lactation suppressed	—	1/-	—	—	—	—	—
Nestodynia	—	—	1/-	—	—	—	—

N = Number of patients receiving that therapy
 NFX = Norfloxacin
 NaI. Acid = nalidixic acid
 SXT = Sulfamethoxazole/trimethoprim

Spec. = spectinomycin
 Amp = Ampicillin
 Ery = Erythromycin
 Plac = Placebo

Summary of Medical Officer's Comments:

1. Animal Data:

a) Hemoglobinuria occurred in all monkeys from which urine could be obtained at the 50 mg/kg/day dose and the 200 mg/kg/day dose. The 50 mg/kg/day dose is 2-3 times the expected human dose. The "no-effect" dose for hemoglobinuria in monkeys is not known and should be reported.

b) The presence of drug crystals in the urine of these monkeys cannot be evaluated because urine was not examined microscopically. Crystals may have been present and may have been the cause of the hemoglobinuria. The "no-effect" crystalluria dose in monkeys is not known and should be reported.

c) Crystalluria occurred in dogs at 50 mg/kg/day, a dose which will be 2-3 times the recommended human dose. Three dogs, one in the 150 mg/kg/day group and two in the 300 mg/kg/day group were found dead or were sacrificed due to urinary obstruction from drug crystals. The "no-effect" crystalluria dose is not known and should be reported. There may be a possibility that crystalluria could occur at the recommended doses in some patients. Labeling should advise about this possibility.

2. Adverse effects and abnormal laboratory reports in the 949 cases which were studied by Kyorin in Japan are not summarized. If this information is available, it should be summarized in a report. The report should describe how these patients were monitored for the presence of adverse reactions.

3. The question as to whether norfloxacin precipitates in the human urine and whether drug crystals can cause renal obstruction in humans, as happened in dogs, has not been answered. (The reader is referred to the MO's comments on pages 9 and 82 of this MOR.) Crystals which were present in Dr. Ferguson's study No. 1, in Dr. Zimney's study No. 13, and in other studies have not been identified. It is not known if these are crystals of norfloxacin or the metabolites of norfloxacin or crystals of something else.

Most of the time in efficacy studies the presence or absence of crystals during treatment is not reported. In Dr. Zimney's bioavailability study, up to 40% of subjects had non-amorphous crystals after dosing. The presence or absence of crystalluria in Dr. Cohn's gastroenteritis study, Study No. 14, cannot be evaluated because urine sediment was only examined before treatment and again two days after treatment was discontinued. Urine sediment should have been examined for the presence of drug crystals during treatment at the height of the drug excretion period.

There is a discrepancy between the printout and several case report forms regarding the presence of nonamorphous crystals.

Case #302 - Printout shows 50 nonamorphous crystals/HPF on Day 7. The case report shows "Many" nonamorphous crystals two days after treatment.

Case #308 - Printout shows 4/HPF before treatment. The case report

shows 4+ before treatment.

Case #113 - Printout shows 1/HPF on Day 8. The case report shows 1+ calcium oxalate two days after treatment.

The applicant should be requested to summarize all information in this NDA regarding crystalluria. A summary addressing crystalluria cannot be located in what has already been filed.

4. Underage patients:

a) Three patients that were under 18 years of age in the domestic urinary tract infection study which compared norfloxacin with TMP-SMZ (Protocol No. 002) should be disqualified. They were norfloxacin cases #1498 (13-yr old male treated by Dr. Landes), and #908 (17-yr old female treated by Dr. Ryan), and TMP-SMZ case #916 (17-yr old female treated by Dr. Ryan).

b) The following seven underage applicant-qualified patients should be disqualified from the efficacy evaluation and safety evaluation. The lower age limit for the use of the quinolones in humans has been set at 18 years because of the development of arthropathy in juvenile animals in all species that have been tested. This represents a serious protocol violation.

Carcelen #4022 15-yr old in 800 mg Nor. - V. parahaemolyticus -Eradicated
 Carcelen #4056 15-yr old in 800 mg Nor. - S. flexneri - Eradicated
 Salazar #4122 13-yr old in 800 mg Nor. - E. coli, enterotox. - Eradicated
 Carcelen #4029 16-yr old in 1200 mg Nor. - V. parahaemolyticus -Eradicated
 Carcelen #4109 17-yr old in TMP-SMZ - S. flexneri - Eradicated
 De Godoy #4451 15-yr old in TMP-SMZ - Salmonella - Eradicated
 Rodriguez #4641 17-yr old in TMP-SMZ - Shigella boydii- Eradicated

c) Patients under 18 years of age in the international, multiclinic, controlled urinary tract infection study (Protocols No. 504 and 505) and in other studies should be disqualified.

d) Outcome rates should be corrected accordingly.

5. Approval of the prophylactic use of norfloxacin in the suppression of bowel flora in granulocytopenic patients is not recommended. Data are inadequate to support this indication.

a) In regard to Dr. Joshi's study, No. 16:

(1) The route of administration of amphotericin B in this study, swishing it in the mouth for one minute then swallowing it, is an investigational route for the use of intravenous vials. Amphotericin B was provided in 50 mg intravenous vials for oral use. Efficacy and safety of amphotericin B by the oral route have not been established. (Oral amphotericin B, however, is available as a fixed combination with tetracycline (Mastecilin-F[®] (Squibb): NAS/NRC rated as ineffective). It is labeled as being "extremely well tolerated and is virtually nontoxic in prophylactic doses." Adverse

reactions which are reported in this labeling are those due to tetracycline rather than to amphotericin B.) This study should be disregarded because two investigational drugs cannot be evaluated at the same time.

The applicant's conclusion regarding fungemias is not valid since amphotericin B was given to all patients in each group.

(2) No decision regarding prophylactic efficacy can be made on the basis of this study not only because of the use of another investigational drug, but also because of the small size of the treatment groups. The conclusion regarding the superiority of norfloxacin in patients treated 35 days or less is based upon success in two of only four patients. This does not represent substantial evidence.

(3) Since patients randomized to receive norfloxacin and graded as evaluable were five times more likely to be profoundly neutropenic at the time of randomization as were the patients in the control group, there must have been a randomization bias. There must also have been a duration-of-treatment bias in that the norfloxacin group was treated longer than the control group, 49 days versus 38 days.

b) Regarding Dr. Winston's study, No. 17:

(1) Polymyxin B capsules and vancomycin capsules must be regarded as investigational drugs. The routes of administration of polymyxin and vancomycin in this study are investigational routes for these products.

(2) This study must be regarded as an uncontrolled trial because the control was not approved for this indication. Two investigational regimens cannot be evaluated at the same time.

(3) No decision regarding prophylactic efficacy can be made on the basis of this study not only because of the use of investigational drugs, but also because of the small size of the treatment groups. (Refer to page 52.)

6. Approval of the use of norfloxacin in the treatment of gonorrheal infection is not recommended. Data are inadequate to support this indication.

a) In regard to Dr. Berg's Subic Bay study in males, No. 30:

(1) Failure to randomize lessens the value of this study and removes it from the list of controlled trials.

(2) In spite of the 100% cures in each group, the medical officer can only accept 27 of the 90 male patients that the applicant found qualified because only these 27 cases had susceptibility testing, 22 in the norfloxacin group and 5 in the spectinomycin group. (One cannot be accounted for.) Cases for which there was no susceptibility testing should be disqualified.

(3) Post therapy cultures should have been obtained 4-7 days after therapy instead of 3-7 days after therapy.

(4) The presence or absence of drug crystals is not reported.

b) In regard to the study by Drs. Simpson and Kaplowitz, Nos. 48/49:

(1) Although norfloxacin is probably effective, data from this study are inadequate to show that norfloxacin is effective in treating gonococcal urethritis and cervicitis. There were only two evaluable females in the norfloxacin group and only five in the control group. Susceptibility was not tested for one of the two norfloxacin females and for four of the five control female cases. For a common infection like gonorrheal infection, at least 75 or 100 cases would be needed. The same is true for males: in this study, there were only 24 evaluable males in the norfloxacin group and only 17 in the control group. These low numbers might be acceptable for a rare infection but they do not represent the substantial data needed for a common infection like gonorrheal infection.

2. The applicant's clinical outcome criteria which mistakenly included microbiological outcomes were disregarded. The medical officer graded clinical outcome on the presence or absence of signs and symptoms.

3. The fact that one norfloxacin-treated patient had nonamorphous crystals after only two 600-mg doses four hours apart may be significant.

4. Post-therapy cultures should have been obtained 4-7 days after therapy instead of 3-7 days after therapy.

5. The applicant has mistakenly classified isolates for which there was no susceptibility testing with evaluable cases. These cases should be disqualified. Strains from only 19 of the 24 males in the norfloxacin group, 13 of 17 males in the control, and for only two females were tested for susceptibility.

7. The uncontrolled, international, multiclinic urinary tract infection study (Protocols No. 506/508) has not been analyzed in such a manner that the applicant's conclusions are supported. The applicant should re-analyze this study so that the following deficiencies are corrected:

a) The clinical outcome criteria which contain microbiological assessments should be disregarded. The clinical outcome should be based upon a comparison of the presence or absence of signs and symptoms before and after therapy.

b) "Assessable" patients should be regarded as unevaluable patients.

c) Patients with pretherapy urine cultures obtained earlier than 48 hours before the initiation of treatment should be considered unevaluable. In this study pretherapy cultures were considered if they were obtained

within 12 days of the initiation of treatment.

d) Culture timing requirements are not acceptable and should be revised to be in keeping with FDA guidelines for the treatment of urinary tract infections. In this study, they were changed from those specified in FDA's guidelines that were used in other studies to read as follows:

Relative-Day Ranges (page I-6157, Vol 2.17)

Protocol	Actual	Nomenclature Used in Text
Day 3 or 4 during therapy	Days 2 to 5 during therapy	During therapy
5 to 9 days post-therapy	5 to 20 days post-therapy	Post-therapy
4 to 6 weeks post-therapy	25 to 48 days post-therapy	Late post-therapy

e) Patients under 18 years of age should be disqualified. There are approximately eight, the youngest was 9 years old.

f) No effort should be made to separate upper and lower urinary tract infections because of the impreciseness of the diagnostic technique.

g) The report lacks a summary table which gives the microbiological outcome according to uropathogens.

h) Adverse reactions are tallied in the appendix but the report lacks a summary table to show all 43 adverse reactions. Unfortunately, no patient diaries were used in this study.

i) Summary tables compare pretherapy mean values with post-therapy mean values but do not list the 40 adverse laboratory experiences.

7. The applicant did not include the eleven isolates from ten compassionate patients in the total data of efficacy in this NDA. They should have been included. These cases were multiple antibiotic resistant infections (Section 3 c (2), above).

8. The applicant should be requested again to submit a report of tests of brain function during treatment with norfloxacin. This was discussed in a conference with the applicant August 18, 1982 following a detailed consideration of a quinolone product by FDA's Anti-Infective Drugs Advisory Committee. This request was included in our letter to the applicant dated September 10, 1982. The applicant agreed to perform brain function tests and addressed this point in the response letter to FDA dated Nov. 10, 1982, response to item #2 h.

Although not labeled as a test of brain function, it is noted that 1/14 norfloxacin patients and 2/15 TMP-SMZ patients in Dr. Joshi's suppression of the bowel flora study improperly performed the straight-line walk test.

9. The applicant should be requested to conduct a study of the enteral absorption of norfloxacin in the presence of antacids. A report by Hoffken and coworkers (European Journal of Clinical Microbiology, Vol. 4: 1985, p. 345) indicates that antacids reduce the enteral absorption of ciprofloxacin, another new fluoroquinolone, in the presence of antacids. The pronounced effect of antacids on the bioavailability of ciprofloxacin should be considered if both these drugs are administered to a patient. This could be an effect with all members of the drug class and norfloxacin should be tested for this interaction.

10. The applicant's microbiological outcome summary table should be revised. The denominators do not include those cases which developed superinfections and symptomatic outcome information should be deleted.

11 Patient Diaries:

a) Only 86 acceptable patient diaries have been filed. A minimum of 100 were requested. Only 63 of the 83 diaries in the original application were acceptable. Diaries from Dr. Zinney's study #59 were not accepted because this was a single dose study. Diaries from courses with the recommended dose for the recommended length of treatment were requested. Only 23 of the 50 diaries in the amendment were acceptable. Those with check-off sheets are disqualified. At least 14 more acceptable patient diaries should be filed.

b) Diaries reported to have been kept by the patients in the following studies are still missing:

Study No. 36 Dr. Anthony Joseph Schaeffer - The applicant reported in a telephone conversation 10-25-85 that Dr. Schaeffer threw his diaries away. Nineteen patients were treated.

Study No. 35 Dr. Frank E. Thomas - Only one patient was treated.

Patient diaries were to be handwritten by the patient and were not to be transcribed or altered in any way. Original unaltered diaries were to have been filed as part of the case report forms. During the norfloxacin IND period, we talked about patient diaries as follows: Conference with Merck 8-18-82, TC 12-13-82, MOR 8-19-82, Letter to Merck 9-10-82, Letter from Merck 11-10-82, TC 3-11-83, MOR 12-19-83, and End of Phase II Conference 12-8-83.

c) The applicant failed to provide an overall summary of patient diaries in this application and should be requested to analyze and summarize them. Patient diaries, a minimum of 100, were specifically requested for norfloxacin studies so that adverse reactions could be characterized and their frequencies observed. There is a high incidence of adverse reactions with most members of this drug class. Virtually all of them are reversible when the drug is discontinued or they subside during the course of treatment. The investigator misses most of them, especially when he has outpatients and does not see the patient until the follow-up visit after treatment has been discontinued.

d) The medical officer summarizes the most frequently occurring entries in the patient diaries as follows:

<u>Diary Entry</u>	<u>Frequency</u>
Tired, lack of energy	35
Headache	28
Sleepy or drowsy	24
Nausea, Sick to stomach, Upset stomach, Vomiting	18
Dizziness, Head swirling	10
Not steady on feet	
Impaired vision, Burning eyes, Eyes tired, Eye sore, Eyes itch, Wavy lig s in eyes	8
Lightheaded	6
Weakness or sluggish, Washed out feeling	6
Dry mouth or lips	4
Slept poorly	4
Stomachache, Belly pain	4
Nervous, Tense	4
Lump in throat	3
Backache	3

e) The applicant's report of adverse reactions when compared to the information on patient diaries shows that there is underreporting of the frequency of adverse reactions. Both the investigator's and the applicant's adverse reaction rates are too low. (See pages 16 and 80 of this MOR.)

12. Cases being treated for gastroenteritis should not be considered in the evaluation of adverse effects due to norfloxacin because the very adverse effects that one would monitor are symptoms of the disease and are not reported as adverse reactions when they occur. Symptoms of gastroenteritis, besides diarrhea that were used in the evaluation of outcome, were abdominal cramps, nausea, vomiting, anorexia, etc. Gastrointestinal-type adverse effects that would be anticipated with norfloxacin are gastrointestinal cramps, nausea, vomiting, heartburn, flatulence, anorexia, abdominal pain, dyspepsia, etc. One cannot distinguish between disease symptoms and adverse drug effects.

13. Cases receiving norfloxacin in the neutropenia prophylaxis studies should not be included in the evaluation of adverse reactions because they were all receiving multiple drugs. The 80% adverse reaction rate and 71% abnormal laboratory report rate should be disregarded. These patients are not good subjects for drug safety evaluation.

14. Adverse reaction rates for the labeling should be recalculated so that only those patients who received a dose schedule of 400 mg twice daily, the dose to be recommended in the labeling, are included. Adverse reaction rates associated with other dosing schedules can be determined separately.

15. Some adverse reactions which the investigator has labeled not-drug-related reactions are very likely drug related and are typical of the type of adverse reactions that occur with the quinolones.

16. The following organisms should be re-tallied to give a count for each individual species:

Klebsiella species
Pseudomonas species

Enterobacter species
Staphylococcus species

One species in each will probably account for practically all of the isolates reported.

17. The applicant should be requested to report EEG findings in humans. At least one quinolone has epileptogenic potential. At least one norfloxacin-treated patient had a convulsion.

Biopharmaceutics Consultation: Requested April 2, 1985.

Labeling Review: Proposed labeling is unsatisfactory. A separate MOR will be provided for labeling.

Foreign Clinical Data: This application contains foreign clinical data. See pages 19, 29, 39, 64, 75, 77, and 80 in this MOR.

✓ Conclusion: If the deficiencies and comments in this MOR can be resolved, the efficacy data in this application may support the use of norfloxacin in the treatment of the following two indications:

Urinary tract infections caused by E. coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Pseudomonas aeruginosa, Citrobacter species, and Staphylococcus species to be specifically named.

Gastroenteritis caused by enterotoxigenic E. coli, Shigella species, Salmonella species, and Campylobacter species.

✓ Recommendation: Before this application can be considered to be approvable, a meeting should be held with the applicant to consider the deficiencies and comments listed above. 

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc
Orig NDA
HFN-315
HFN-815/Reed
HFN-815/CSO
HFN-340
4432b pages 1-87
4593b pages 88-109

27 1/21/86 See Division Director's Memorandum

WAD 2/1/85 - See appended supervisor's comments dated 2/1/85

NDA 19-387

May 2, 1986

MEDICAL OFFICER'S REVIEW OF LABELING

and MEMORANDUM OF TELEPHONE CONVERSATIONS

Amendment ()

Applicant: Merck Sharp & Dohme Research Laboratories
West Point, Pennsylvania

Name of Drug: Trade: NOROXIN

Generic: Norfloxacin

Pharmacological Category: Fluoroquinolone

The applicant submits another revised version of proposed labeling.

Medical Officer's Comments: Revised proposed labeling has greatly improved and we are essentially in agreement. This new version was discussed with Mr. Norton. There are a few recommended sentences that have been omitted and there are a number of suggestions regarding sentence structure.

April 29 and 30, 1986: I called Dr. David Blois to discuss labeling.

May 2, 1986: I received the new version and I called Dr. David Blois, Senior Director of Regulatory Affairs (215-834-2304), to discuss these changes and to dictate my recommendations. Dr. Blois will consider these changes with his staff and will file revised proposed labeling in two or three days.

Recommendation: Approval is recommended but labeling is still unsatisfactory.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc

Orig NDA

SHFN-840

HFN-840/Reed

HFN-840/CSO

4783h

JRD 5 May 86

8:5 E.T. 5/23/86

NDA
19-304

May 16, 1986

MEDICAL OFFICER'S REVIEW OF LABELING
and MEMORANDUM OF TELEPHONE CONVERSATION

Amendment ()

Applicant: Merck Sharp & Dohme Research Laboratories
West Point, Pennsylvania

Name of Drug: Trade: NOROXIN

Generic: Norfloxacin

Pharmacological Category: Fluoroquinolone

The applicant submits another revised version of proposed labeling.

Medical Officer's Comments: Revised proposed Labeling is satisfactory.

Telephone Conversation May 16, 1986: I called Dr. Blois (215-834-2304) to tell him that I had received this amendment. He told me that the safety update is ready and will be delivered to me Monday, May 19, 1986.

Recommendation: Approval is recommended.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc
Orig NDA 575/23/86 HFN-815, HFN-815/Reed, HFN-815/CSO, HFN-815/Norton, 4802b

16 May 86

April 19, 1986

**MEDICAL OFFICER'S REVIEW OF NDA 19-384
and MEMORANDUM OF TELEPHONE CONVERSATIONS**

Amendments

**Applicant: Merck Sharp and Dohme Research Laboratories
West Point, PA**

Name of Drug: Generic: Norfloxacin

Trade: NOROXIN[®]

Pharmacological Category: Fluoroquinolone antibacterial agent for oral use

**Amendment In response to our requests, the applicant
files the following two items:**

1. An overall summary for the patient diary data previously submitted on Feb. 14, 1986. Additional diaries had been filed but no diaries were summarized.

These data characterize and compare the number of patients with, and days of, each complaint. The percentage of complaints per person was obtained by dividing the number of persons voicing a complaint by the total number of persons receiving each drug. The percentage of days for each complaint was determined by dividing the total number of days of each complaint by the total number of treatment days. Corrected frequencies were obtained by subtracting the percents for placebo-treated subjects from the percents for norfloxacin-treated patients. A negative percent denotes a higher frequency in the placebo group.

ANALYSIS OF PATIENT DIARIES

Complaints	<u>Placebo Cases</u> (N=51)		<u>Norfloxacin Cases</u> (N=100)		<u>Norfl. vs Placebo</u>	
	Total 468 days of Rx		Total 995 days of Rx		%	
	# Cases	Days of Complaint	# Cases	Days of Complaint	# Cases	% of total days of Complaint
Tired, etc	12 (2%)	21 (4%)	22 (22%)	61 (6%)	-2%	2%
Headache	13 (25%)	31 (7%)	22 (22%)	58 (6%)	-3%	-1%
Sleepy, etc	5 (10%)	6 (1%)	12 (12%)	25 (2.5%)	2%	1.5%
Nausea, etc.	2 (4%)	2	18 (18%)	49 (5%)	14%	5%
Dizzy, etc.	1 (2%)	3 (0.6%)	3 (3%)	5 (0.5%)	1%	-0.1%
Lightheaded			2 (2%)	6 (0.6%)	2%	0.6%
Eye Complaints	2 (4%)	6 (1%)	4 (4%)	14 (1.4%)	0%	0.4%
Stomachache	2 (4%)	2	8 (8%)	11 (1%)	4%	1%
Rotten, sick, etc.			5 (5%)	5 (0.5%)	5%	0.5%
Hyperactive	1 (2%)	1	1 (1%)	1	-1%	0
Numbness, etc.			2 (2%)	3	2%	0.2%
Flank pain			1 (1%)	1	1%	0.1%
Lump in throat			1 (1%)	3	1%	0.3%
Diarrhea			2 (2%)	2	2%	0.2%
Depressed	1 (2%)	1			-2%	-0.2%
Metallic taste	1 (2%)	1			-2%	-0.2%
Poor sleep			8 (8%)	13 (1.3%)	8%	1.3%
Backache			3 (3%)	10 (1%)	3%	1%
Nervous, etc.			2 (2%)	3	2%	0.2%
Constipated			1 (1%)	1	1%	0.1%
Anorexia	1 (2%)	1	1 (1%)	2	-1%	0
Itching, rash			2 (2%)	5 (0.5%)	2%	0.5%
Swollen hands, etc.			2 (2%)	7 (0.7%)	2%	0.7%
Vaginal itching			4 (4%)	7 (0.7%)	4%	0.7%
Dry mouth			1 (1%)	1	1%	0.1%
Tinnitus			1 (1%)	2	1%	0.2%
Joint complaints			1 (1%)	1	1%	0.1%
No comments	28 (55%)	412 (88%)	37 (37%)	768 (77%)		

About 400 placebo treatment days are compared to about 1000 days norfloxacin treatment days. The rates were greater for norfloxacin than placebo, particularly for two complaints, nausea (14% greater), and poor sleep (8% greater). Others that were greater for norfloxacin were stomachache, feeling rotten or sick, and vaginal itching. Rates were greater for placebo than for norfloxacin for several complaints but none were as high as those given above.

2. Two issues that this medical officer asked to be clarified are explained. "Qual no" means qualitative numbers. Computer coding used a scale of 0-4+ for some reports. This scale was used to report urine protein and urine glucose concentration and appeared on the computer printout as "Qual no." In like manner, words on the case report forms were converted to numerical figures for platelets and other laboratory reports. Therefore, "Many" epithelial cells and nonamorphous crystals on Dr. Cohn's case report #302 was converted to 50 per high power field in the computer printout.

Amendment) in response to the medical officer's request, the bacterial efficacy tables for urinary tract infection studies have been revised to exclude underage patients, to include micro-organisms which were not evaluable for the microbiological evaluation for a number of reasons, and to provide separate counts for individual species in five genera. Compassionate cases that had been excluded are included.

These revised bacterial outcome tables should be disregarded because the applicant failed to include data from the control groups. This revision is superseded by the Amendment () which includes data from the controls.

Amendment) The applicant files final reports of the three following studies which were requested by the FDA pharmacologist at the January 14, 1986 meeting with the firm:

1. Teratology study of norfloxacin in cynomolgus monkeys,
2. Metabolism study of norfloxacin in pregnant and nonpregnant cynomolgus monkeys, and
3. Embryotoxicity study of norfloxacin in cynomolgus monkeys.

The reader is referred to the review by the pharmacologist.

The results of the teratology study indicate that the oral administration of norfloxacin during organogenesis in the cynomolgus monkey at doses of 75 mg/kg/bid and greater induced dose-related embryotoxicity. The no-effect dose was 50 mg/kg/bid. Doses sufficient to cause embryonic loss are not tolerated in some monkeys. The mechanism of norfloxacin-induced embryotoxicity is most likely hormonal (some aspect of placental progesterone synthesis) and not a direct effect on the embryo. Norfloxacin was not teratogenic in any species.

The applicant concludes that in view of the embryo lethality in monkeys, although the relevance of this to humans is not known, norfloxacin should be used in pregnancy only if the benefits justify the potential risk to the fetus.

Reviewer's Comment: Like other quinolones, norfloxacin already is not to be recommended for use in pregnancy because of the development of arthropathy in juvenile animals of all species tested. Embryotoxicity is a second reason.

Amendment ()

1. In response to the medical officer's request the bacterial efficacy tables for urinary tract infection studies have been revised to exclude underage patients, to include micro-organisms which were not evaluable for the microbiological evaluation for a number of reasons, and to provide separate counts for individual species in five genera. Data from control groups have been added. Compassionate cases that had been excluded are included.

The applicant's revised summary of efficacy data for urinary tract infections for evaluable patients in this application is shown below. (Number eradicated/No. Isolated. Protocol numbers are in parentheses.)

Indication & Claim No.	Organism	Controlled Trials			Uncontrolled Trials -		
		Norfloxi- acin	Control	Protocol #	PE/PI	col #	
1.1	<u>E. coli</u>	46/46	44/44	(#001)	13/13	(#011)	
		27/27	17/22	(#002)	28/29	(#017)	
					0/1	(#019)	
		53/53	52/55	(#504/505)	61/63	(#506/508)	
	Total	126/126	113/121		102/106	(96.2%)	
		(100.0%)	(93.4%)				
1.2	<u>Klebsiella pneumoniae</u>	1/1	2/2	(#001)	5/5	(#011)	
		6/8	5/5	(#002)	3/3	(#017)	
		1/5	3/4	(#504/505)	6/6	(#506/508)	
		Total	8/14	10/11		14/14	(100.0%)
		(57.1%)	(90.9%)				
	<u>K. oxytoca</u>				2/2	(#506/508)	
	<u>Klebsiella</u> sp.	0	1/1	(#504/505)			
1.3	<u>Enterobacter aerogenes</u>	1/1	1/1	(#002)	2/3	(#011)	
		0/1	1/1	(#504/506)			
		Total	1/2	2/2		2/3	
	<u>E. cloacae</u>	4/4	1/1	(#504/505)	1/2	(#306/508)	
	<u>E. agglomerans</u>	1/1	0	(#504/505)	1/1	(#011)	
	<u>Enterobacter</u> sp.	0	2/2	(#504/505)			
1.4	<u>Proteus mirabilis</u>	3/3	1/1	(#001)	4/4	(#011)	
		5/5	3/4	(#002)	4/4	(#017)	
		9/9	8/9	(#504/505)	15/15	(#506/508)	
		Total	17/17	12/14		23/23	(100%)
		(100%)	(85.7%)				
1.5	<u>Proteus, indole positive group</u> (3 species) Total	1/1	1/1	(#002)	4/4	(#506/508)	
		2/2	1/1	(#504/505)			
		3/3	2/2		4/4	(100%)	
1.6	<u>Pseudomonas aeruginosa</u>	4/4	0	(#001)	11/13	(#011)	
		4/8	0	(#002)	2/3	(#017)	
					2/6	(#019)	
		5/5	0/1	(#504/505)	8/9	(#506/508)	
		Total	13/17	0/1		23/31	(74.2%)
		(76.5%)					
	<u>Pseudomonas capsula</u>				1/1	(#506/508)	
	<u>P. fluorescens</u>	0	1/1	(#002)			

Indication & Claim No.	Organism	Controlled Trials			Uncontrolled Trials - Proto-	
		Norflox- acin	Control	Protocol #	Trials - Proto- #X/#I	col #
1.7	<u>Serratia</u> <u>marcescens</u>	0	1/1	(#504/505)		
1.8	<u>Providencia</u> <u>stuartii</u> and <u>Providencia</u> sp.	2/2	0/0	(#504/505)		
1.9	<u>Citrobacter</u> <u>freundii</u>	1/2	0/0	(#002)	2/2	(#017)
	Total	1/2	0/0		2/2	(#506/508)
	<u>Citrobacter diversus</u>	0/0	0/0		1/1	(#506/508)
	<u>Citrobacter</u> sp.	0/0	1/1	(#001)		
		1/1	0/0	(#002)		
1.10	<u>Staphylococcus</u> <u>aureus</u>	1/1	0/0	(#001)	2/3	(#011)
		3/3	2/2	(#002)	3/3	(#017)
	Total	4/4	2/2		3/3	(#506/508)
					8/9	(88.9%)
	<u>Staphylococcus</u> <u>epidermidis</u>	3/3	0/0	(#002)	1/1	(#011)
		0/0	1/1	(#504/505)	2/2	(#017)
	Total	3/3	1/1		2/2	(#506/508)
					5/5	
	<u>Staphylococcus</u> <u>saprophyticus</u>	1/1	0/0	(#001)		
		0/0	1/1	(#002)		
	1/1	0/0	(#504/505)	1/1	(#506/508)	
1.11	<u>Staphylococcus</u> <u>cong. neg</u>				1/1	(#011)
					1/1	(#017)
	Group D streptococci	7/8	0/1	(#002)	5/6	(#011)
	cluding <u>S. faecalis</u>	1/1	5/5	(#504/505)	1/2	(#017)
Total	8/9	5/6		3/3	(#506/508)	
	(88.9%)	(83.3%)		9/11	(81.8%)	
1.12	Group B streptococci Beta-hemolytic strep.	1/1	1/1	(#002)	1/1	(#011)

Medical Officer's Comments: (Percents were added by the medical officer.)

a) This revised table responds to the medical officer's requests and is satisfactory. It is the final bacteriological outcome table and takes the place of the applicant's table shown on pages 88-89 and the medical officer's preliminary outcome table shown on pages 91-91 of the original

MOR of this application.

b) Therefore, satisfactory efficacy data have been filed to recommend norfloxacin in the treatment of urinary tract infections caused by Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus aureus, and Group D streptococci. Staphylococcus epidermidis, Citrobacter freundii, and Enterobacter cloacae should also be added to this list but with an asterisk to show that there were less than ten cases.

Tallying individual species separately in this revised table deletes Enterobacter aerogenes (only 1/2 eradications in controlled trials and 2/3 eradications in uncontrolled trials).

c) Treatment of gastroenteritis will not be recommended.

2. In response to the medical officer's request, adverse reaction data and laboratory data have been retabulated to provide counts in separate categories by the size and frequency of the dose.

Distribution of Adverse Experiences by Dose
(Only rates greater than 0.15% are shown)

	200 mg bid 60 pts.	400 mg bid 1015 pts	400 mg bid 27 Vol.	400 mg tid 25 Vol.	Total N=1127	% hav- ing AE	% of D Relate AEs
Abdominal Swelling		1	1		2	0.17	0
Fatigue		3	3		6	0.53	0
Fever		2		1	3	0.27	0
Myocardial Infarct.		2			2	0.17	0
Abdominal Pain		4 (2)	1		5 (2)	0.44	3.5
Constipation		4			4	0.35	-
Diarrhea		3 (1)			3 (1)	0.27	1.8
Dry Mouth		3 (2)			3 (2)	0.27	3.5
Dyspepsia		5 (4)			5 (4)	0.44	7
Flatulence		3	1		4	0.35	-
G.I. Cramps		2 (1)			2 (1)	0.17	1.8
Heart Burn		4			4	0.35	-
Mouth Ulcer		2			2	0.17	-
Nausea		28 (13)		1	31 (13)	2.75	23
Vomiting		2			3	0.27	-
Depression		4 (-)			4 (1)	0.35	1.8
Dizziness		16 (6)	4		20 (6)	1.77	10.5
Headache		21 (4)		9	30 (4)	2.66	7
Insomnia		4 (2)			4 (2)	0.35	3.5
Somnolence		5 (1)			5 (1)	0.44	1.8
Pruritis		2 (2)			2	0.17	3.5
Rash		6 (3)			6 (3)	0.53	5.5
Taste Perversion		2 (2)			2 (2)	0.17	3.5
Other (Under 1%)		40 (13)	2	2	44 (15)		
Total		168 (57)	15	13	196 (57)		

The most frequently occurring adverse reactions for 1127 subjects in multiple-dose, non-neutropenic studies that were predominantly urinary tract infection studies with the recommended 400 mg bid dose schedule were nausea - 2.75%, headache - 2.66%, dizziness - 1.77%, rash - 0.53%, and fatigue - 0.53%.

Distribution of Adverse Laboratory Experiences by Dose
(Only rates greater than are shown)

	200 mg bid 60 pts.	400 mg bid 1015 pts	400 mg bid 27 Vol.	400 mg tid 25 Vol.	Total N=1127	% hav- ing AEs	% of Dr ing Related AEs
Hemoglobin Dec.		4			4	0.35	0
Hematocrit Dec		2	3		5	0.44	0
WBC Count Dec.*		6 (3)	8		14 (3)	1.2	30
WBC Count Inc.		3	1		4	0.35	0
Neutrophils Dec.*		7 (3)			7 (3)	0.62	30
Lymphocytes Rel Inc.		3 (1)			3 (1)	0.17	10
Eosinophilia		19 (1)	1		20 (1)	1.8	10
Thrombocytopenia		4			4	0.35	0
BUN Elevated		11			11	0.98	0
Ser. Creat. Elev.		5			5	0.44	0
Tot. Biliru. Elev.	1	3			4	0.35	0
AST, ALT Inc.		20 (1)			20 (1)	1.8	10
Alk. Phos. Inc.		16 (1)			16 (1)	1.4	10
Ser. LDH inc.		7			7	0.62	0
Ser. Chloride Dec.		4			4	0.35	0
Ser. Chloride Inc.		3			3	0.27	0
Urine Protein Inc.		3	1		4	0.35	0
Urine RBCs Inc.		3			3	0.27	
Other (Under 2%)	0	14	1		15		
Total	1	137 (10)	15	0	153 (10)		

*In most instances, WBC decreases and neutrophil decreases came from the same patients.

In both tables, numbers in parentheses are the number of reactions thought to be drug-related.

The most frequently occurring laboratory adverse experiences were eosinophilia - 1.8%, AST or ALT increase - 1.8%, increased alkaline phosphatase - 1.4%, decreased WBC count - 1.2%, and elevated BUN - 0.98%. No single adverse laboratory experience in urinary tract infection studies was as high as 2%.

Amendment: The applicant responds to the request from FDA's Division of Biopharmaceutics for in vitro dissolution data on various lots and formulations of norfloxacin tablets. Dissolution data as agreed upon in a telephone conversation with Dr. Gene Mason of this Division are filed.

The final market image 400-mg formulation, the Kyorin 400 mg-tablet, the Merck Sharp & Dohme Research Laboratories direct compression 400 mg-tablet, and

production scale tablets are compared. The final market image formulation dissolves faster and peaks faster than any of the previous products and has less coating. Eighty percent of the tablet dissolved in 30 minutes. The matter is referred to the chemist's review and to the review by Dr. Gene Mason of the Division of Biopharmaceutics. That Division has accepted this report.

Amendment (): Revised proposed labeling is filed. Many of the comments listed in my MOR dated March 14, 1986 have been included. Some were not included. Comments on the new version are listed below.

Clinical Pharmacology:

1. (Page 6, line 7) Insert "Alteration of dosage is necessary (See DOSAGE AND ADMINISTRATION)." in regard to patients with impaired renal function.
2. (Page 6, line 19) Insert "in the urine" in the sentence, "Within 24 hours of drug administration, 26 to 32% of the dose is recovered in the urine as norfloxacin ..."

Microbiology:

1. (Page 9, lines 4-6) Revise this sentence to read, "Nalidixic acid resistant organisms are generally susceptible to norfloxacin in vitro; however, these organisms (particularly P. aeruginosa, K. pneumoniae, Acinetobacter, and enterococci) may have higher MICs to norfloxacin than nalidixic acid-susceptible strains. For this reason, cultures and susceptibility testing may have to be repeated.

Indications and Usage:

(Page 15) Revise the first paragraph to read as follows

"NOROXIN is indicated for the treatment of adults with aplicated and uncomplicated urinary tract infections that are caused by susceptible strains of the designated micro-organisms listed below:

Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,
Pseudomonas aeruginosa, Staphylococcus aureus, Staphylococcus epidermidis,* Citrobacter freundii,* Enterobacter cloacae,* and group D streptococci.

*Efficacy for these micro-organisms in urinary tract infections was studied in fewer than ten infections."

Warnings:

1. (Page 16, lines 14-15) Revise the sentence to read, "The oral administration of single doses of norfloxacin, 4 times the recommended human clinical dose, caused lameness in immature dogs."
2. (Page 16, lines 7-12) Switch phrases and revise the first sentence so

that it will read "Needle-shaped crystals in the urine were found in some volunteers who received either 800 mg norfloxacin, 1600 mg norfloxacin (at or twice the recommended dose), or placebo while participating in a single double-blind, crossover study comparing single doses of norfloxacin with placebo." Delete the next sentence "These crystals were not identified."

3. (Page 16, line 17) Add "and an adequate rate of urine flow" to the end of the last sentence.

Precautions:

1. (Page 18, line 3) Insert two paragraphs that were recommended in the last labeling discussion.

⁶⁴ "Norfloxacin should be used with caution in patients with a history of hepatic disease or in patients with impaired hepatic function."

"The effects of norfloxacin on brain function or on the electrical activity of the brain have not been tested. Central nervous system-type adverse experiences such as headache, dizziness, lightheadedness, hyperactivity, visual changes, and insomnia have been reported with some antibacterial agents in the quinolone drug class. Seizures which were not thought to be drug related occurred in two norfloxacin-treated patients that had existing CNS disorders that predispose to seizures and that fully accounted for the events. Until more information becomes available, quinolones should be used with caution in patients with known factors that predispose to seizures."

2. (Page 19, lines 2-7) Revise the Information for Patients section to read as follows:

"Patients should be advised to drink fluids liberally and that antacids should not be taken concomitantly or within two hours after dosing.

"NOROXIN may cause dizziness or lightheadedness; therefore, patients should know how they react to norfloxacin before they operate automobiles and machinery or engage in activities requiring mental alertness and coordination."

3. (Page 20, lines 12-19) Switch the first two sentences in the Pregnancy Category C section.

(Page 21, lines 1-3) The last sentence in the pregnancy section should be revised to read, "Since norfloxacin, like other drugs in this class, causes arthropathy in immature animals, its use during pregnancy is not recommended (See Warnings)."

Adverse Reactions: (Pages 22-23) Revise this whole section to read as follows:

"NOROXYN generally is well tolerated. The overall incidence of drug-related side effects in clinical trials involving 1127 subjects was approximately _____ % (Percent figure will be inserted).

"The most common side effects (less than 3%) observed during clinical trials were either gastrointestinal or neurological and include nausea-2.8%, headache-2.7%, and dizziness-1.8%. Additional reactions with frequencies greater than 0.3% were fatigue, rash, abdominal pain, dyspepsia, somnolence, depression, insomnia, flatulence, and heart burn. Less frequent reactions were dry mouth, diarrhea, fever, vomiting, and erythema. Although not reported with norfloxacin, visual disturbances have been reported with other drugs in this class."

"Abnormal laboratory values observed in clinical trials were eosinophilia-1.8%, elevation of ALAT (SGPT) and ASAT (SGOT)-1.8%, increased alkaline phosphatase-1.4%, and decreased WBC-1.2%. Those occurring less frequently were elevated BUN, serum creatinine, and LDH, and decreased hematocrit.

Dosage and Administration: (Page 24, lines 1-12) Revise this section to read as follows:

"Norfloxacin should be taken orally one hour before or two hours after a meal with a glass of water. Patients receiving norfloxacin should be well hydrated to prevent crystallization of norfloxacin in the urinary tract.

Normal Renal Function

"The recommended norfloxacin dose is 400 mg twice daily for adults with normal renal function, and for patients with creatinine clearance rates greater than 30 mL/min/1.73 m².

For uncomplicated urinary tract infections, the recommended treatment period is 7 to 10 days.

For complicated urinary tract infections, the recommended treatment period is 10 to 30 days.

Doses higher than 800 mg/day are not recommended.

Animal Pharmacology: The Anti-Infective Advisory Committee has recommended that labeling for members of the quinolone drug class have an Animal Pharmacology section. The following text is recommended:

Animal Pharmacology: Norfloxacin and related drugs have been shown to cause arthropathy in immature animals of most species tested (See Warnings).

doses of 50 mg/kg/day and higher.

Embryolethality and slight maternotoxicity were observed in cynomolgus monkeys at doses of 50 mg/kg/day or higher.

Oculotoxicity, seen with some related drugs, was not observed in any norfloxacin-treated animal."

Memoranda of Telephone Conversations: A number of telephone conversations were held with Dr. David W. Blois, Senior Director of Regulatory Affairs (215-661-2304) to discuss these amendments and proposed labeling.

April 16, 1986 I called to dictate labeling recommendations. Dr. Blois will edit the brain function paragraph.

April 17, 1986 I called to discuss adverse reaction data. Dr. Blois discussed the Indications section. Dr. Blois wants E. cloacae, C. freundii, and indole positive Proteus listed in the Indications section.

April 19, 1986 In a conference call, Mr. Norton and I gave them comments on the Microbiology section. We agreed to add E. cloacae and C. freundii with asterisks. These pathogens are exquisitely susceptible to norfloxacin. Indole positive Proteus, however, represents a group.

Conclusion: All requests have been answered satisfactorily and the applicant has responded to all comments except a few labeling comments.

Recommendation: This application should be made approvable. Labeling is unsatisfactory but labeling discussions are progressing very well.

Theresa Greene Reed
Theresa Greene Reed, M.D., N.P.H.

cc
Orig NDA
HFN-815
HFN-815/Reed
HFN-815/CSO
4731b

BRD 22 Apr 86

4/28/86 Division Director's Comments
wording of the "asterisk footnote"
should be consistent with that in
other recent drug labeling - per
identical. S. Tabor

March 3, 1986

MEDICAL OFFICER'S REVIEW OF NDA 19-384
and MEMORANDA OF TELEPHONE CONVERSATIONS

Amendment (

Applicant: Merck Sharp and Dohme Research Laboratories

MOR

Name of Drug: Trade: NOROXIN™

Generic: Norfloxacin

Pharmacological Category: Fluoroquinolone antibacterial agent

Amendment Dated February 14, 1986: The applicant responds to comments raised by Drs. Mason and Hunt regarding the biopharmaceutical aspects of the application as follows:

"Following oral administration of norfloxacin, 25-30% of that dose is recovered in urine unchanged within 48 hr. Additionally, in the same period of time, another 6-10% of the dose is recovered as norfloxacin metabolites. It is known that norfloxacin and its metabolites are also excreted in bile. In other studies, feces were collected following oral norfloxacin doses and assayed microbiologically. Assuming that all antimicrobial activity was attributable to norfloxacin, fecal recovery would account for another 30% of the dose. Hence, approximately 70% of an oral norfloxacin dose may be accounted for in this manner. The remaining 30% of the dose could very likely be attributed to the following.

"The deficit does not result from improper urine collection procedures or shortcomings in the analytical procedure for urine. Since the solubility of norfloxacin in urine is dependent on pH and temperature, every precaution is taken to obtain a representative urine sample for analysis. Urine aliquots are taken after each urination rather than at the end of a collection interval to avoid the urine being stored and/or chilled. At the analytical lab, urine samples are warmed to 38°C and agitated until all materials have redissolved. Since standards for the HPLC analytical procedure are prepared in freshly-voided human urine, representative estimates of norfloxacin urinary excretion would be anticipated.

"Known norfloxacin metabolites are excreted in bile and are probably present in feces. The bacterial species used in the microbiological assay of fecal specimens cited earlier, *E. coli* (ATCC 25922), is variably less sensitive to norfloxacin metabolites than to norfloxacin itself. Furthermore, unknown metabolites of norfloxacin which could be formed in the G. I. tract and to which the organism is insensitive would not be detected. Both of these events would have an additive effect on estimates of norfloxacin-related species eliminated via fecal excretion.

"Finally, it has been demonstrated by van Saene, et al [Scand. J. Infect. Dis. 17: 295, 1985] that the inherent antimicrobial activity of antibiotics in feces is significantly decreased. This would cause underestimation of the amount of drug actually there if microbiological assay techniques were used.

"Hence, efforts to delineate excretion patterns in man following oral

administration of norfloxacin using microbiological assays, and specific, sensitive, and quantitative HPLC techniques rather than radiometric procedures, can conservatively account for 70% of the dose as norfloxacin and its metabolites in urine and feces. Shortcomings with microbiological procedures for analysis of fecal specimens and the possibility of unknown metabolites or degradates of norfloxacin being present in feces would conceivably account for much of the remainder."

Two publications are included.

Amendment () The applicant responds to comments from Dr. Taylor regarding the chemical aspects of the application and files the following information:

1. Additional stability data for the reformulated product,
2. Impurity specification by thin layer chromatography of the bulk drug,
3. Dissolution specification,
4. The pH solubility profile of norfloxacin at 25°C and 37°C,
5. Thin layer chromatography identity test for the finished product as stated in their July 11, 1985 letter to FDA, and
6. A more specific description of the aluminum foil strip that was briefly described in the NDA.

Amendment () As agreed in a telephone conversation between Dr. Mason of the Division of Biopharmaceutics, the applicant submits published articles concerning the lack of interaction between norfloxacin and probenecid, and about the excretion of norfloxacin in mother's milk. These articles were referenced in the NDA but were not included.

1. "Basic and Clinical Studies on AM-715 in the Field of Obstetrics and Gynecology." by Zenjiro Takase et al, Kawasaki Medical School (Chemotherapy, Dec. 1981).

The peak level in umbilical cord blood was 0.37-0.38 mcg/ml at 6-10 hours after an oral administration of 200 mg of AM-715, and that in amniotic fluid was 0.92 mcg/ml at 10 hrs after, but the levels in neonate blood and excretion in milk were less than the assay limit.

2. "Clinical Studies on AM-715 in the Field of Obstetrics and Gynecology" a 12-line abstract by Seiji Matsuda et al at Juntendo University School of Medicine (Chemotherapy, Dec. 1981).

In a few cases, transference of AM-715 into umbilical cord blood was observed and its concentration was about 50% of the maternal serum concentration. The transference of the drug into umbilical cord blood and amniotic fluid varied.

3. "Mechanism of Renal Excretion of AM-715, a New Quinolonecarboxylic Acid Derivative, in Rabbits, Dogs, and Humans" by Jingoro Shimada et al at the Jikei University School of Medicine in Tokyo and the Central Research Laboratories, Kyorin Pharmaceutical Co. Ltd., Tochigi, Japan (Antimicrobial Agents and Chemotherapy. 1983 (Jan); 23 (1): 1-7).

The mechanisms of the renal excretion of AM-715 were studied in

rabbits, dogs, and humans. In both rabbits and humans, AM-715 clearance was greater than creatinine clearance and was profoundly decreased by the administration of probenecid. Thus, in these subjects, AM-715 was cleared by both tubular secretion and glomerular filtration. In dogs, however, the excretion ratio (close to unity), biological half-life, and stop-flow pattern of AM-715 were not affected by probenecid, indicating that the renal excretion of AM-715 took place mostly through glomerular filtration. These results suggest that renal excretion of AM-715 differs with animal species.

Amendment (#3 Dated February 24, 1986): The applicant responds to four of the comments on the list of comments from the medical officer.

1. The applicant files a set of new tables to provide a retabulation of all UTI studies to show bacterial outcome by bacterial pathogen for 474 evaluable patients. This time FDA guidelines for urine-specimen collection were used. Also, patients under 18 years of age have been disqualified.

✓ Medical Officer's Comment: This is a partial response to the original request. The MO's original request was to revise the overall summary table to delete underage patients that should have been disqualified and to delete cases which should have been disqualified where FDA guidelines for urinary tract infections were not followed. Specifically, the firm was asked to revise the final overall summary table on pages I-08282 through I-08286 in Volume 2.23 to delete all of these disqualified cases. This table, when properly revised, will show what micro-organisms will qualify for the Indications section in the labeling. Micro-organisms for the labeling can be identified when this table is corrected. (Generating new tables at this point is not helpful.)

2. The applicant files similarly revised information for the gastroenteritis study, No. 519.

✓ Medical Officer's Comment: Same as above. The final summary table in Volume 2.23 is the one that should be revised.

3. The uncontrolled multiclinic international urinary tract infection study, described on page 65 of my MOR dated November 14, 1985, had not been analyzed satisfactorily. In response to the MO's request at the meeting with the applicant, it is re-analyzed in this submission to correct a long list of deficiencies. Clinical outcome criteria were incorrect. "Assessable" patients should be unevaluable patients. Patients were to be disqualified if pretherapy cultures were obtained earlier than 48 hours before treatment. Culture timing should comply with FDA guidelines. Patients under 18-yrs. old should be disqualified. UTI's should not be subdivided into upper and lower infections. There should have been a microbiological outcome summary table and an adverse reaction summary table. The 40 adverse laboratory values should have been listed.

With this re-analysis of these 340 cases, there were 232 disqualified cases instead of 131. Ninety-six more cases were disqualified for inadequate culture timing and five were disqualified because they were underage. There were 108 evaluable cases instead of 209.

ADVERSE EXPERIENCES

	Serious/ Drug Related	Serious/ Not Drug Related	Not Serious/ Drug Related	Not Serious/ Not Drug Related
Anxiety disorders	1			
Dry mouth	1			
Tachycardia	1			
Rash	1			1
Tongue enlargement	1			
Euphoria	1			
Overflow of tears	1			
Fever		1		
Purpura		1		
Knee pain		1		
Convulsive disorder		1		
Cerebrovascular accident		1		
Shock		1		
Hypovolemia		1		
Myocard. infarct., acute		1		
Hypovolemic shock		1		
Congestive heart failure			1	
Pruritus			2	
Erythematous condition			2	1
Depression			1	
Nausea			2	4
Headache			1	
Digestive system disorders			1	
Abdominal or GI pain			1	1
Dyspepsia			2	
Dysphagia			1	
Constipation				1
Vomiting				3
Pruritus ani				1
Pneumonia				1
Total	7	9	14	13

*All seven serious/drug-related reactions occurred in the same patient.

Fourteen patients discontinued therapy due to clinical adverse reactions.

Forty patients had laboratory adverse experiences. None was serious, definitely or probably drug related. Drug crystalluria which was reported in one patient disappeared in the post-therapy urinalysis.

ADVERSE LABORATORY EXPERIENCES

	Not Serious/ Drug Related	Not Serious/ Not Drug Related	Not Serious/ Relationship Not Stated
WBC count	1	1	
Elevated ASAT		9	
Elevated ALAT		11	
Elevated monocytes		2	
Urine crystals (circled)		1	
Elevated hemoglobin		1	
Elevated eosinophils		6	2
Elevated alkaline phos.		7	1
Elevated serum LDH		6	
Elevated serum sodium		1	
Elevated serum creatinine		4	
Elevated urine protein		1	
Elevated serum potassium		1	
Abnormal neutrophils		1	
Elevated blood urea		1	
Elevated BUN		3	
Elevated platelet count		2	
Elevated ESR		1	
Elevated urine WBCs			1

The applicant concludes that norfloxacin is effective in women and men in the treatment of complicated and uncomplicated UTI caused by susceptible bacteria. It is effective in the treatment of UTI caused by P. aeruginosa in patients without severe structural or functional abnormalities of the urinary tract. It was well tolerated at oral doses of 400 mg twice daily for ten days and has a good safety profile when given in this dosage schedule.

Reviewer's Comment: With the re-analysis of this study, the applicant's conclusions can be accepted.

Memoranda of Telephone Conversations March 4 and 5, 1986: In Dr. David Blois' absence, I called Dr. Berger and Dr. Picot to discuss my comments on the clinical data in the amendment. Dr. Berger will see that the overall summary table in Volume 2.23 (pages I-08282-I08286) is revised to delete disqualified patients as described above. This revised table will be available within the next few days. Controls should be included in the revised table.

I asked Dr. Berger to tell me where the bioequivalence study was located. He replied that it is Dr. Zinney's study, Study No. 59, and is located in Volume 2.4, page I-01006.

Status of this NDA: This application will probably be approvable but a statement of this fact is deferred.

1. The pharmacology review is being completed. There are so many safety issues with the quinolones that consideration of the recommendations of the

pharmacologist is a requirement before a recommendation of approval can be made.

2. The biopharmaceutics review is being completed and is being discussed in the Biopharmaceutics Division. It is not available yet but an in-house discussion of these recommendations will be needed. There is a question about the need for a bioequivalence study.

3. Labeling is unsatisfactory. The medical officer and the applicant have agreed to discuss labeling within the next four days. The overall summary table will be revised and ready for these discussions. Mr. Norton, the microbiologist for this application (who replaced Mrs. Eckert when she was given other assignments), is ready to discuss the microbiology section of the labeling at the same time.

4. The question about the potential of norfloxacin to induce crystalluria has been answered in discussions with the biopharmaceuticists. The saturation point of norfloxacin in human urine at body temperature is way above the highest urine concentrations which might be expected with the doses that shall be recommended.

5. There are two remaining unresolved comments, the report of tests of brain function in humans and a report of EEG findings in humans. The applicant suggested that these might be considered Phase IV studies.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc

Orig Form 19-384

HPN-815 FT 3/6/86

HPN-815/Reed

HPN-815/CSO

HPN-340

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dkd 6 Mar 86

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs and Biologics

NDA 19,384

MEMORANDUM

Date: September 26, 1986

From: Director, Division of Anti-Infective Drug Products
HFN-815

Subject: Summary Basis of Approval for NDA 19-384, Noroxin (norfloxacin)
Tablets, 400 mg.

To: Director, Office of Biologics Research and Review
HFN-800

Division Director's Memorandum dated January 2, 1986, Group Leader's Memorandum dated November 21, 1985, Medical Officer's Reviews dated November 14, 1985, February 24, March 3, March 14, April 19, May 9, May 20, August 19(2) and August 25, 1986, and Pharmacologist's Review dated February 3, 1986 should serve as the Summary Basis of Approval for Noroxin Tablets.

Edward Tabor, M.D.

CC:

ORIG. NDA 19-384

HFN-815

HFN-815/CSO/RLinkous/sdj/9/5/86

R/D init. by: ETabor/9/12/86

F/T: 9/26/86/9/29/86

0476u

ET 10/2/86

January 2, 1986

Division Director's Memorandum

The claim for Norfloxacin for the treatment of gastroenteritis should not be granted. Three studies were submitted in support of the claim.

1. Study 005 (p. 35 of M.O.R.), conducted in Denver, Colorado. The medical officer felt that too few patients were evaluable to prove efficacy (p. 38). Although Norfloxacin cured 6/9 patients with Campylobacter jejuni, this was fewer than erythromycin cured (12/13). Norfloxacin cured 3/3 patients with Shigella spp. No other organism was present in more than one patient. No E. coli infections were present. The overall efficacy was 79% compared to 93% for Erythromycin.
2. Study 519-01 (p. 39 of M.O.R.), conducted in seven countries in Mexico, Costa Rica, South American countries, and Italy. Norfloxacin was effective against E. coli, Shigella spp., Salmonella spp., but was not tested against Campylobacter spp. (p. 41). In addition, this is a foreign study without an adequate U.S. study to support it.
3. Study 31 (p. 61 of M.O.R.), conducted in Danbury, CT. Norfloxacin eradicated Campylobacter jejuni in 8/9 patients in an uncontrolled study. No other organisms were studied in evaluable patients. The medical officer should add an addendum to the review stating whether the clinical outcome was also favorable in these patients.

Thus, two adequate well-controlled studies have not been provided for this indication.

I have the following additional comments:

1. Shouldn't the UTI claim be for "Klebsiella spp. including K. pneumoniae?" Similarly for Enterobacter spp.?
2. Asterisks will be needed for UTI for Citrobacter spp. and Staphylococcus spp.
3. The gonorrhea claim should not be denied solely on the failure to provide susceptibility testing, in view of the 100% efficacy against both PPNG and non-PPNG strains.



Edward Tabor, M.D.

cc:
 Orig NDA
 HFN-815
 HFN-815/CSO
 HFN-815/TGReed
 HFN-815/ETabor:mas-1/3/85-0144d
 HFN-815/GRStanley

February 24, 1986

MEDICAL OFFICER'S REVIEW OF NDA 19-384
and MEMORANDUM OF TELEPHONE CONVERSATION

Amendment Dated February 14, 1986

Applicant: Merck Sharp & Dohme Research Laboratories

MOR #2

Name of Drug: Generic: Norfloxacin

Trade: NOROXIN™

Pharmacological Category: Fluoroquinolone antibacterial agent

Background: The reader is referred to my MOR #1 dated November 14, 1985 [REDACTED]. In this submission, the applicant responds to requests that the review team gave at the meeting. I called Dr. Girard Picot at Merck (in Dr. Blois' absence) to give him my comments on this amendment.

1. The original report of Dr. Zinney's Phase I study, No. 45, said that, "There were no norfloxacin crystals found in the urine at 1 to 2 hours post norfloxacin and placebo dosing." My MO's comment was that, "The report does not say whether drug crystals or crystals of the metabolites were found in other specimens of urine sediment anytime during the study." Specimens were not only collected 1 to 2 hours after dosing, but also at 0-1, 2-4, 4-6, 6-8, and 8-12 hours on days 1, 2, 7, 14, 22, 23, 28, and 35.

The applicant has not answered this question about Study No. 45 in this amendment. Instead, the applicant reports for Dr. Zinney's Study No. 66, another Phase I tolerance study, that no crystals of norfloxacin were found in the urinalysis samples. There was a difference between these studies. In Study No. 45, volunteers received 400 mg twice daily or placebo for fourteen days in crossover design. In Study No. 66 volunteers received 400 mg or placebo three times daily for five days.

Dr. Picot said he will try to answer the question about the presence of crystals in the other specimens.

2. Although not requested, the applicant provides results of the neurological examinations of subjects in Dr. Zinney's studies Nos. 45 and 66.

3. At the meeting, the medical officer called attention to discrepancies between information in four case report forms and the information in the computer printout regarding the presence of crystals in urine sediment. The applicant now explains these discrepancies by saying that the differences were consistent with coding conventions for this project. The laboratory value "Many" on the case report form was coded as a numerical "50." The 1+ calcium oxalate crystals on the case report form was coded as "1.0" with units equal to "qual no." ("Qual no" was not defined.) The non-amorphous crystals value of 4+ on the case report form was coded as 4/hpf by mistake and should have been coded as "4.0 qual no."

Reviewer's Comment: These are striking examples of how raw data in the

case report forms can be changed when they are transferred to or coded for the applicant's summary tables and how they might have an entirely different meaning. Such changes should be not be permitted and case report forms should always be filed for verification of the data.

Dr. Picot will try to define "qual no."

4. At the meeting, the applicant was asked to add data from the eleven compassionate cases to the summary tables. Eight of these eleven cases were treatment failures and these cases had been omitted.

The applicant did not comply with this request. Instead, an abstract of each case report is filed.

Dr. Picot was specifically requested to revise the summary table of overall results and conclusions on pages I-08282 through I-08286 in Volume 2.23 to include these cases where qualified.

5. At the meeting, the applicant was requested to retabulate adverse reactions in order to separate data from neutropenia, gastroenteritis, and gonorrhoea case report forms from other data. This has been done, in part, in several different tables.

Dr. Picot was asked to provide one large summary table arranged sideways on the page and with the following column headings:

	Phase I		UTI		Total (%)	Gastroenteritis		Ph I	Gonorrhoea
Body Site/	400 mg bid	400 mg tid	400 mg bid	200 mg bid	(First four columns)	400 mg bid	400 mg tid	All Single Dose	600 mg x 135
Adverse Effect	x	x	1015	60		146	184		
	subj.	subj.	pts.	pts.		pts.	pts.	subj.	pts.

Adverse reactions in neutropenic cases should be reported on a separate page.

6. In response to our request, patient diaries have been summarized. They were summarized by individual studies. Dr. Picot was asked to provide one summary table for all the diaries to show the complaints in patient/days.

Dr. Picot will discuss all of these comments with the staff and will reply.

This is the first part of a two-part response to our comments at the meeting.

Recommendation: Deferred until all responses have been received.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc
Orig NDA 19-384
HFN-815 ET 3/11/82 HFN-815/CSO 4683b
HFN-815/Reed

YAD 25 Feb 86

prostatic fluid, umbilical cord blood, and amniotic fluid, and to give these concentrations. However, this information should only be added if these concentrations are clinically significant. Dr. Blois will check these concentrations.

Microbiology: The Microbiology section is being prepared by our microbiologist. This section will be discussed with the applicant later.

(Page 6, lines 7-8) The statement that "There is generally no cross-resistance between norfloxacin and other antibacterial agents presently marketed." is not true. Cross resistance with nalidixic acid has been reported. (See page 37 or the paper by Duckworth and Williams in the J. of Antimicrob. Chemother. (1984; Volume 13: Suppl. B.).

Indications and Usage:

1. (Page 10) Begin this section with the sentence, "NOROXIN is indicated for the treatment of complicated and uncomplicated urinary tract infections in adults that are caused by susceptible strains of"(give names of micro-organisms). Micro-organisms cannot be named until the summary table in Volume 2.23 (Pages I-08282-08286) has been corrected. The Medical Officer's preliminary review shows that we might have Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Pseudomonas aeruginosa, Citrobacter species, and Staphylococcus species to complete this sentence.

Delete everything else on pages 10 and 11.

Insert, at the end of the Indications section, "Uropathogens should be tested in vitro for their susceptibility to norfloxacin prior to administration of the drug and when clinically indicated." This is a class labeling sentence for the quinolones.

Contraindications: (Page 12) Revise this section to read, "NOROXIN is contraindicated in patients with a history of hypersensitivity to norfloxacin or other members of the quinolone group of antibacterial agents (e.g., nalidixic acid, oxolinic acid, cinoxacin).

Warnings: In keeping with the Anti-Infective Drug Advisory Committee recommendations, a Warnings section should be added. The first sentence should be in heavy print or bold type. The section should read as follows:

WARNINGS: "THE USE OF NORFLOXACIN IN PREPUBERTAL CHILDREN AND DURING PREGNANCY IS NOT RECOMMENDED. The oral administration of single doses of norfloxacin, four times the recommended human dose, caused lameness in immature dogs. Histologic examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs (e.g., nalidixic acid, cinoxacin, and oxolinic acid) also produced erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species.

"Crystalluria has been reported in patients receiving doses that are 1/2 and 2 times the recommended daily dosage. Although crystalluria is not expected to occur under normal conditions with a dosage regimen of 400 mg

Bacteriological outcome is summarized as follows:

<u>Pathogen</u>	<u>Eradicated/No. Isolated</u>
<u>Citrobacter diversus</u>	1/1
<u>Citrobacter freundii</u>	2/2
<u>Enterobacter cloacae</u>	1/2
<u>Enterococcus</u>	3/3
<u>Escherichia coli</u>	62/64
<u>Gram-negative rods</u>	1/1
<u>Klebsiella pneumoniae</u>	6/6
<u>Klebsiella oxytoca</u>	2/2
<u>Proteus indole positive</u>	2/2
<u>Proteus mirabilis</u>	16/16
<u>Proteus vulgaris</u>	2/2
<u>Proteus species</u>	1/1
<u>Providencia stuartii</u>	1/1
<u>Pseudomonas aeruginosa</u>	8/9
<u>Pseudomonas cepacia</u>	1/1
<u>Staphylococcus aureus</u>	3/3
<u>Staphylococcus epidermidis</u>	2/2
<u>Staphylococcus saprophyticus</u>	1/1
Total	115/119

Strains were isolated in 108 patients; 10 patients had polymicrobial infections. The eradication rate for the 108 patients was 96.2%.

A clinical outcome of cured was reported for 106 of the 108 qualified patients or 98%. This includes 10 evaluable patients with polymicrobial infections.

There were 43 adverse clinical experiences in 27 patients. The applicant lists them by body system without naming individual reactions. One 65-year old patient had convulsions due to hypoxemia caused by respiratory insufficiency. This was not considered to be drug-related. Five patients who were over 70 years of age died, none of these was considered to be drug-related but were related to the underlying diseases.

	Norfloxacin			TMP/SMZ		
	Eradi- cated	Pers- isted	Total	Eradi- cated	Pers- isted	Total
Complicated Cases						
Gram Positive Cocci	15 (94%)	1	16	8 (80%)	1	9
Gram Neg. bacilli	149 (89%)	18	167	34 (87%)	5	39
Uncomplicated Cases						
Gram Positive Cocci	30 (88%)	4	34	7 (88%)	1	8
Gram Negative UTIs	290 (97%)	9	299	174 (91%)	18	192

2. The majority of complicated urinary tract infections were treated for 10-30 days.

Treatment Period	Number of Evaluable Cases
1-9 days	9
10-30 days	147 (92.5%)
31-99 days	3
Total	159

Approximately 90% of all adverse reactions occurred within the first four days of norfloxacin therapy. Dyspepsia, nausea, headache, dizziness, etc. appeared to occur very early in the course of treatment and continued therapy did not seem to appreciably increase the incidence of adverse experiences. Three adverse experiences occurred in patients treated beyond ten days for complicated urinary tract infections: rash on day 12 was probably related to treatment, hemorrhagic shock on day 31 was definitely not related to treatment, and eosinophilia on day 11 was probably not related to treatment. Of the 150 patients receiving therapy beyond 10 days, 147 did not experience adverse reactions.

Dr. Picot will confer with his coworkers and respond as soon as possible.

Recommendation: Approval is recommended but labeling is still unsatisfactory.

Theresa Greene Reed
Theresa Greene Reed, M.D., N.P.H.

cc Orig NDA, HFN-815, HFN-815/Reed, HFN-815/CSO 5008b

WAD 19 Aug 86

ET 8/7/86

August 18, 1986

AMENDMENT TO MEDICAL OFFICER'S REVIEW OF NDA 19-384

Applicant: Merck Sharp & Dohme Research Laboratories
Division of Merck & Co., Inc.
West Point, Pennsylvania 19486

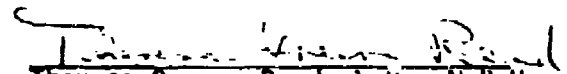
Name of Drug: Generic: Norfloxacin, MSD

Trade: NOROXIN™

The reader is referred to page 24 of the Medical Officer's Review dated Nov. 14, 1985. This is a review of the domestic multicentric randomized controlled trial to compare norfloxacin with TMP/SMZ in the treatment of uncomplicated and complicated urinary tract infections. This review is amended to add the following information taken from Volume 2.6, page 1-01667:

CLINICAL RESPONSE

UTI	Susceptible to both drugs		Regardless to Susceptibility		Susceptible to Drug Received	
	Norflox.	TMP/SMZ	Norflox.	TMP/SMZ	Norflox.	TMP/SMZ
Complicated	95% (19)	83% (12)	81% (37)	87% (15)	85% (34)	83% (12)
Uncomplicated	94% (33)	82% (38)	95% (42)	82% (39)	95% (39)	82% (38)


Theresa Greene Reed, M.D., M.P.H.

cc
Orig HDA
HFN-815
HFN-815/Reed
HFN-815/CSO
5040b

OKS for E.T. 18 Aug 86

August 15, 1986

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

~~CONFIDENTIAL~~

Applicant: Merck & Co., Inc. Research Laboratories
West Point, Pennsylvania

Name of Drug: Trade: NORFLOXIN[®]
Generic: Norfloxacin

Pharmacological Category: Fluoroquinolone anti-infective agent

The applicant submits revised proposed labeling and answers to Dr. Tabor's question in response to my telephone conversation August 18, 1986.

Labeling:

1. Microbiology Section (page 11, line 11) The phrase "for the organism" has been inserted as requested.
2. Indications and Usage Section (page 13, line 12) An asterisk (*) has been added following the listing of the organism "Staphylococcus aureus."
3. Indications and Usage Section (page 13, lines 14-16) The sentence after the asterisk has not been revised to add "in this organ system" as requested. The applicant feels that this addition would lead the reader to think that norfloxacin was indicated for more organ systems than the urinary tract.
4. Precautions Section (pages 18 and 19) These two paragraphs have not been revised as requested to say that norfloxacin should not be used in pregnancy or in children. The applicant indicates that the wording is identical to that used in the approved labeling for cinoxacin, a related drug. It is felt that the reasons for the wording in these sections is the same for both drugs and, therefore, that the wording should be identical.

Medical Officer's Comment: The wording in the Precautions section of the cinoxacin labeling, that use of norfloxacin in pregnancy and in children is not recommended, was one of several recommended wordings for quinolones given us by the Anti-Infective Drug Advisory Committee.

Microbiological Outcome:

In response to our request, the applicant reports the microbiological outcome for norfloxacin in Study No. 2 according to organism for both complicated and uncomplicated urinary tract infections as follows:

Study No. 2	Number Eradicated/Total Number	
	Complicated UTI	Uncomplicated UTI
<u>S. epidermidis</u>	1/1	2/2
Group D streptococci	5/6	4/4
<u>Citrobacter species</u>	1/1	
<u>C. freundii</u>	1/2	1/1
<u>E. coli</u>	13/13	24/24
<u>K. pneumoniae</u>	2/4	4/5
<u>M. morgani</u>	1/1	
<u>P. vulgaris</u>	1/1	
<u>P. mirabilis</u>	3/3	3/3
<u>P. rettgeri</u>	2/2	
<u>P. aeruginosa</u>	9/12	1/1
<u>Corynebacterium</u>		0/1
Group B streptococci		1/1
<u>E. aerogenes</u>		1/1
<u>Lactobacillus species</u>		1/1
Total	39/46 (85%)	42/44 (95%)

A similar table is provided for all evaluable norfloxacin cases as follows:

All evaluable norfloxacin cases	Number Eradicated/Total Number	
	Complicated UTI	Uncomplicated UTI
<u>Gram Positive Bacteria</u>		
<u>Corynebacterium sp.</u>		0/1
<u>Lactobacillus sp.</u>		1/1
<u>Micrococcus species</u>		1/1
<u>Staphylococcus species</u>		1/1
<u>S. aureus</u>	1/1	5/6
<u>S. epidermidis</u>	2/2	7/8
<u>S. saprophyticus</u>	2/2	4/4
Coag. Neg. Staph.		1/1
Gp. B Streptococcus		1/1
Gp. D streptococci	10/11	9/11
Beta hemolytic Strep.	1/1	
Total	15/16 (94%)	30/34 (88%)

(Continued on next page)

All evaluable norfloxacin cases	Number Eradicated/Total Number	
	Complicated UTI	Uncomplicated UTI
<u>Gram Negative Bacteria</u>		
<u>Acinetobacter sp.</u>	0/1	
<u>Alcaligenes species</u>		1/1
<u>Citrobacter species</u>	2/2	1/1
<u>C. diversus</u>	1/1	
<u>C. freundii</u>	3/4	4/6
<u>Enterobacter species</u>	1/1	1/1
<u>E. aerogenes</u>	1/3	2/2
<u>E. agglomerans</u>		3/3
<u>E. cloacae</u>	2/4	3/3
<u>E. coli</u>	56/68	207/210
<u>Klebsiella species</u>		1/2
<u>k. oxytoca</u>	1/1	2/2
<u>K. pneumoniae</u>	11/14	15/19
<u>M. morgani</u>	1/1	
<u>Proteus species</u>	1/1	1/1
<u>Proteus indole pos.</u>	1/1	1/1
<u>Proteus rettgeri</u>	2/2	
<u>P. vulgaris</u>	2/2	2/2
<u>P. mirabilis</u>	21/21	27/27
<u>Providencia rettgeri</u>	2/2	
<u>P. stuartii</u>	1/1	
<u>Providencia species</u>		1/1
<u>P. aeruginosa</u>	27/34	16/17
<u>P. cepacia</u>	1/1	
<u>S. liquifaciens</u>	1/1	
<u>S. marcescens</u>	1/1	
<u>Total</u>	149/167 (89%)	290/297 (98%)

Duration of Treatment:

In response to one of the questions, the applicant gives the duration of treatment in days for all patients who received norfloxacin for complicated urinary tract infections as follows:

<u>Duration of Treatment</u>	<u>Number of Norfloxacin Cases</u>
1-9 days	39
10-20 "	221
21-24 "	2
25-30 "	12
31-93 "	4
<u>Total</u>	<u>278</u>

No. with 10 days or more 239

Since only three adverse experiences occurred beyond 9 days of therapy, it appears that prolonging norfloxacin therapy up to 30 days does not significantly increase the rate of adverse experiences.

Indole-positive Proteus species

The following seven indole-positive species were reported in the NDA:

<u>Lot/Case No.</u>	<u>Study No.</u>	<u>Plate No.</u>	<u>Micro-organism</u>
504/50	50	500	<u>Morganella morganii</u>
504/50	50	501	<u>Proteus rettgeri</u>
504/50	50	502	<u>Proteus rettgeri</u>
506/508	50	503	<u>Proteus, indole pos.</u>
506/508	50	504	<u>Proteus, indole pos.</u>
506/508	50	505	<u>Proteus vulgaris</u>
506/508	50	506	<u>Proteus vulgaris</u>
Total			7 of 7 eradicated

Recommendation: Revised proposed labeling is satisfactory. Approval is recommended.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc Orig NDA, (HFN-815) HFN-815/Reed, HFN-815/CSO 5008b

DRD 27 Aug 86

ST 8/27/86

MEDICAL OFFICER'S REVIEW OF NDA 19-384

Safety Update Period May 19 1986

Applicant: Merck Sharp and Dohme Research Laboratories
West Point, Pennsylvania 19386

Name of Drug: Trade: NOROXIN
Generic: Norfloxacin

In keeping with our request, the applicant files a safety update report covering the period from the NDA cut-off date, June 26, 1984, through September 30, 1985. This report gives adverse clinical and laboratory events from domestic and international controlled trials and compassionate therapy. Also, serious adverse experiences from the period since September 30, 1985 are presented. Since the NDA was compiled, an additional 3,797 patients have been treated with norfloxacin in controlled clinical trials, and over 17 million patients have been treated in worldwide marketing experience.

The following patients have been treated with norfloxacin since June 27, 1984:

Study	Approximate Number to 3-31-86
MSDRL controlled (domestic)	708
MSDRL controlled (international)	1,085
Japan Marketing Experience	11,900,000
Local Registration Studies	30,000
Clinical Development Study Program (CDSP)	1,945
MSDI Marketing Experience (excluding Japan)	5,600,000

Domestic and Foreign Applicant-Sponsored Studies: Between June 27, 1984 and Sept. 30, 1985, case report forms were received for the following 806 patients and volunteers who received norfloxacin in MSDRL-sponsored clinical trials:

Program	Dosage	No. Pts/Volunteers
Urinary tract infection (UTI)	400 mg bid	327
Travelers diarrhea (prophylaxis)	400 mg qd	60
Gastroenteritis (treatment)	400 mg bid	10
Gastroenteritis (treatment)	400 mg tid	30
Neutropenia (infection prophylaxis)	400 mg bid	27
Neutropenia (infection prophylaxis)	400 mg gid	9
Gonorrhea (treatment)	600 mg x 2 doses	8
Gonorrhea (treatment)	800 mg single dose	222
Compassionate program (U.S.)	400 mg qd, bid, tid	14
Compassionate program (Intern't)	400 mg bid	57
Pharmacology study	400 mg x 2 doses	24
Pharmacology study	400 mg single dose	18
	Total	806

(The number 806 differs from the number 708 because there were different cut off dates.)

NDA-19384

March 14, 1986

MEDICAL OFFICER'S REVIEW OF LABELING
and

MEMORANDUM OF CONFERENCE TELEPHONE CONVERSATION

Applicant: Merck Sharp & Dohme Research Laboratories
West Point, PA

Name of Drug: Generic: Norfloxacin

Trade: NOROXIN[®]

Review of Labeling: Labeling dated December 11, 1984 filed on January 14, 1985 in the original application (page I-09306 ff in Volume 2.25) was reviewed. Comments on the labeling were discussed with David W. Blois, Ph.D., Senior Director of Regulatory Affairs, and his staff (215-834-2304). (Underlining, below, means new additions. Editorial changes are not mentioned.)

Description: (Page 1, Line 3) Insert the class name "fluroquinolone" on the third line.

(Page 2) At the end, add "Examples of other antibacterial drugs that are quinolones are nalidixic acid, cinoxacin, and oxolinic acid."

Clinical Pharmacology:

1. (Page 3, Lines 1-12) Revise the first paragraph to read

"In healthy volunteers, at least 30-40% of an oral dose of NOROXIN is absorbed. Absorption is rapid following single doses of 200 and 400 mg. The presence of food may affect absorption. Mean peak serum and plasma concentrations of 0.8 and 1.5 mcg/mL, respectively, are attained approximately one hour after dosing. Levels in bile exceed serum levels. 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 on either regimen."

2. (Page 4, Line 7) Add Alteration of dosage is necessary. in regard to patients with impaired renal function.

3. (Page 4, Line 18) "Within 24 hours of drug administration, approximately 28-30%," instead of 30%, "of the dose is recovered in the urine as norfloxacin with an additional 5-8% being recovered as six active metabolites of lesser antimicrobial potency."

4. (Page 5) On the first line, insert: "Fecal recovery accounts for another 30% of the dose."

5. (Page 5 Lines 6-8) "The antibacterial efficacy of norfloxacin is not affected by the pH of the urine but its solubility is."

6. The Clinical Pharmacology section should end with a new paragraph to say that following oral administration, norfloxacin has been detected in bile,

Adverse reactions which were not seen in the NDA patients treated for urinary tract infections are listed below:

Adverse Reaction	No. Pts	No. Drug Related
Malaise	5	0
Jaundice	1	0
Stomatitis	1	1
Muscle cramps	1	0
Hypertonia	1	0
Irritability	1	1
Lung cancer	1	0
Hyperhidrosis	1	1

Among post-NDA urinary tract infection cases, the most frequent adverse reactions were those related to the digestive system. Nausea was the most common complaint. The second most common complaint was neuropsychiatric in nature, namely, headache. Most common complaints are shown below:

System	All NDA	Drug Related NDA	All Post-NDA	Drug Related Post-NDA
Digestive:				
Nausea	2.75%	1.15%	2.45%	0.92%
Dyspepsia	0.44%	0.35%	0.31%	0.31%
Neuropsychiatric:				
Headache	2.66%	0.35%	1.83%	0.61%
Dizziness	1.77%	0.53%	0.61%	0.61%
Skin/Allergic:				
Rash	0.53%	0.27%	0.61%	0
Erythema	0.27%	0.17%	-	-

Adverse reactions with frequencies greater than five in combined data from the NDA and safety update and the total number are shown in the next table.

Adverse Experience	NDA UTI & volunteer N=1127	Safety Update UTI N=327	Combined NDA & Safety Update N=1454	Combined % of p.s. with AEs	Combined % with drug- related AEs
Constipation	4	2	6	.41	0.41
Diarrhea	3 (1)	2 (1)	5 (2)	.34	.14
Dry mouth	3 (2)	2 (1)	5 (3)	.34	.21
Dyspepsia	5 (4)	1 (1)	6 (5)	.41	.34
Nausea	31 (13)	8 (3)	39 (16)	2.68	1.10
Depression	4 (1)	1 (1)	5 (2)	.34	.14
Dizziness	20 (6)	2 (2)	22 (8)	1.51	.55
Headache	30 (4)	6 (2)	36 (6)	2.47	.41
Somnolence	5 (1)	-	5 (1)	.34	.07
Rash	6 (3)	2	8 (3)	.55	.21

(The number that were drug related is shown in parentheses.)

In the NDA, there were 196 adverse reaction reports for 1127 UTI patients and volunteers: 55 were drug related. In the safety update, there are 61 adverse reaction reports for 327 patients: 21 were drug related. Combined, there were 256 reactions of which 76 were drug related.

There were ten deaths. None of the deaths were considered to be drug related. Adverse experiences that were considered to be serious were convulsive disorders in two patients, intracerebral hemorrhage, jaundice, and confusion. One convulsive disorder and the intracerebral hemorrhage were probably not drug related. The other three were definitely not drug related.

Adverse clinical experiences resulted in discontinuation of therapy in 14 of 534 (2.6%) of all safety update report patients (including patients treated for diagnoses other than UTI), excluding the two-dose and single-dose gonorrhea studies. The most common reasons were nausea and rash.

The most common laboratory adverse experiences were elevated AST, ALT, followed by eosinophilia, elevated creatinine, elevated alkaline phosphatase, and leukopenia. None of the leukopenias or elevated creatinines were drug-related while one each of the other aforementioned observations were considered related to norfloxacin. Others were thrombocytosis (2 cases), increased serum GGT (1), increased blood glucose (2), decreased serum sodium (2), and decreased creatinine clearance (1). None of these were considered drug-related.

As with clinical adverse experiences, the types of laboratory adverse experiences from NDA and post-NDA patients are similar.

Adverse laboratory experiences resulted in discontinuation of therapy in 6 of 534 (1.1%) of safety update report patients, excluding the two-dose and single dose gonorrhea and pharmacology studies. The most common reasons for discontinuation were elevated liver function tests. None of the adverse laboratory experiences were considered related to norfloxacin therapy.

The applicant concludes that the safety profile for norfloxacin during the post-NDA period covered by this report is consistent with that seen in NDA data and described in the package circular.

Safety Update Report - Japan: The applicant reports that safety data from Japan have been derived from the post-marketing surveillance study (PMS) and spontaneous reports from prescribing physicians using marketed drug. The PMS study is a compulsory study required for all drugs after launching, maintained for three years after approval, and reported annually. Adverse experiences are looked for and reported in accordance with Koseisho Regulations. As of February 14, 1986, 8,827 patients had been enrolled in the PMS study. Between March 1984 and March 31, 1986, it is estimated that approximately 11,900,000 people received treatment with norfloxacin manufactured by Kyorin and Torii Pharmaceutical Companies.

Two deaths are listed: the cause was unknown for one and the other was due to acute renal failure which was reported as probably drug related. The patient had a history of hypertensive cerebral hemorrhage and asthma. The attacks led to a pulmonary infection followed by disseminated intravascular coagulation.

Twenty-four serious adverse experiences are listed in the report. The most frequent clinical AR's were allergic-type reactions, while the most frequently reported laboratory adverse events were elevated liver function tests. Their frequency is far below those described in clinical trials.

Local Registration Studies: In addition to the Japanese and clinical development studies, local studies to support product registration are on-going worldwide. The studies are conducted by the local Merck subsidiary and do not have case report forms. Approximately 30,000 patients had been treated in these local studies as of March 31, 1986. Prompt reporting of any deaths or serious adverse experiences are required and these are the only data that are available for the period between June 27, 1984 and March 31, 1986.

There are 21 reports. Eleven were deaths: ten of the eleven deaths were definitely not drug related. One death was due to interstitial nephritis and was listed as probably drug related. Other reactions are consistent with previous information.

Clinical Development Study Program: The Clinical Development Study Program supplements Merck's program in which the drug has been established as safe and effective. It gives physicians overseas an opportunity to form their own opinion concerning the efficacy and safety of norfloxacin. A total of 1,945 patients have received treatment with norfloxacin in CDSP studies through March 31, 1986. Three deaths have been reported to FDA on Forms 1639. None were drug-related. No serious adverse laboratory experiences were reported.

Marketing Experience (Excluding Japan): In addition to Japan, norfloxacin was being marketed in the following countries as of March 31, 1986:

Argentina	El Salvador	Mexico
Austria	Germany	New Zealand
Belgium	Guatemala	Pakistan
Brazil	Holland	Peru
Columbia	Honduras	Portugal
Costa Rica	Italy	Spain
Ecquador	Lebanon	Switzerland

Excluding Japan, approximately 5,600,000 patients have received marketed norfloxacin worldwide. As with the clinical studies, deaths and serious adverse experiences occurring within 14 days of norfloxacin therapy are promptly reported to FDA on Form 1639. One death due to exfoliative dermatitis has been reported. Reports which were possibly or probably drug related included one anaphylactic reaction, thrombocytopenia, and thrombophlebitis. Drug relationship was not stated for one case of anuria, and one case of increased prothrombin time and hematuria. A congenital malformation was definitely not drug related.

Recommendation: Approval of norfloxacin is recommended.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc Orig ND: HFN-815, HFN-815/Reed, HFN-815/CSO, HFN-815/Norton, 4806b

Dr. [unclear]

b.i.d., as a precaution, preventive measures to be taken include keeping the dose as low as possible, maintaining an adequate rate of urine flow, maintaining a urine pH below 7.0, and keeping the patient well hydrated."

Precautions:

1. (Page 12, line 7) Insert the following new paragraphs at the beginning of the section.

"Alteration in dosage regimens is necessary for patients with impaired renal function (See Dosage and Administration)."

"Norfloxacin should be used with caution in patients with a history of hepatic disease or in patients with impaired hepatic function."

The effects of norfloxacin on brain function or on the electrical activity of the brain have not been tested. Central nervous system-type adverse experiences, such as headache, dizziness, lightheadedness, hyperactivity, visual changes, and insomnia, have been reported with some antibacterial agents in the quinolone drug class. Seizures which were not thought to be drug related occurred in two norfloxacin-treated patients that had existing CNS disorders that predispose to seizures and that fully accounted for the events. Until more information becomes available, quinolones should be used with caution in patients with known factors that predispose to seizures."

2. (Page 12, Lines 1-9) Revise the sentence to read, "Diminished urinary excretion of norfloxacin has been reported following the concomitant administration of probenecid and norfloxacin. Serum concentrations, however, are not affected."
3. (Page 12, Line 10) Revise this sentence to read, "The concomitant use of nitrofurantoin is not recommended since nitrofurantoin may antagonize the antibacterial effect of NOROXIN in the urinary tract."
4. (Page 12, Line 12) Add the following new paragraphs:

"The concomitant administration of norfloxacin with antacids is not recommended."

"Information for the Patient:

"Patients should be advised to drink fluids liberally and that antacids should not be given concomitantly or within two hours after dosing."

"Patients should know how they react to norfloxacin before they operate automobiles and machinery or engage in other tasks requiring mental alertness and coordination."

5. (Page 13, Line 16) The Pregnancy Category letter should be "C" instead of "B".

Dr. Blois agreed with the Category C letter.

We shall postpone further consideration of the pregnancy paragraph temporarily because the review team is waiting for the report of a monkey study. Norfloxacin is a known abortifacient in monkeys.

Dr. Blois will file the report of this monkey study next week.

The Medical Officer added that in keeping with our advisory committee recommendations, class labeling for the quinolones calls for this section to end with the sentence, "Since norfloxacin, like other drugs in this class, causes arthropathy in immature animals, its use during pregnancy is not recommended (See Warnings)."

6. (Page 14, line 1.) Revise the Nursing Mothers paragraph to read as follows:

"It is not known whether norfloxacin is excreted in human milk. When a 200 mg dose of NOROXIN was administered to nursing mothers, norfloxacin was not detected in human milk. However, because the dose studied was low, because other drugs in this class are excreted 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."

7. (Page 14, Line 21) Delete the first sentence of the Pediatric Use paragraph. The full section shall read, "NOROXIN is not recommended for use in prepubertal children (See Warnings)."

Adverse Reactions: Recommendations for this section are deferred until the applicant files a revised adverse reaction table with corrected rates and a revised adverse laboratory experiences table.

Dosage and Administration:

1. (Page 17, Line 10) Revise the first section to read, "In patients with normal renal function and in patients with creatinine clearance rates greater than 30 ml/min/1.73 m²." Delete the word "apparently" and the phrase "including elderly patients."
2. (Page 17, Lines 15-17) Revise the recommendation to read, "Uncomplicated urinary tract infections: The recommended dosage is 400 mg with a glass of water twice daily one hour before or two hours after meals for 7 to 10 days."
3. (Page 17, Lines 18-20) Revise the recommendation to read, "Complicated urinary tract infections: The recommended dosage is 400 mg with a glass of water twice daily one hour before or two hours after meals for 10 to 30 days."

We discussed the mealtime relationship that the MO added. This will be adjusted for the appropriate time of the day. We also discussed the

CHEM

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possibility of taking the tablet with fruit juice as an innocuous way of acidifying the urine. The original 60-day maximum treatment period was changed to 30 days. The 60-day period did not appear to be supported by clinical studies.

4. (Page 17, end) Insert the following two paragraphs.

"Patients receiving norfloxacin should be well hydrated to prevent crystallization of norfloxacin in the urinary tract."

"Doses higher than 800 mg/day are not recommended."

The medical officer explained that the Division of Biopharmaceutics recommended a ceiling dose. She arbitrarily selected a 1000 mg/day ceiling because drug crystals have been reported at 1200 mg/day. However, the applicant stated that they are not recommending a dose higher than 800 mg/day.

5. (Page 18, Lines 1-9 are deleted.) (Page 18, Line 10) Revise the renal impairment paragraph to read as follows:

"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/1.73 m² or less, the recommended dosage is one 400-mg tablet with a glass of water once daily one hour before or two hours after meals. At this dosage, the urinary concentration exceeds the MICs for most urinary pathogens susceptible to norfloxacin, even when the creatinine clearance rate is less than 10 mL/min/1.73 m². The serum creatinine should represent a steady state of renal function and..."

(Continue on page 19.)

Animal Pharmacology: In keeping with the advisory committee recommendations, there should be an animal pharmacology section after the How Supplied section. The wording of this section is being prepared by our pharmacologist. Examples are the Animal Pharmacology sections in cinoxacin, nalidixic acid, and oxolinic acid package inserts.

Dr. Blois will review these comments and recommendations with his staff and will prepare a revised draft of proposed labeling for additional revision and comment. We have gone as far as we can go without the unfinished sections. He may change the recommended wording in these suggestions to be in keeping with Merck's labeling policy and the firm's views on these subjects.

Conclusion and Recommendation: Labeling is unsatisfactory but labeling discussions with the applicant are progressing very well.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc

Orig NDA 19-384 HFN-815/CSO
HFN-815, 4/1/82 HFN-815/Reed

4717b

4/21/82 S6

A.1. NDA 19-384

Sponsor: Merck Sharp & Dohme Research Laboratories
Division of Merck & Co., Inc.
West Point, PA 19486

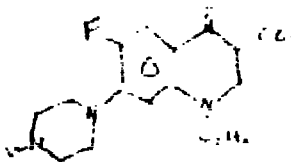
2. Product Names:

Proprietary: Noroxin
USAN: norfloxacin
Code: MK-366, 6-643, 316-00J, AM-776

3. Dosage Form & Route of Administration: 200 mg, 400 mg. 10 tablets
for oral use.

4. Pharmacological Category and/or Principal Indication: For treatment
of VTI, uncomplicated gonococcal infections, acute gastroenteritis
caused by susceptible organisms.

5. Structural Formula and Chemical Name(s):



1-ethyl-6-fluoro-1, 4
dihydro-4-oxo-7-(1-piperazinyl)
-3-quinoline carboxylic acid.

B. 1. Initial Submission 12/5/84

2. Amendments:

3. DMF Referrals: N/C

4. Related Material: N/C

C. Remarks:

Sponsor has replied to each concern adequately.

D. Conclusions and/or Recommendations:

Application is approvable from manufacture and controls standpoint pending
a reply from the Division of Biopharmaceutics re adequacy of the
dissolution specifications for the dosage form.

CSO to request copies of all draft labeling.

John W Taylor
John W. Taylor, Ph.D.

cc: Orig. NDA

HFN-815

HFN-815/MO

0240c

HFN-815/CSO

R/D Initialed by:

HFN-815/Taylor: gm 3/11/86

ARCAsola 3/11/86

KAC 3/17/86

May 9, 1986

MEDICAL OFFICER'S REVIEW OF LABELING
and MEMORANDUM OF TELEPHONE CONVERSATIONS

Amendment ~~XXXXXXXXXX~~

Applicant: Merck Sharp & Dohme Research Laboratories
West Point, Pennsylvania

19-28-1

Name of Drug: Trade: NOROXIN

Generic: Norfloxacin

Pharmacology -1 Category: Fluoroquinolone

The applicant submits another revised version of proposed labeling.

Medical Officer's Comments: Revised proposed labeling is satisfactory except for two sentences.

1. Clinical Pharmacology section (Page 5, line 9): The sentence about pH was deleted by mistake. The following sentence should be inserted in its place:

"The urinary pH may effect the solubility of norfloxacin: at pH 7.5, there is minimum solubility."

2. Dosage and Administration (Page 21): Now that I have a copy of the written Biopharmaceutics review, I am reminded that the dosage of norfloxacin needs to be adjusted in the elderly as well as in patients with impaired renal function. Appropriate information should be added to address this problem.

May 5 through 9, 1986: I called Dr. David Blois and he called me several times to discuss labeling.

May 9, 1986: I called Dr. David Blois, Senior Director of Regulatory Affairs (215-834-2304), to discuss these two changes given above. Dr. Mason, the Biopharmaceutics reviewer, and I discussed the problem of dosing in the elderly. We talked to Dr. Blois about this, and all agreed upon the following changes in the Dosage and Administration section:

1. Change the subheading from "Renal Impairment" to "Renal Impairment and the Elderly."
2. Revise the first sentence to add "and the elderly," to read "NOROXIN may be used for the treatment of urinary tract infections in patients with renal insufficiency and in the elderly."

Recommendation: Approval is recommended. Revised labeling, as agreed upon, is satisfactory.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc
Orig NDA HFN-815, HFN-815/Reed, HFN-815/CSO, HFN-815/Norton, 4792b

9/15/14/86

N. S. O. 9/16

A.1. NDA 13 394

Sponsor: Merck Sharp & Dohme Research Laboratories
Division of Merck & Co., Inc.
West Point, PA 19380

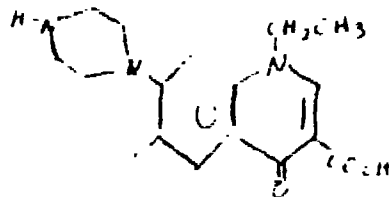
2. Product Names:

Prop. Name: Noroxin
USAN: Norfloxacin
code: MK-304, 1-643, 316-001, AM-715

3. Dosage Form & Route of Administration: 200, 400 mg. film-coated oral tablets

4. Pharmacological Category and/or Principal Indication: For treatment of (II) (complicated or uncomplicated) uncomplicated gonococcal infections, acute gastroenteritis caused by susceptible organisms.

5. Structural Formula and Chemical Name(s):



m.w. 311.34

1-ethyl-5-fluoro-1,4-dihydro-4-oxo-7-(1-piperidinyl)-3-quinoline carboxylic acid.

B. 1. Initial Submission: 12/5/84; Rec'd in Bureau: 12/7/84
Rec'd by Chemist: 12/20/84

2. Amendments: None

3. DMF Referrals:

4. Related Material: (

August 18, 1986

MEDICAL OFFICER'S REVIEW OF NDA 19-384
and MEMORANDUM OF TELEPHONE CONVERSATION

Labeling amendment dated July 25, 1986

Applicant: Merck Sharp & Dohme Research Laboratories
West Point, Pennsylvania

Name of Drug: Trade: NOROXIN^R
Generic: norfloxacin

Pharmacological Category: Fluoroquinolone antibacterial agent

The applicant submits revised proposed labeling to comply with comments from Dr. Ed Tabor which were given to the firm by Mr. Robert Linkous in a telephone conversation on July 21, 1986. Revised proposed labeling is satisfactory except for the following recommendations:

1. Microbiology Section (page 7, line 3) Insert "of the organism" after the first word. The new sentence will read, "Resistance of the organism has developed during therapy with norfloxacin in less than 1% of patients treated."
2. Indications and Usage Section (page 13, lines 14-16) Revise the sentence after the asterisk to read, "* Efficacy for this organism in this organ system was demonstrated in fewer than ten infections."
3. Precautions Section (page 18, lines 10-13) The last sentence in the Pregnancy paragraph should be revised to read, "Since norfloxacin, like other drugs in this class, causes arthropathy in immature animals, it should not be used in pregnancy (see WARNINGS)."
4. Precautions Section (page 19, lines 5-6) The Pediatric Use sentence should be revised to read, "NOROXIN should not be used in children (See WARNINGS)."

In Dr. David Blois' absence, I called Dr. Gerard D. Picot, Assistant Director of Regulatory Affairs at Merck to give him these comments. Dr. Mike Corrado participated in the conversations. I also asked other questions that the Division Director has raised. Did all complicated UTI patients get 10-30 days of therapy? How many patients got 30 days? What were the eradication rates for indole-positive Proteus species (P. vulgaris, P. rettgeri, and M. morganii) and give the study numbers where these uropathogens were isolated? What were the eradication rates for S. aureus and what were these study numbers?

Some of these questions were answered in attachments to the second version of the proposed labeling.

1. The report gives microbiological outcomes for complicated and uncomplicated urinary tract infections after cases which were originally classified as unevaluable had been deleted.

C. Remarks:

There have been a number of formulation changes during drug development which require explanation by the sponsor as to their impact if any on clinical, biopharmaceutic and stability parameters.

The controls section of the application appears basically adequate, but due to formulation changes additional information is required to permit a scientific appraisal.

D. Conclusions and/or Recommendations:

John W. Taylor
John W. Taylor, Ph.D.

cc: Orig. NDA

~~HFN-815~~ HFN-815/CSO HFN-815/Taylor; gm 3/15/85
R/D Init. by: ARCasola 3/15/85 *ARC 3/21/85*
HFN-815/MO
3433b

APPL #: 019384

FIRM: MSD RES LABS

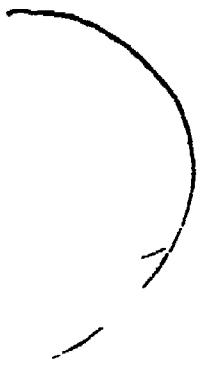
3 OF 4

TRADE NAME: NOROXIN (NORFLOXACIN) 400MG TABLET

GENERIC NAME: NORFLOXACIN

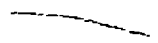
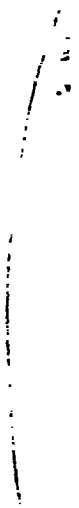
1&2. Components and Composition: Adequate with comment.

3. Facilities:



4. Personnel: Adequate.

5.



6. Controls (raw materials):



7. Other Facilities: See item 3.

8. Manufacturing and Processing:



9. Packaging and Labeling: Adequate.

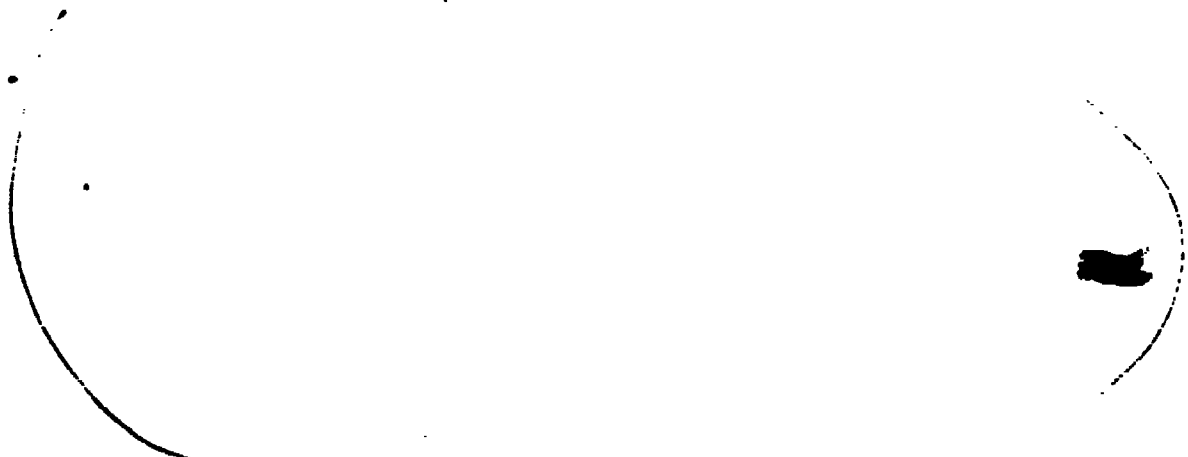
10. Container/Closure Systems:

a)



b) Unit Dose:

11. Controls (dosage form): [REDACTED]



12. Stability Data:



BIO/DIS

REV

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs and Biologics
Office of Drug Standards

DATE : **MAY 6 1986**

TO : Edward Tabor, M.D., Director
Division of Anti-Infective Drug Products, HFN-815

FROM : Jerome Skelly, Ph.D., Director
Division of Biopharmaceutics, HFN-220

SUBJECT : Biopharmaceutics Recommendation of Approval
NDA-19,384 ; Norfloxacin - 400 mg tablet
Merck, Sharp & Dohme Research Labs

Background:

Norfloxacin is a quinoline carboxylic acid antibacterial agent structurally related to compounds such as nalidixic, oxolinic, and pipemidic acids. The proposed indications are for the treatment of infections caused by susceptible strains of micro-organisms, in complicated and uncomplicated cystitis, gonococcal urethritis, acute gastroenteritis and prophylactically in profound neutropenia. The proposed dosing follows.

Uncomplicated UTI - 400 mg BID X 7-10 days
Complicated UTI - 400 mg BID X 10-60 days
Uncomplicated GC urethritis - 600 mg followed by 600 mg 4 hours later
Acute gastroenteritis - 400 mg BID X 5 days
Prophylaxis in neutropenia - 400 mg TID for duration of neutropenia
(no recommendations available beyond 8 weeks)

There is no record of any previous submissions to the Division of Biopharmaceutics concerning norfloxacin, the subject of NDA 19-384. Norfloxacin is licensed by Merck from Kyorin Pharmaceutical Co., Ltd. (Japan).

Results:

Dose proportionality was determined by administration of [redacted], 400, [redacted], [redacted] and [redacted] mg single doses to 14 subjects. Based on AUC, dose proportionality across the single dose range [redacted] mg exists for norfloxacin. However, the peak concentration (C_{max}) of norfloxacin does not increase proportionately with the increase in a single dose beyond [redacted] mg. After a [redacted] mg single dose [redacted], mean C_{max} was approximately 1.6 ug/ml (T_{max} about 1 hour), whereas following a single [redacted] mg dose, C_{max} was approximately [redacted] ug/ml (T_{max} about [redacted] hours). The mean C_{max} observed after a single 400 mg dose (MSD direct compression tablet) was 1.5 ug/ml with a corresponding mean T_{max} of about 1 hour.

Because clinical studies utilized products manufactured by different processes and with different formulations (Kyorin vs MSD), Zinny conducted a bioequivalency study with the MSD direct compression tablet and the Kyorin product. Based on this study, the MSD and clinically studied Kyorin tablet products have equivalent extents of absorption. Based on mean T_{max}, the rate of absorption of the MSD formulation is faster than the Kyorin formulation (1.07 vs 1.35 hrs). The MSD-400 mg tablet proposed for marketing is very slightly different from that studied in the bioavailability and bioequivalency studies. Dissolution data on both dosage forms indicate the equivalence of both dosage forms. The relative bioavailability of the 400 mg tablet compared to a solution showed a mean dose adjusted AUC(0-infinity) ratio of 0.99 (C.V. 49%). While the power is inadequate to establish statistical equivalence to the administered solution, it is adequate to define the pharmacokinetics. About 30-35% of the administered dose of norfloxacin is recovered in the urine over 24-48 hours as parent (25-30%) and metabolites (4-8%). Fecal recovery accounts for approximately 30% of the administered dose but may be much greater. Although fecal recovery is difficult to quantitate because of analytical assay difficulties, it may be accounted for by incomplete GI absorption, biliary excretion and/or other factors. Thus while the fraction of the administered dose orally absorbed cannot be determined on the basis of the data submitted, one may conclude that it is at least 30-35 percent. The elimination half-life of the parent drug norfloxacin is about 5 hours. Protein binding of norfloxacin measured by ultrafiltration is about 14%. The "effective half-life for accumulation" for an 8 hour dosing interval is about 3 hours. The renal clearance of norfloxacin measured in adults with normal renal function is about 300 ml/min.

Because of the effect of pH on the solubility of norfloxacin, as well as data from an inconclusive study by Kumasaka where the administration of norfloxacin with food appeared to alter the absorption characteristics of the drug, the effect of food on the proposed marketed product needs investigation. If food effects are not resolved with a controlled study, then this issue should be addressed in the labeling. In addition, since reduced enteral absorption of ciprofloxacin (a quinoline carboxylic acid derivative) has been demonstrated, coadministration of norfloxacin and a probiotic should be discouraged in the labeling because of the possibility of complexation resulting in a decrease in absorption.

The dose of norfloxacin needs to be adjusted in the elderly and patients with renal dysfunction. We recommend that dosing guidelines provided by the firm be clarified because of drug accumulation/decreased clearance.

Our concerns about crystalluria which were discussed in a meeting with HFN-815 on March 13, 1986 are outlined in Section IX of the attached biopharmaceutics review. It appears that with the recommended doses of norfloxacin, crystallization should not be a problem with the parent compound in most patients. However, concern is expressed about the potential for formation of crystals under conditions commonly seen (e.g. low urine flow, alterations in urine pH), when receiving doses greater than those recommended, and in vegetarians who characteristically have a high urine pH. Crystallization has been reported in subjects given [redacted] and [redacted] mg as a single dose. Although drug crystals were not reported in the bioavailability studies submitted, the fluid loaded condition of the subjects prevents interpretation of the clinical results of these studies for resolving safety issues by the Division of Biopharmaceutics. Labeling should include specific instructions concerning maintenance of a good fluid intake in all patients so as to prevent crystallization of drug in the urinary tract.

The proposed dissolution method and specification are the following,

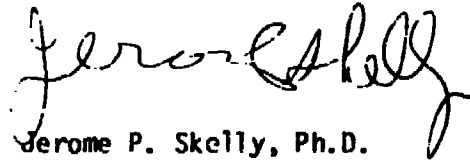
USP Apparatus II, 50 rpm, 37 degrees centigrade,
750 ml of 0.05 M sodium acetate buffer (pH 4.0)
Q specification of [redacted] in [redacted] minutes
Assay via HPLC methodology

The dissolution method and specification are acceptable from a biopharmaceutics perspective.

Overall Conclusion:

The data provided in NDA 19,384 for the 400 mg tablet is acceptable from a Division of Biopharmaceutics point of view. This submission fulfills the bioavailability and bioequivalence requirements set forth in the regulations of 21 CFR, part 320. However, suggested phase IV commitments (i.e. food/antacids effect study) as outlined in the review should be conveyed to the firm.

Comments in the review pertaining to labeling should be considered by HFN-815 when evaluating the package insert. These issues include food effects, co-administration of norfloxacin with antacids and ensuring adequate hydration in patients.



Jerome P. Skelly, Ph.D.

Prepared by Gene D. Mason, Pharm.D.
RD Initialed by John Hunt
FT Initialed by C.T. Viswanathan, Ph.D.

PA
Norfloxacin
Noroxin^R Tablet
400 mg tablet
NDA 19-384
Reviewer: Gene D. Mason, Pharm.D.
Wang # [REDACTED]
11 S, 80, 1 D

Merck Sharp & Dohme
Research Laboratories
West Point, PA 19486
Submissions Dated:
March 14, & July 18, 1985
Feb 14, 24 & March 28, 1986

Review of an NDA

MAY 6 1986

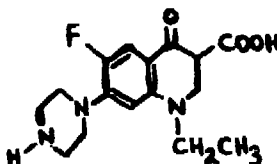
I BACKGROUND

Norfloxacin is a quinoline carboxylic acid antibacterial agent structurally related to compounds such as nalidixic, oxolinic, and pipemidic acids. The proposed indications are for the treatment of infections caused by susceptible strains of micro-organisms, in complicated and uncomplicated cystitis, gonococcal urethritis, acute gastroenteritis and prophylactically in profound neutropenia.

There is no record of any previous submissions to the Division of Biopharmaceutics concerning norfloxacin, the subject of NDA 19-384. Norfloxacin is licensed by Merck from Kyorin Pharmaceutical Co., Ltd. (Japan).

Attachment I of this review is a memo from HFN-815(Dr. Reed) requesting comments on the possibility of crystallization of norfloxacin in the urinary tract based on pharmacokinetic data.

II CHEMISTRY



Structure:

Chemical Name: 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazonyl)-3-quinoline carboxylic acid

Molecular Formula: C₁₆H₁₈FN₃O₃ Mol. Wt.: 319.3 Daltons

pKa: 6.3 and 8.8

Solubility: pH solubility profiles in water and urine are given in figures 2a, b, & c of this submission, respectively.

Practically insoluble in water and methyl ether; freely soluble in glacial acetic acid; slightly soluble in methanol, ethanol, ethyl acetate and benzene.

Generic Name: Norfloxacin

Merck Sharp & Dohme Code Names: MK-366, MK0366, AM-715

It is stated by the sponsor that there are no known polymorphs of norfloxacin.

III FORMULATION

Because norfloxacin is licensed by Merck from Kyorin Pharmaceutical Co., Ltd(Japan) several different formulations have been used in clinical studies prior to the development of the final market image tablet. In addition, different manufacturing processes were utilized by Kyorin Pharmaceutical Co. and Merck Sharp and Dohme. After changing the manufacturing process, MSD subsequently altered the coating formulation. The proposed market image tablet formulation made by direct compression is below. Table 1a of this review compares the proposed formulation to the other formulations used in pivotal bioavailability/pharmacokinetic studies. Table 2 identifies preparations used in pivotal clinical studies. THE FINAL MARKET IMAGE TABLET FORMULATION WAS NOT UTILIZED IN ANY OF THE BIOAVAILABILITY STUDIES OR IN PIVOTAL CLINICAL EFFICACY AND SAFETY STUDIES. THIS ISSUE IS DISCUSSED FURTHER IN SECTION VI-DISSOLUTION.

<u>Ingredient</u>	<u>Merck, 400 mg Market Image Tablet*</u> <u>Amount (mg) per tablet</u>
<u>Core</u>	
Anhydrous Norfloxacin	400.00

IV PROPOSED DOSING

(taken from proposed circular insert, vol [REDACTED], pg [REDACTED])

Uncomplicated UTI - 400 mg QID X 7-10 days
Complicated UTI - 400 mg BID X 10-60 days
Uncomplicated GC urethritis - 600 mg followed by 600 mg 4 hours later
Acute gastroenteritis - 400 mg BID X 5 days
Prophylaxis in neutropenia - 400 mg TID for duration of neutropenia
(no recommendations available beyond 8 weeks)

One multiple dose study submitted(reference #16, Zinny) utilized the regimen 400 mg BID and submitted relevant pharmacokinetic data in 23 subjects. The regimen of 400 mg TID was used in clinical study #66(Zinny ref #17), however, pharmacokinetic data was obtained in only 4 subjects in this study. A single dose of 1600 mg was administered in study #15(Ferguson).

V STUDIES REVIEWED

Study Reference #	Title/Location	Objective
1 / Bland, et al, (literature reference)		Assay
2 / Paulukonis, et al, (literature reference)		Assay
8 / Nagatsu, et al, (literature reference)		Metabolism-Animal
9 / Ozaki, et al, (literature reference)		Metabolism-Human
11 / Nagatsu, et al, (literature reference)		Metabolism-Animal
12 / Kumasaka, et al,	?? tab/cap 200 mg PO (literature reference)	Food Effects (SD)
16 / Zinny(#45)	tabs 400 mg BID	Mult-dose (N=23)
17 / Zinny(#66)	tabs 400 mg TID	Mult-dose (data, N=4)
18 / Zinny(#13)	tabs 400 mg soln 400 mg	BA/BE (SD)
19 / Martin(#661)	tabs 400 mg	Elderly (SD)
20 / Asscher(#576)	tabs 400 mg	Renal Failure
21 / Zinny(#59)	tabs 400 mg (old vs new formulation)	BE
26 / Anon,		Assay

SECTION VII OF THIS REVIEW CONTAINS THE SUMMARY AND CONCLUSIONS FROM THE ABOVE STUDIES. APPENDIX A CONTAINS A DETAILED DESCRIPTION OF EACH OF THE STUDIES AND THEIR INDIVIDUAL RESULTS. ALL CORRESPONDING TABLES AND GRAPHS ARE ATTACHED IN APPENDIX B.

VI DISSOLUTION

The following dissolution methods and specifications were proposed by the firm. Table 1b of this review contains dissolution information.

USP Apparatus II, 50 rpm
750 ml of 0.05 M sodium acetate buffer (pH 4.0) 37 degrees centigrade,

Q specification of [REDACTED] in [REDACTED] minutes
Assay via HPLC methodology

The firm provided the following,

1. individual dissolution characteristics of 12 tablets in the final market image,
2. justification/data to support the above dissolution method and specification, and
3. individual in-vitro dissolution profiles for various lots used in the bioavailability studies utilizing the proposed methodology for the purpose of comparing the dissolution characteristics of the different formulations.

Inspection of table 1a shows that the MSD-direct compression tablet utilized in study reference #21 (Zinny study #59) and the MSD-final market image tablet are identical in core components and differ slightly in amounts of coating constituents (excluding coloring). The amounts of [REDACTED] and [REDACTED] in the coating on the MSD-final market image product were each decreased by [REDACTED] mg. The MSD-final market image tablet was not utilized in any bioavailability study submitted. Because of the magnitude and direction of the changes made, it was decided that the MSD-final market image tablet could be evaluated with in-vitro dissolution methods. Several discussions with the firm about the appropriate dissolution conditions (i.e. pH, sampling times, lots to study) and the purpose of the investigation occurred on 3/14, 3/24 & 3/27/86. After evaluation of dissolution data submitted by the sponsor with justification for the chosen methodology (submission dated 3/28/86) the Division of Biopharmaceutics agreed that the proposed methodology appears to be discriminating between Kyorin and MSD manufactured products and produces data consistent with the results of in-vivo investigations. Thus, the Division of Biopharmaceutics concluded that it was appropriate to employ in-vitro dissolution methods to evaluate the various formulations and support/justify approving the 400 mg MSD-final market image tablet.

VII SUMMARY OF RESULTS AND CONCLUSIONS

Bioavailability

Reference # 18 - Zinny(single dose; 400mg-Kyorin F vs 430mg Soln)
Reference # 12 - Kumasaka(food effects)

Below are the results of the relative bioavailability study conducted by Zinny (#18).

Parameter	ANOVA	Power*	% Ratios w/in 75/75-125	
For all treatments			T400/S400	T400(b)/T200
AUC(a)	NS	50%	5/13=38.5	7/12=58.3
Cmax(b)	NS	42%	6/15=40.0	5/15=33.3
Tmax	Sig (P LT 0.05)			

2 One-Sided Hypothesis

AUC

Tab 400 vs Soln 400 - Accept Ho: Not BE

Cmax

Tab 400 vs Soln 400 - Accept Ho: Not BE

* 20% diff, alpha = 0.05; T = Tablet, S = Solution;
a - natural log, dose adj'd to 400mg; b - dose adj'd to 200mg

The mean time to peak concentration for the 400mg and 400 mg tablet was significantly longer(P LT 0.05) than that for the reference solution(1.03, 1.03 vs 0.70 hrs). No significant difference was found for the parameter Tmax between the two tablets. The mean(+/- S.D.) relative bioavailability for dose adjusted Cmax, 400 mg tab/400 mg tab, was 1.1(0.52).

Based on the above observations it is concluded that the 400mg tab and the 400 mg tab have similar rates and extent of absorption. It cannot be concluded that the solution is bioequivalent to the tablets.

The relative bioavailability(using the methods of Kwan & Till) for the comparisons 400 mg tab/soln and 400 mg tab/soln are 0.90 and 0.99 respectively. The power(as determined by firm) to detect a 25% difference for the comparisons 400 mg tab/soln and 400 mg tab/soln, are 0.78 and 0.99 respectively. The relative bioavailabilities(mean +/- S.D.) based on dose adjusted AUC(0-infin) for the ratios tab 400/soln 400, 400 mg tab/soln 400, are 0.99 +/- 0.49(50% C.V.), 0.99 +/- 0.49(50% C.V.), respectively. At this time, the Division of Biopharmaceutics conventionally uses AUC to compare product bioavailability(extent of absorption) and not the methods of Kwan and Till.

The effect of food was investigated by Kumasaka(#12) in 5 volunteers. The results are inconclusive because the AUC was measured only for 8 hours after the dose, and thus incomplete, and the product utilized was not the proposed marketed tablet. In addition, meal composition and timing relative to dose was not specified. Tmax for both treatments was 1-2 hours. Mean(S.D.) Cmax in plasma for fasting subjects was 0.46(0.13) vs 0.32(0.16) ug/ml for non-fasting subjects. The Cmax in urine was higher in the fasting group(334 vs 206 ug/ml). In one nonfasting subject, norfloxacin could only be detected() hours after the single dose. It appears that administration of the product utilized in this study with food can alter the absorption characteristics of the drug. Because the formulation, dosage form(tablet vs capsule) and source(probably manufactured by Kyorin) of the product administered in this study was not provided, extrapolation of the results of this study to the proposed marketed product is not possible. Because of the effect of pH on the solubility of norfloxacin, the effect of food on the proposed marketed product needs investigation.

A correspondence published in the European Journal of Clinical Microbiology, Vol 4, 1985, p 345(see Attachment II), reported reduced enteral absorption of ciprofloxacin(a quinoline carboxylic acid derivative) when coadministered with antacids. Ten healthy fasting volunteers randomly received 500 mg of ciprofloxacin orally either in a fasting state or "24 hours after administration of 10 X 600 mg Mg-OH + 900 mg Al-OH (Maalox)". A pronounced decrease of the peak serum concentration from a mean of 1.7 mg/L(range 1.3-2.6) after ciprofloxacin alone to a mean of 0.1 mg/L(range 0.06-0.2 mg/L) after ciprofloxacin plus antacid(P LT 0.001) was reported. Tmax was only slightly prolonged(73 +/- 13 min versus 87 +/- min). The cumulative urinary excretion of parent drug over 24 hours after ciprofloxacin administered alone was 24%(range 19-34%) of the administered dose as compared to 2.1%(range 0.9-4.7%) after prior administration with antacids. It was postulated that the drug forms chelates of Mg++ or Al++ resulting in reduced absorption. The potential for a similar interaction may also exist for norfloxacin, although the reviewer is not aware of any related investigations. Coadministration of norfloxacin and antacids containing magnesium and aluminum(even possibly calcium) should be discouraged until definitive data is available. It should be noted that in the above study the exact time of administration of antacids relative to ciprofloxacin dosing is unclear.

Another concern related to the above is absorption of norfloxacin in the elderly, who characteristically have a higher gastric pH and often are achlorhydric. Based on the pH solubility profile of norfloxacin, it is predicted that dissolution will be retarded in the pH range 6-9. The mean (S.D.) percent of a single dose recovered in the urine over 24 hours in an elderly population(age 67-74 yrs) was 22.3 %(S.D. 6.9) and ranged from 10.5 to 29.4%(ref #19, Martin). This contrasts with mean percents of 27-32 observed in younger subjects reported by other investigators based on urinary recovery to time infinity(#18,21). Even if absorption in the elderly differs from that of younger patients the clinical significance of this observation is not known at this time.

Bioequivalence

Reference #21 - Zinny(single dose x over, 400 mg Kyorin vs 400 mg MSD)

Because Kyorin and MSD used different manufacturing methods to produce norfloxacin tablets, a bioequivalency study using products produced by both processes was conducted. IT SHOULD BE NOTED THAT THE MSD PRODUCT USED IN THIS STUDY IS DIFFERENT FROM THE PROPOSED MARKET IMAGE TABLET.

The following results were obtained.

	ANOVA	Power*	% w/in 75/75-125	Other
AUC	NS	85.6	----	
Cmax	NS	75.4	12/20 = 60 %	2 1-Sided Hyp Accept H1: Bio Equivalent
Tmax	Sig (P LT 0.05)			2 1-Sided Hyp Accept Ho: Not BE

* 20 % diff, alpha = 0.05

Based on the above results, it is concluded that the MSD and Kyorin tablets have equivalent extents of absorption. The Cmax for the two products were not statistically significantly different(1.56 +/- 0.48-Kyorin, 1.54 +/- 0.42ug/ml-MSD), however, the power for this evaluation was 75.4% and 75/75-125 Ratio Evaluation was 60 % within 75-125% of the reference product(Kyorin). A statistically significant difference(P LT 0.05) in mean Tmax was observed(1.35 +/- 0.43 hrs-Kyorin vs 1.07 +/- 0.37 hrs-MSD). It is concluded that the rate of absorption is similar(but not statistically equivalent) for the MSD and Kyorin products.

AN ACROSS STUDY COMPARISON OF CMAX, TMAX, AUC AND URINARY EXCRETION FROM A 400 MG DOSE FOLLOWS. THIS IS PROVIDED BECAUSE OF THE DIFFERENT FORMULATIONS UTILIZED IN INDIVIDUAL STUDIES.

	mean (S.D.) Cmax (ug/ml)	Tmax (hrs)	AUC*(ug/ml*hr)	% Dose Urin Recov
Zinny(#16) tab(Kyorin-B), n=25	1.15 (0.41)	1.5 (0.6)	6.7 (2.8) (day 14)	18.9 (8.2) (day 14, 0-12hr)
Zinny(#18) tab(Kyorin-A), n=15	1.5 (0.58)	1.03 (0.35)	7.1 (3.6)	26.5 (9.1) (0-48hr)
Zinny(#21) tab(MSD), n=18	1.54 (0.42)	1.07 (0.37)	6.9 (1.7)	27.0 (8.5) (0-48)

* AUC(0-12) at steady-state for the Multiple Dose study(#16) and AUC(0-infin) for the single dose studies(#15,18,21);

Note that the Cmax, Tmax and Urinary Excretion of norfloxacin in study # 16 differs from that in the other studies. The reason for the discrepancy is not apparent. Study #16 lacked a 1.5 hour plasma sampling time that was used in the other 3 studies. This explanation, as well as a decreased rate of absorption, could explain the difference in Cmax and Tmax. It could be suggested that the bioavailability(extent of absorption) of Kyorin-B product is less than that of the other products based on urinary excretion data, however, evaluation of AUC values does not support this conclusion. The data in study #16 should be interpreted with caution.

Pharmacokinetic Parameters

Adults(#18,21) - See "BIOEQUIVALENCE" Section Above For Cmax, Tmax, AUC & Urinary Excretion Comparison.

Elderly (#19), n=6

	Mean	S.D.	Range
Cl Renal(ml/min) =	154	15.7	
Plasma* T 1/2 alpha(hr) =	1.2	0.32	
T 1/2 beta(hr) =	5.6	2.1	
Effective T 1/2 (hr) =	3.9	--	
For Accumulation** (harmonic mean)			

* based on 2-COM with 1st order absorption and elimination, ESTRIP program. Values for Cl & Vol were not reported.

** for a dosing interval of 8 hours

Protein Binding

It is reported that protein binding measured by ultrafiltration using pooled human serum at a concentration of 2.5 ug/ml was 13.8% (Vol ~~was 13.8%~~). Negligible binding to serum protein was reported at a drug concentration above 20 ug/ml.

Probenecid Effects

The excretion of norfloxacin with and without coadministration of 1 Gm of probenecid was investigated in 5 healthy volunteers in a crossover designed study (Shimada, et al, Antimicrob. Agents Chemother., 23(1):1-7, 1983). In the presence of probenecid the renal clearance of norfloxacin decreased from a mean(+/- S.D.) of 334.9(62.4) to 163.6(18.8) ml/min. The urinary recovery of unchanged norfloxacin decreased from a mean(S.D.) 28.0(+/- 15.5) % of the dose administered to 13.9(+/- 4.7) % when norfloxacin was given with probenecid as compared to control (Table 3 of this review). The renal clearance of norfloxacin was 2.4-3.4 times greater than the creatinine clearance

when norfloxacin was administered alone, compared to 1.2-1.5 times greater during coadministration of probenecid and norfloxacin. Probenecid had little effect on the mean plasma concentrations of norfloxacin (Figure 3 of this review). Because the data was quite variable and results for individual subjects were not provided any possible trends in plasma concentrations were not observed. It cannot be concluded that coadministration of probenecid does not effect norfloxacin concentrations.

Metabolism/Elimination

Reference # 9 - Ozaki (single dose, 200 or 1600 mg tablet)

24 hour urinary excretion - Study #9

<u>Dose</u>	Parent	M-1	M-2	M-3	M-4	M-5	Total**
	(% of administered AM-715 units)						
200 mg PO, SD (N=3)	26.6 (9.0)	5.1 (0.8)	1.5 (0.4)	0.33 (0.15)	0.5 ---	0.7 (0.1)	34.7 (9.4)
% of total recovered in urine	76.7	14.7	4.3	0.9	1.4	2.0	

M-4 consists of M-4(1) & M-4(2) which could not be separated under study conditions.

It is reported that no conjugates of norfloxacin or its metabolites were detected in urine (Vol. [redacted] summary)

Fecal Recovery - Study #18(Zinny) & #21(Zinny)

	% Dose
24-48 hrs Specimen collection	30.0*

* Based on antimicrobial activity, thus includes parent and metabolite activity

Norfloxacin is recovered in urine and feces after oral administration to humans. Of drug recovered in the urine (parent and metabolites), approximately 80% represents unchanged parent compound. Approximately 30-35% of the dose administered is recovered in the urine over 24-48 hours as parent (25-30%) and metabolites (4-8%). Fecal recovery over 24-48 hours accounts for approximately 30% of the administered dose. Limited evidence suggests that biliary excretion of parent and metabolites also occurs. In a meeting with representatives of the firm on January 10, 1986, it was suggested by the firm that the remaining 35-40% of the drug not accounted for in urinary and fecal recovery is believed to be bound to feces. The firm later indicated that fecal inactivation of norfloxacin is possible and submitted supportive literature references (submission dated 02/14/86). This would cause underestimation of drug recovery from fecal specimens assessed with microbiological assay techniques.

Renal Insufficiency

Reference # 20 - Asscher (single dose, 400 mg MSD tablet)

The disposition of a single, oral, 400 mg dose of norfloxacin was studied in 18 patients with varying degrees of renal dysfunction. A statistically significant difference in AUC(0-infinity) and % Urinary Recovery was observed overall. No significant difference in Cmax and Tmax was observed (P Greater than 0.2). Significant pairwise comparisons of AUC(0-inf) and % Urinary Recovery are below.

Parameter	Overall	Significant Pairwise Comparisons
Uri Recov(% Dose)	p LT* 0.0001	I,II vs III p = 0.0002 I,II vs IV p = 0.0001
AUC(0-infinity)	p = 0.03	I vs III p = 0.004 II vs III p = 0.04 I vs IV p = 0.06

* - LT = less than, GT = greater than
Group I - CrClr GT 100 ml/min/1.73 meters squared
Group II - CrClr 31-80 ml/min/1.73 meters squared
Group III - CrClr 10-30 ml/min/1.73 meters squared
Group IV - CrClr LT 10 ml/min/1.73 meters squared

Generally, the greatest differences in AUC and Urinary Recovery are observed in subjects with ClCr less than 30 ml/min/1.73 meters squared (Groups III & IV). It is recommended by the firm that the regular dose be administered QD rather than BID in patients with ClCr less than 30 ml/min/1.73 meters squared. It should be noted that the lowest ClCr in Group II was 46 ml/min and no subjects between 28 and 46 ml/min/1.73 msqd were enrolled in this study. It is unclear whether the above recommended cutoff for a dose change should include patients in this range. A conservative recommendation is to use approximately 45 ml/min/1.73 meters squared as a cutoff value. In all cases, monitoring of norfloxacin levels is indicated in renal failure patients receiving long term therapy to insure adequate antimicrobial activity without excessive dosing.

Special Population - Elderly

Reference # 19 - Martin

The disposition of a single 400 mg dose of norfloxacin was studied in six, healthy, elderly subjects with a ClCr greater than 70 ml/min/meters squared. The percent of the dose recovered in the urine as parent compound was 22.3 %, a value lower but comparable to that observed in younger subjects (approx. 30 %). The renal clearance of norfloxacin in this group of subjects was 154 ml/min., compared to approximately 300 ml/min in younger subjects (#15). Despite this difference it appears that dose adjustment is not necessary in elderly subjects with ClCr greater than 70 ml/min/1.73 meters squared.

VII ANALYTICAL METHODOLOGY

Assay methodology employed and comments follow each study listed below.

Ref 9(Ozaki) - HPLC with detection via fluorophotometric analyzer for urine and plasma samples. This assay lacks adequate sensitivity with plasma samples for use in clinical studies. Limits: 1-2 ug/ml for ~~AM-715~~(parent drug) and metabolite M-1, 0.5-1 ug/ml for other metabolites

Ref 12(Kumasaka) - antimicrobial activity measured via paper disc method employing E. Coli. Validation of assay methodology was not provided. The results of the study were not utilized for reasons other than lack of assay documentation.

The following studies employed similar methodology--HPLC with uv detection(urine) and fluorescence detection(plasma). Documentation of assay specificity, sensitivity and reproducibility was provided.

Refs 16 & 17 (Zinny) - MSD

Ref 18(Zinny) - MSD; antimicrobial activity in stool specimens & rectal swabs was quantitated by Dr. S Landman of SUNY-Downstate Med School.

Ref 19(Martin) - MSD, assay cited in JPS 73(1);99-102, 1984, "Quantitation of Norfloxacin, a New Antibacterial Agent in Human Plasma and Urine by Ion-Pair Reverse-Phase Chromatography", Pauliukonis, et al(Ref # 2, [REDACTED], pg. [REDACTED].
Ref 21(Zinny) - MSD; antimicrobial activity in stool specimens & rectal swabs was quantitated by Dr. S Landsman of SUNY-Downstate Med School.

The following is a summary of results of a bioassay procedure for norfloxacin. The procedure is published in Eur J Clin Microbiol, 2(3):249-252, June 1983.

Ref 1(Huber) - MSD(plasma, urine, tissue); A disk-diffusion bioassay procedure employing *Klebsiella pneumoniae* ATCC 10031 was developed. The assay sensitivity(when incubated at 28 degrees C) was reported to be 0.2 ug/ml. Urine and serum standard curves were similar. Bioassay values in urine were comparable to those obtained by HPLC.

VIII COMMENTS(For Labeling and For Reviewed BA/PK Studies)

1. The following comments pertain to labeling and the proposed package insert in vol. [REDACTED] pg [REDACTED].

a. pg 3 - "The effective half-life...is 3-4 hours". The mean(harmonic) values reported by [REDACTED] and those by Zinny(ref #18) 3.0-3.3. Individual values exist outside these ranges. Reporting 2-4 hours is probably more representative of the data, however, 2.5-3.5 is probably more exact. Whenever effective half-life for accumulation is reported the corresponding dosing interval used to calculate the effective half-life should also be reported. Since the value of effective half-life for accumulation is different for QD, BID and TID dosing, and each patient will not necessarily receive the same regimen, several values for effective half-life for accumulation should be provided in the package insert. The reviewer is concerned that the concept "effective half-life for accumulation" is unfamiliar to practitioners and needs an explanation when used. The conventional "elimination half-life"(about 5 hours) needs to be included in the package insert.

b. pg 4 - "In healthy elderly...renal function". Criteria for entry into the Martin study(Ref #19) was ClCr greater than or = to 70 ml/min/1.73 meters squared. This should be the basis of the recommendation in the labeling rather than normal renal function based on age.

c. pg 5 - "Disposition of the drug...creatinine clearance greater than 30 ml/min/1.73 meters squared". Although the limits for GFR used by Asscher(Ref #20) in Group II were 31 to 80 ml/min, no data was obtained in subjects with a measured GFR between 31 and 46 ml/min. The mean(+/- S.D.) GFR value in group II was 54.5(14.6). The drastic difference in AUC and Urinary Recovery observed between Group II and III may be due to failure to enroll subjects

representative of the entire GFR range in Group II. Thus, extrapolation of the results of this study to the GFR range 31-46 should be done with caution. It is recommended that approximately 45 ml/min be used in the package insert as the critical value for dose adjustment in patients with renal impairment.

d. pg 5 - "Norfloxacin is eliminated...and renal excretion". It is useful to specify the major route of elimination of norfloxacin. The data suggest that renal elimination of parent drug is the major route of elimination and metabolism of norfloxacin is minor. The extent of biliary excretion is unclear, however, a biliary concentration of 5 ug/ml was measured 1-2 hours after a 200 mg single dose. This information should be included in labeling.

e. pg 5 - "Within 24 hours of drug...of lesser antimicrobial potency." Insert 'in the urine' between the words 'recovered' and 'as', to clarify the statement.

f. pg 5 - "Two to three hours...200 mcg/ml or more...in the urine". Inspection of table 15-16 of this review (Ferguson, Ref #15) shows that 8 of 13 subjects (61 %) had urinary concentrations below 200 mcg/ml during the 2-3 hour urinary collection period. However, a concentration of 200 mcg/ml or greater was observed during either the 0-1, 1-2 or 2-3 hour urine collection period after the dose in 3 of 14 subjects (64 %). The data is variable and the information provided should reflect this. If excretion of drug is independent of urine flow, then the concentration of drug in the urine will vary with urine flow. Thus, the urine concentrations observed in fluid loaded subjects will be comparable to urine concentrations in fluid loaded patients.

g. pg. 13 - "Coadministration of probenecid does not...drug diminishes".

Based on the study provided, it cannot be concluded that coadministration of probenecid does not effect norfloxacin concentrations. The data was quite variable and the results for individual subjects were not provided.

h. pg 15 - "When a 200 mg dose...nursing mothers...in human milk". Additional information obtained in this investigation follows. At various times after administration of a 200 mg single oral dose, norfloxacin was detected in umbilical cord serum (0.1-0.5 ug/ml) at the time of delivery and amniotic fluid samples (0.18-0.92 ug/ml). However, drug concentration in the blood of neonates after delivery was below the limits of detection (approximately 0.1 ug/ml). It should be noted that human milk samples were only obtained from 1 to 6 hours after the dose.

i. pg 20 - "In patents with apparently normal renal function...greater than 30 ml/min/1.73 meters squared". Concern is expressed over the 30 ml/min/1.73 meters squared value used as the critical point for dose adjustment. See comment c. above in this section.

j. Labeling should include a caution against coadministration of norfloxacin with antacids until evidence demonstrating lack of an interaction resulting in decreased absorption is available.

k. Because of the effect of pH on the solubility of norfloxacin, the effect of food on the proposed marketed product needs investigation. For labeling purposes, administration of norfloxacin with food should be discouraged as a precaution until definitive data is available.

1. Labeling should include specific instructions to maintain a good fluid intake in all patients to prevent crystallization of drug in the urinary tract. Even greater emphasis on the potential for developing crystalluria with resulting complications should be stated in the package insert section "Overdosage". Maintaining adequate hydration should be directed toward this potential problem.

2. Each of the following comments pertain to the specific study referenced with the comment.

Reference #9

1. Biliary excretion data was obtained in only 1 patient. Raw data was not provided. The concentration of AM-715 reported in bile was 5 ug/ml. It is unclear how concentrations of metabolites M-3 thru M-5 in bile were determined. Based on the lower limits of quantitative determination reported by the firm, the concentrations implied by the report are lower than the limits given if 5 ug/ml is the highest concentration observed for AM-715. Little can be concluded from the data presented.

2. The less than 100% recovery observed is consistent with incomplete urinary collection, elimination via other routes, incomplete GI absorption of drug and/or incomplete recovery of drug using the stated analytical methods.

3. The formulation and/or lot number of the tablet dosage form utilized in this study was not provided.

4. Age and weight of the patient with gallstone disease was not provided. Exclusion/inclusion criteria for volunteers was not provided.

Reference #12

1. The usefulness of the data in this pilot study is questioned. Urine and blood samples were collected for a period of 8 hours after dosing. It is possible that sample collection was incomplete, as the elimination half-life of norfloxacin is approximately 5 hours. A trend is observed in the data, however, the ability to extrapolate the results to the general population is limited, at best. The formulation and source (Kyorin vs MSD) of the product used in this study was not provided.

2. Validation of assay methodology was not provided.

3. For mean C_{max} in urine, the firm reported a value of 320.0 ug/ml. It appears that 320.0 is the result of using a 0-2hr urine concentration of [redacted] ug/ml rather than the 6-8hr urine concentration of [redacted] ug/ml in patient [redacted]. If this subject is atypical then none of his values should be used. unacceptable. Total AUC(0-infinity) was used by the reviewer in the comparison of AUC across the dose

strengths. However, it should be pointed out that Total AUC was estimated (not measured directly) using the measured renal clearance. It was concluded by the reviewer that Total AUC was calculated by dividing $X_u(\infty)$ by Renal Clearance.

2. C_{max} of MK0366 in serum dose not increase proportionately with increasing dose across the single-dose range [redacted] to [redacted] mg (see table 15-6 of this review).

3. Subjects were fluid loaded in this study. Subjects received 250 ml of water 1 hour prior to dosing, 250 ml with dose administration, and 250 ml at 1, 2, 4, 6, and 8 hours post-dosing (total of 1750 ml over 9 hours). Fluids were subsequently permitted ad libitum.

4. The firm should have stated the lower limits of the assay for plasma samples and provided data on the specificity in plasma.

Reference # 16

1. In general, the data in this study should be used with caution because of the extrapolations and estimations made by the sponsor in the calculation of $AUC(0-12)$, C_{min} values and obtaining urinary excretion data. These issues are discussed below in parts A, B, and C.

A. It is reported that the area under the plasma concentration-time curve (AUC) from 0 to 8 hours was measured directly by the sponsor using the trapezoid method. The remaining area through 12 hours was estimated using renal clearance or the norfloxacin half-life or measured directly using a log-linear trapezoidal approximation. Renal clearance was estimated from corresponding increments of urinary recovery and (AUC) for norfloxacin. It is unclear why the area under the curve from 8 to 12 hours was estimated rather than measured directly when plasma samples were obtained at 12 hours in all subjects and measurable values were reported in almost all of the subjects (see table 16-4 of this review). There is no need to estimate the area from 8 to 12 hours when it can be measured directly. The reviewer calculated $AUC(0-12)$, when used, by the trapezoidal method. AUC values reported by the sponsor should be used with caution.

B. It is reported that blood samples for determination of Cmin after the second drug dose on days 1, 6 & 13, were actually drawn 30 minutes ahead of schedule. Plasma concentrations for these determinations were extrapolated to the end of the dosing interval using individual estimates of norfloxacin half-life.

C. The urinary excretion data in this study is inconsistent with that observed in other studies reviewed. The percent of the norfloxacin dose administered that was excreted over 12 hours on days 7 & 14 (under steady state conditions) was 17.7 and 18.9 %, respectively, in this study by Zinny (Ref #16). In addition, the mean Cmax appears to be lower, and Tmax longer than that in other studies. The urinary excretion data in this study contrasts with 25-30% of a single 400 mg dose excreted in the urine over 48 hours reported in other studies. This discrepancy could suggest reduced bioavailability of the Kyorin-B product utilized by Zinny compared to the other formulations studied. However, this suggestion is not supported by the plasma AUC data for the various studies. An across-study comparison of mean Cmax and Tmax (after the first dose of the multiple dose study), AUC and urinary recovery follows. Because of the inconsistencies in the data from this study (#16), the results should be interpreted with caution.

Mean*(S.D.)	Cmax (ug/ml)	Tmax (hrs)	AUC**(ug/ml*hr)	% Dose Urin Recov
Zinny(#16) tab(Kyorin-B), n=25	1.15 (0.41)	1.5 (0.6)	6.7 (2.8) (day 14)	18.9 (8.2) (day 14, 0-12hr)
Ferguson(#15) cap, n=14	1.6 (0.45)	1.1 (0.35)	6.2 (1.8)	31.3 (6.7) (0-48hr)
Zinny(#18) tab(Kyorin-A), n=15	1.5 (0.58)	1.03 (0.35)	7.1 (3.6)	26.5 (9.1) (0-48hr)
Zinny(#21) tab(MSD), n=18	1.54 (0.42)	1.07 (0.37)	6.9 (1.7)	27.0 (8.5) (0-48)

* 400 mg dose compared;

** AUC(0-12) at steady-state for the Multiple Dose study(#16) and AUC(0-infin) for the single dose studies(#15,18,21);

2. It is unclear whether or not the timing of meals relative to dosing is consistent for each dose. The protocol on page [redacted] vol. [redacted], says the following; "Volunteers will be fasting since midnight of the day prior to initial dosing (which should take place at approximately 0800 hours) and may resume a normal diet at lunchtime (approximately 3 to 4 hours after dosing... The subsequent dose of medication will be taken at 2000 hours, and no food shall be consumed from 1 hour before dosing until 1 hour after dosing". Ideally, food should be avoided 2 hrs before and 4 hours after the dose is given to satisfy fasting conditions. It is unclear whether or not patients fasted before each 0800 hour dose or only before the first dose of the 14 day treatment period. If subjects fasted only before the first dose, then fasting or nonfasting conditions for subsequent 0800 doses is not specified. It appears that subjects

received the first 0800 hour dose under fasting conditions, subsequent 0800 hour doses under unspecified conditions, and the 2000 hour dose regularly under less than ideal conditions. The significance of this depends on whether or not the presence of food effects the absorption characteristics of norfloxacin.

3. Subjects were fluid loaded in this study. Subjects received 250 ml of water 1 hour prior to dosing, followed by 250 ml of water with dose administration. Subjects were instructed to maintain a good fluid intake and to consume 250 ml of water every 2 hours after the dose up to 4 hours after the first dose each day.

Reference #17

1. The data in this study should be interpreted with caution because of the small number of subjects(4).

2. It is unclear whether or not the timing of meals relative to dosing is consistent for each dose. Subjects fasted overnight before starting the study and were instructed to avoid food 1 hour before to 1 hour after subsequent doses. The reviewer recognizes the restraints that TID dosing puts on attempts to ensure fasting conditions. The significance of inconsistent dosing conditions depends on whether or not the presence of food effects the absorption characteristics of norfloxacin.

2. Patients were instructed to drink 250 ml of water 1 hour prior to dosing, 250 ml with administration of the dose, and 250 ml every 2 hours postdosing up to 4 hours after the first dose of the day. Subjects were encouraged to maintain a good fluid intake.

Reference #18

1. It should be noted that patients were fluid loaded during each treatment of the study(1440 ml of water over an 8 hour period).

2. The dosing interval that corresponds to the effective half-life should be stated whenever values for effective half-life are reported.

Reference #19

1. Subjects were fluid loaded in this study. Subjects received 750 ml of water(including 150 ml with the dose) over a 4 hour period after administration of the drug. Subjects also received 150 ml of water several hours prior to dosing.

2. On pg [redacted](Vol [redacted] of the Biopharmaceutics Report, it is predicted that norfloxacin plasma levels should accumulate by approximately 32% on an 8-hour dosing regimen and by 13% on an 12-hour dosing regimen. The reviewer agrees with the value 32% but not with the 13% reported. The accumulation half-life for 12-hour dosing will differ from that calculated with 8-hour dosing. The accumulation fraction of 1.13 for 12 hour dosing was calculated using the effective half-life calculated for 8 hour dosing. The actual accumulation fraction for 12 hour dosing is probably less than 1.13.

Reference #20

1. Subjects were fluid loaded in this study. Subjects received 850 ml of water over a 4 hour period after dose administration(including 250 ml with the dose). Subjects were also instructed to take 250 ml of water upon rising the morning of the study, which begun at 0800.

2. Most patients in this study were also taking other medications during the study. The effect of these drugs on the disposition of norfloxacin is not known. Thus, the results of this study must be interpreted with caution.

3. Although the stated range of GFR in Group II is 31 to 80 ml/min, 5 of 6 subjects had a GFR greater than 46. The mean (+/- S.D.) GFR for subjects in Group II is 54.5 (14.6). Subject #6 had a GFR of 31 ml/min but was excluded in the evaluation of Renal Clearance, Urinary Recovery and AUC because of "questionable urinary recovery". Thus, no data was obtained in subjects with a measured GFR greater than 28 ml/min and less than 46 ml/min in this study. Extrapolation of the results of this study to this GFR range should be done with caution.

Reference #21

1. It should be noted that patients were fluid loaded (received 1440 ml of water over an 8 hour period) during each treatment of the study.

VII Comments (con't)

3. The following comment pertains to the Biopharmaceutics Summary, section ~~Metabolism~~ Metabolism in volume ~~2-2~~.

References 8 and 11 contain supportive metabolism data in animals. The values presented in the summary section are inconsistent with the data in the corresponding reference. It appears as if the individual study results were combined although the two studies measured different parameters. The discrepancy is not large, yet it is recommended that information on drug metabolism in animals be obtained from the individual studies submitted rather than from the Biopharmaceutics Summary section.

4. The following are general comments.

a. The sponsor investigated 400 mg BID in a multiple dose study (ref #16, Zinny). The regimen of 400 mg TID was utilized in clinical study #66 (Zinny ref #17), however, pharmacokinetic data was obtained in only 4 subjects. The extent of accumulation with TID dosing can be predicted using a linear system and basic pharmacokinetic principles (1-COM). Based on an elimination half-life of 5 hours and an 8 hour dosing interval, C_{min} at steady state should be approximately 1.5 times the C_{min} observed after a single dose (Gibaldi M, Biopharmaceutics and Clinical Pharmacokinetics, 3rd Ed, 1984).

IX CRYSTALLURIA ANALYSIS(see attachment I of this review)

The Division of Biopharmaceutics was asked to comment on the possibility that norfloxacin might precipitate into crystals in the human kidney and cause obstruction there or elsewhere in the urinary tract.

A Solubility

As shown in Figures 1 and 2, the solubility of norfloxacin in urine varies greatly with pH, being lowest between 6 and 10. Because urinary pH normally ranges from pH 6-8, the solubility of norfloxacin over this range is the focus of this discussion. Figure 2 shows the relative solubility of norfloxacin in urine at 25 and 37 degrees centigrade.

In animal studies of norfloxacin, crystalluria consisted of the dihydrate and magnesium salts of norfloxacin. It is unclear at this time whether the parent compound and/or the above salts should be the focus of discussion of the possibility of crystallization in humans. Swanson, et al(ref below), observed "drug crystals" in freshly voided urine specimens collected after administering single oral 1200 and 1600 mg doses to human volunteers. Crystals were not found at lower doses(200-800 mg). Urine pH of specimens with crystals was between 7 and 7.8. Drug was administered with only 250 ml of water under fasting conditions.

B Pharmacokinetic Predictions

Using data in the Ferguson(ref #15) and Zinny(ref #16) studies, it is possible to do calculations to determine if, on a theoretical basis, drug crystals of the parent compound norfloxacin are likely to be formed.

Assumptions/Conditions;

1. a worst case scenario is most useful
2. high single doses and/or the recommended multiple dose regimen
3. maintenance of a constant plasma concentration
4. solubility of norfloxacin in urine at 25 and 37 degrees C.

- I. Using the urinary excretion rate, compare the concentration of drug in the kidney with the solubility of the drug.

The ratio, (A)drug excretion rate/(B)rate of urine formation, estimates the concentration of drug in the kidney tubules.

The solubility of norfloxacin was obtained from the pH solubility profile in urine.

Swanson B, et al, 1983. Norfloxacin Disposition After Sequentially Increasing Oral Doses. Antimicrob. Agents Chemother. 23(2):284-288.

A. Single dose evaluation

1600 mg PO

$$Cl_{renal} \times C_{max} = \frac{\text{maximum excretion rate}}{\text{(introduction of drug to kidney)}}$$

$$300 \text{ ml/min} \times 4.0 \text{ ug/ml} = 1200 \text{ ug/min (1.2 mg/min)}$$

(Consistent with actual values reported by the firm in table 15-14 of the BA review)

In normal individuals, the rate of urine formation(B) is approximately 1 ml/min(Guyton, Textbook of Medical Physiology, 6th Ed., 1981).

$$\frac{A}{B} = \frac{1200 \text{ ug/min}}{1 \text{ ml/min}} = 1200 \text{ ug/ml (1.2 mg/ml)}$$

1200 mg PO - $C_{max} = 3.0 \text{ ug/ml}$,
Excretion rate = 900 ug/min(0.9 mg/min)

Ratio A/B = 0.9 mg/ml

B. Multiple dose regimen,

	<u>C_{max}</u>	<u>Est'd Drug Exct'n Rate</u>	<u>Ratio A/B</u>
400 mg BID	2.0 ug/ml	600 ug/min(0.6 mg/min)	0.6 mg/ml
400 mg TID	3.0 ug/ml*	900 ug/min(0.9 mg/min)	0.9 mg/ml

* predicted value(actual value in 4 subjects was approx. 2.0 ug/ml)

COMPARISONS WITH SOLUBILITY OF NORFLOXACIN IN URINE

Regimen	Ratio A/B	Solubility(mg/ml)		
		25 C	37 C	
1600 mg SD	1.2 mg/ml	pH 6 :	OK	OK
		pH 7 :	Exceeded	OK
		pH 8 :	Exceeded	OK
1200 mg SD	0.9 mg/ml	pH 6 :	OK	OK
		pH 7 :	Exceeded	OK
		pH 8 :	Exceeded	OK
400 mg BID	0.6 mg/ml	pH 6 :	OK	OK
		pH 7 :	OK	OK
		pH 8 :	Borderline OK	OK
400 mg TID	0.9 mg/ml	pH 6 :	OK	OK
		pH 7 :	Exceeded	OK
		pH 8 :	Exceeded	OK

II. It is well documented that the crystalluria can be avoided by assuring an adequate rate of urine flow (Gibaldi, Biopharmaceutics and Clinical Pharmacokinetics, 3rd Ed., 1984). Thus, the minimum rate of urine flow may be calculated by dividing the excretion rate of drug by its solubility at a given pH.

$$\text{Minimum Rate of Urine Flow} = \frac{\text{(A) Excretion Rate of Drug}}{\text{(B) Solubility in urine at a given pH}}$$

At TEMP 25 C

	pH 6	pH 7	pH 8
B(solubility)	= 3.2 mg/ml	= 0.75 mg/ml	= 0.6 mg/ml
Ratio	A/B	A/B	A/B
S.D. - 1600 mg C _{max} = 4 ug/ml A* = 1.2 mg/min	0.375 ml/min	1.6 ml/min	2 ml/min
S.D. - 1200 mg C _{max} = 3 ug/ml A = 0.9 mg/min	0.28	1.2	1.5
M.D. - 400 BID C _{max} = 2 ug/ml A = 0.6 mg/min	0.19	0.8	1.0
M.D. - 400 TID C _{max} = 3 ug/ml A = 0.9 mg/min	0.28	1.2	1.5

AT TEMP 37 C

	pH 6	pH 7	pH 8
B(solubility)	= 10 mg/ml	= 1.5 mg/ml	= 1.9 mg/ml
Ratio	A/B	A/B	A/B
S.D. - 1600 mg C _{max} = 4 ug/ml A* = 1.2 mg/min	0.12 ml/min	0.8 ml/min	0.63 ml/min
S.D. - 1200 mg C _{max} = 3 ug/ml A = 0.9 mg/min	0.09	0.6	0.47
M.D. - 400 BID C _{max} = 2 ug/ml A = 0.6 mg/min	0.06	0.4	0.31
M.D. - 400 TID C _{max} = 3 ug/ml A = 0.9 mg/min	0.09	0.6	0.47

* Drug Excretion Rate

C STUDY DOSING CONDITIONS

The possibility of crystalluria decreases if a water diuresis is created. A water diuresis of up to 8 ml/min urine output can occur within 1 hour of ingesting 1000 ml of water. EXAMINATION OF EACH BIOAVAILABILITY STUDY REVIEWED SHOWS THAT PATIENTS WERE FLUID LOADED TO VARIOUS DEGREES. Below is a summary of dosing conditions.

- Ref #15(Ferguson) - 1750 ml of water over a 9 hr period
- Ref #16(Zinny) - 1000 ml of water over a 5 hr period
- Ref #17(Zinny) - 1000 ml of water over a 5 hr period
- Ref #18(Zinny) - 1440 ml of water over an 8 hr period
- Ref #19(Martin) - 750 ml of water over a 4 hr period
- Ref #20(Asscher) - 1100 of water over a 5 hr period
- Ref #21(Zinny) - 1440 ml of water over a 9 hr period

It is standard practice that the drug under investigation be administered under conditions identical to those proposed for the general patient population. If conclusions about the safety of norfloxacin are drawn from these investigations then they should be limited to patients with a similar state of hydration. It is recommended that dosing conditions(hydration status) used in clinical studies be evaluated for additional information and consider the need to include in the package insert instructions to patients to ensure a sufficient fluid intake.

D CONCLUSION

Based on the above pharmacokinetic predictions, it appears that crystallization should not be a problem with the parent compound norfloxacin when using a solubility curve produced at 37 degrees centigrade(body temperature). Mixed results are obtained from a solubility curve produced at 25 degrees centigrade(room temperature). It should be emphasized that the above manipulations are theoretical and their limitations are demonstrated by the observations of crystals after large single doses(i.e. 1200 & 1600 mg) as reported by Swanson(1) et al. These predictions should be used in conjunction with actual clinical data to make conclusions about the safety of this drug with regards to crystalluria. The fluid loaded conditions used in the BA studies complicate interpretation of the clinical results of these studies for resolving safety issues. The above manipulations and conclusions do not apply to the dihydrate, magnesium or other salts of norfloxacin.

Concern is expressed about the potential for formation of crystals under abnormal conditions commonly seen. Some of these conditions are periods of low urine formation(e.g. dehydration), alterations in urine pH which effect renal tubular secretion and the solubility of the drug, and pathological conditions that alter kidney physiology. The labeling should include specific instructions to maintain a good fluid intake in all patients to prevent crystallization of drug in the urinary tract.

In conclusion, at pH 6, it appears that crystallization should not be a problem with the parent compound norfloxacin. The results are less clear at pH 7 and 8. However, since a worst case scenario was used, crystallization of norfloxacin at pH 7 is possible but unlikely. It should be emphasized that the above manipulations are theoretical and are likely to favorably change (crystallization less likely) if a norfloxacin solubility curve created at 37 degrees C (body temperature) is used rather than a curve produced at 25 degrees C (room temperature). The fluid loaded conditions used in the BA studies complicate interpretation of the clinical results of these studies for resolving safety issues. The above manipulations and conclusions do not apply to the dihydrate, magnesium or other salts of norfloxacin.

X OVERALL APPLICATION CONCLUSION

The Division of Biopharmaceutics concludes that the data submitted by the sponsor satisfies the requirements set forth in 21 CFR, part 320 describing bioavailability and bioequivalence requirements.

The data is summarized below.

1. Based on AUC, dose proportionality across the single dose range 200-1600 mg exists for norfloxacin. However, the Cmax of norfloxacin does not increase proportionately with the increase in a single dose beyond 800 mg. After a 400 mg single dose (capsule), mean Cmax was approximately 1.6 ug/ml (Tmax about 1 hour), whereas Cmax was approximately 3.8 ug/ml (Tmax occurs at about 2 hours) after a single 1600 mg dose. The mean Cmax observed after a single 400 mg dose (MSD direct compression tablet) was 1.5 ug/ml with a corresponding mean Tmax of about 1 hour.
2. The MSD and clinically tested Kyorin tablet products have equivalent extents of absorption. Based on mean Tmax, the rate of absorption of the MSD formulation is faster than the Kyorin formulation (1.07 vs 1.35 hrs).
3. Relative to a solution, the mean ratio of dose adjusted AUC(0-infinity) for a 400 mg tablet (Kyorin) to a solution administered as a single dose is 0.99 +/- 0.49. Statistical equivalence was not demonstrated.
4. Norfloxacin is recovered in urine and feces after oral administration to humans. About 30-35 % of the dose administered is recovered in the urine over 24-48 hours as parent (25-30 %) and metabolites (4-8 %). Fecal recovery accounts for approximately 30 % of the administered dose but is probably much greater. Fecal recovery is accounted for by incomplete GI absorption, biliary excretion and/or other factors. Thus the fraction of the administered dose absorbed orally is at least about 30-35 %.
5. The elimination half-life of the parent drug norfloxacin is about 5 hours. The "effective half-life for accumulation" for 8 hour dosing intervals is about 3 hours. The renal clearance of norfloxacin measured in adults with normal renal function is about 300 ml/min.
6. Because of the effect of pH on the solubility of norfloxacin, the effect of food on the proposed marketed product needs investigation.
7. Coadministration of norfloxacin and antacids should be discouraged in the labeling because of the possibility of complexation resulting in a decrease in absorption.

3. The dose of norfloxacin needs to be adjusted in the elderly and patients with renal dysfunction. Guidelines provided by the firm need clarification.

9. Protein binding of norfloxacin measured by ultrafiltration is about 14 %.

XII RECOMMENDATION

The Division of Biopharmaceutics recommends that the biopharmaceutic/pharmacokinetic data submitted to support NDA 19-384(the 400 mg tablet) be accepted.

HFN-815 should consider comment # 1(a-1) of section VIII above (pertaining to labeling) when evaluating the package insert. It is recommended that comment # 1 be forwarded to the sponsor.

The Division of Biopharmaceutics recommends that the proposed dissolution specification be accepted; Q= [redacted] in [redacted] minutes using USP Method II at 50 rpm in 750 ml of 0.05 M sodium acetate buffer (pH 4.0), at 37 degrees C. The sponsor should use the USP Acceptance Table criteria for this specification.

Gene D. Mason Pharm.D. 4/18/86

Gene D. Mason, Pharm.D.
Pharmacokinetic Evaluation Branch

RD Initialed by John Hunt 4/18/86

FT Initialed by C.T. Viswanathan, Ph.D. CTV 4/28/86

cc: Orig. NDA 19-384, HFN-815(2), HFN-815(Tabor), HFN-226(Mason), Chron, Drug and FOI files

GDM:gdM [redacted] 2/15/86

Appendix A

Individual Study Results

Study Reference: #9; Vol. [REDACTED], pg [REDACTED]

Title: Study of the Metabolism of AM-715 in Humans by Means of High-Performance Liquid Chromatography

Investigator/Site: Ozaki T, Uchida H, Irikura T
normals - Department of Internal Medicine, Oyama City Hospital
patient - Department of Surgery, Kawasaki Municipal Hospital

Objective: To elucidate the distribution ratio of metabolites of AM-715 in the serum and urine of healthy volunteers and in the bile of one patient with choledocholithiasis following oral administration of AM-715 tablets.

Design:

- I. 7 normal adult(35-45 years old) males, 50 - 75 Kg in body wt.
 - 3 subjects received - 200 mg AM-715 Tablets, with a cup of water (three hours after a "light meal")
 - 4 subjects received - 1,600 mg AM-715 Tablets, with a cup of water (three hours after a "light meal")
- II. 1 patient with choledocholithiasis (?age & wt)
 - received - 200 mg AM-715 Tablets,

Hydration: Drug was administered with a cup of water

Specimens:

Normals -

200 and 1600 mg dose groups

Urine(intervals) - 0 to 2.5, 2.5-5, 5-9 and 9-24 hours after dosing

1600 mg group

Blood : 0.5, 1, 2, 3, 4, 6, 8 and 16 hours after dosing

Patient - Bile was collected for one to two hours(after the dose).

Analytical Methods:

Methods used to treat serum, urine and bile were provided. HPLC with fluorophotometric detection was used for separation and detection of parent and metabolites.

Limits of quantitative determination:

AM-715 & M-1 1-2 ug/ml

M-2 thru M-5 0.5-1 ug/ml

Tables:

Table 9-1 -Serum concentrations of AM-715 after PO 1,600 mg

Table 9-2 -Urine concentrations of AM-715 and metabolites post PO 200 mg

Table 9-3 -Urine concentrations of AM-715 and metabolites post PO 1,600 mg

Table 9-4 -Urinary excretion of AM-715 and metabolites post PO 200 mg

Table 9-5 -Urinary excretion of AM-715 and metabolites post PO 1,600 mg

Figure 9-3 -Metabolite pattern in urine

Figure 9-1 -Chemical structure of parent and metabolites

Figure 9-2a,b,c -Chromatograms and calibration curves

Results:

Serum

With the 1,600 mg dose, only unchanged parent drug could be detected in serum because the serum concentration of metabolites M-1, M-2, M-3, M-4 and M-5 was below the detection limits of the assay.

Urine (% of dose*)

Species	mean (S.D.)	200 mg (N=3)	1,600 mg (N=4)
AM-715 - parent		26.6 (9.0)	23.0 (8.0)
range		20.5 - 37.0	17.0 - 34.8
M-1 metabolite		5.1 (0.8)	3.6 (7)
range		4.6 - 6.0	3.1 - 4.6
M-2 metabolite		1.5 (0.4)	0.57 (0.25)
range		1.1 - 1.8	0.3 - 0.9
M-3 metabolite		0.33 (0.15)	0.15 (0.06)
M-4 metabolite		LT** or = 0.5	0.05 (0.04)
M-5 metabolite		0.7 (0.1)	0.14 (0.06)
Total - 24 hours		34.7 (9.4)	27.5 (8.8)
range		28.4 - 45.5	21.7 - 40.5

* % of administered AM-715 units

** LT = less than

It is stated that the results after treatment with beta-glucuronidase-arylsulfatase did not differ from those determined quantitatively in the urine which did not undergo enzyme treatment. It was concluded that the drug and its metabolites were all unconjugated when excreted in the urine.

Bile - The concentration of AM-715 found in the bile one to two hours after a 200 mg dose was reported as 5 ug/ml. It is reported that the concentrations of M-1, M-2, M-3, M-4 and M-5 observed relative to AM-715 are 13%, 10%, 1%, 2% and 2%, respectively. No raw data was provided.

Study Reference: # 12; vol 2,145, pg VII-00309

Title: Fundamental Study of AM-715

Investigator/Site: Kumasaka Y, Nakahata H, Imamura K, Takebe K
The Third Department of Internal Medicine
Hirosaki University, School of Medicine

Objective: 1) To investigate antibacterial activity and 2) to compare serum and urine levels after a single 200 mg dose.

Design: Single dose, cross-over

5 healthy male adults received (dosage form, formulation & source not identified)

- a. 200 mg non-fasting (meal composition not specified)
- b. 200 mg fasting

Hydration: Administration of drug with water was not stated.

Specimens:

Serum - 0.5, 1, 2, 4, 6 and 8 hours after dosing

Urine(intervals) - 0 to 2, 2-4, 4-6, and 6-8 hours after administration

Analytical Methods: Norfloxacin levels were determined with the paper disc method employing E. Coli NIHJ JC-2 as the test bacterium. Standard curves were prepared with human serum for serum level determination and pH 7.0 M/15 phosphate buffer was used for the urinary level determinations. Validation of assay methodology was not provided.

Tables:

Table 12-1 : Individual urinary excretion and recovery of AM-715

Table 12-2 : Individual concentrations of AM-715

Figure 12-1 : Urinary excretion displayed graphically

Results:

	Urinary Excretion (ug/ml)			% Recovery	
	0 - 2H	2-4H	4-6H	6-8H	(0-8 hrs)
Fasting mean	290	162	102	104	28.3
(N=5) S.D.	250.6	70.3	45.4	41.5	8.19
range	68 - 640	48 - 240	66 - 160	50 - 156	
Non-Fasting	182	135	72	53.2	19.9
(N=5)	109.5	54.8	44.2	24.1	3.2
	56 - 312	92 - 156	32 - 142	30 - 88	

	Plasma		Urine		
	Cmax	Tmax	Cmax*	Tmax	
	ug/ml	hours	ug/ml	hours	
Fasting mean (N=5) (S.D.)	0.46 (0.13)	1-2	334.4** (209.2)		mean 0-2hrs(550 ug/ml): 2 subs 2-4hrs(208 ug/ml): 2 subs 6-8hrs(156 ug/ml): 1 sub
Non-Fasting (N=5)	0.32 (0.16)	1-2	206.0 (80.5)		0-2hrs(257 ug/ml): 3 subs 2-4hrs(129 ug/ml): 2 subs

* The value reported represents the mean value of the highest concentration observed for the 4 urine collection periods in each subject.

** The reviewer calculated this value. The firm reported a value of 320.0 ug/ml. It appears that 320.0 is the result of using a 0-2hr urine concentration of 84 ug/ml rather than the 6-8hr urine concentration of 156 ug/ml in patient Y.K. If this subject is atypical then none of his values should be used.

Firm's Conclusion:

1. The levels in serum and urine in the non-fasting state were slightly lower than those in the fasting state, but they are of a sufficient concentration to produce antibacterial activity and should have not influence on the clinical effectiveness.

Purged

P merged

Purple

Study Reference: # 16 ; vol [REDACTED], pg [REDACTED] study # 45

Title: A Double-Blind, Multiple Dose, Crossover Study to Investigate the Safety and Tolerance of Norfloxacin (MK0366) Versus Placebo

Investigator/Site: Miguel A Zinny, M.D.
Medical and Technical Research Associates
Clinical Unit
410 South Huntington Avenue
Jamaica Plain, MA 02194

Objective: 1) To investigate the safety and tolerability of these multiple doses of norfloxacin with respect to clinical, hematologic, neurologic and biochemical parameters and 2) to determine the plasma levels and urinary excretion following multiple oral doses of norfloxacin in healthy adult males and females.

Design: multiple dose, randomly assigned crossover with placebo, double-blind, healthy volunteers

Dosing: Oral administration using the following scheme,

1 x 400 mg norfloxacin tablet(Kyorin-B), q 12 hours x 14 days
1 matching norfloxacin image placebo tablet, q 12 hours x 14 days

Day 1 thru 14 - Treatment Period 1
Day 15 thru 21 - washout
Day 22 thru 35 - Treatment Period 2
Day 37 - Sampling Day

Volunteers fasted since midnight of the day prior to the 0800 hour dose until 3-4 hours after dosing and avoided food 1 hour before until 1 hour after the 2000 hour dose(see comment # 2). Time of dosing is referred to as zero (0) hour.

Hydration: Treatments were given with 250 ml of water, followed by 250 ml every 2 hours up to 4 hours post first dose of the day.

Concurrent Medications: None allowed from 7 days prior to study until its completion. See table 16-9 for a listing of volunteers who recieved medications other than the study drug and reasons for use.

Subjects: 27 (24 males, 3 females) healthy volunteers entered the study, however, 23 (20 males, 3 females) completed the study. Three volunteers were discontinued because of adverse clinical effects and 1 volunteer did not ingest one placebo dose. Subjects ranged in age from 19-50 years old, were to weigh within 15% of IBW for ages and height according to the Metro Life Ins Co Stat Bull #40, 1959, and judged normal on basis of medical history, physical examination and clinical laboratory screening.

Exclusion Criteria: hx of, or lab evidence of renal, hepatic, cardiac, pulmonary or hematologic disease, hx of epilepsy, neurologic disease, psychiatric disturbance, emotional instability or ophthalmologic conditions, ingestion of drugs of any kind(including alcohol) in the 7 days preceding initiation of the study, pregnant or lactating women, inability to complete the study.

Specimens:

Blood

Days 1 and 22

1 hour prior to dosing

Days 1, 2*, 7, 14, 22, 23*, 28 and 35

(1 hour prior to dosing), 1, 2, 3, 4, 6, 8, and 12 hours after dosing

Urine (intervals)

Days 1 and 22

collected for a one hour period prior to dosing

Days 1, 2*, 7, 14, 22, 23*, 28 and 35

0-1, 1-2, 2-4, 4-6, 6-8, and 8-12 hours after dosing

* urine and blood collections on Days 2 and 23 were only collected during period 2.

Analytical Methods: Plasma and urine samples were shipped to MSD for analysis by Drug Metabolism Department. Plasma samples were analyzed for norfloxacin by a HPLC method utilizing fluorescence detection. It is reported that this method is specific for norfloxacin and the daily standard curve is linear from a range of 0.05 to 2.5 ug/ml of control plasma. The results for the validation of this method for plasma samples, quality controls, and a representative curve is given in Table 16-10 and Figure 16-2. Urine samples were analyzed for norfloxacin by a HPLC chromatographic system utilizing a spectrophotometric ultraviolet detector. It is reported that this method is specific for norfloxacin and the daily standard curve is linear from a range of 1 to 500 ug/ml of control urine. The results for the validation of this method for urine samples, quality controls, and a representative standard curve is given in Tables 16-11 and Figure 16-3.

Tables:

Table 16-1 - Volunteer Demographic Data

Table 16-2 - Individual Urinary Excretion of norfloxacin

Table 16-3 - Individual renal Clearance

Table 16-4 - Individual Plasma concentrations of norfloxacin

Table 16-5 - Individual Peak Plasma concentrations of norfloxacin

Table 16-6 - Individual Tmax values

Table 16-7 - Individual Cmin concentrations

Table 16-8 - Individual AUC(0-12hrs) values

Table 16-9 - Other medications taken by volunteers

Table 16-10 - Assay validation in plasma

Table 16-11 - Assay validation in urine

Figure 16-1 - Mean norfloxacin plasma concentrations displayed graphically

Figure 16-2 - Plasma calibration curve

Figure 16-3 - Urine calibration curve

Results:

(Post 1st dose on...)		Day 1	Day 2	Day 7	Day 14
Renal Clearance (ml/min)	mean	276.6	330.4	239.6	266.0
	S.D.	112.0	39.0	39.5	72.6
	(n)	(9)	(3)	(8)	(9)
C _{max} (mcg/ml)	mean	1.15	1.18	1.27	1.35
	S.D.	0.41	0.55	0.50	0.39
	(n)	(25)	(13)	(26)	(25)
T _{max} (hr)	mean	1.5	2.2	2.2	1.4
	S.D.	0.6	1.6	2.0	0.6
	(n)	(25)	(13)	(26)	(25)
AUC(0-12hr)*	mean	5.23	5.69	6.57	6.52
	S.D.	2.02	1.99	2.99	2.86
	(n)	(23)	(13)	(25)	(25)

C_{min}** (mcg/ml) following dose number...

Dose #	1 (Day 1)***	2 (Day 2)	3 (Day 2)	2 (Day 7)	13 (Day 7)	26 (Day 14)	27 (Day 14)
mean	0.12	0.20	0.15	0.20	0.17	0.23	0.18
S.D.	0.09	0.11	0.05	0.14	0.11	0.21	0.13
(n)	(25)	(13)	(13)	(26)	(26)	(25)	(25)

* In the majority of the subjects on each day, a portion of the total AUC(0-12) was estimated (not measured directly) using norfloxacin half-life or renal clearance(see Comments section of this review).

** It is reported that blood samples for determination of C_{min} after the second drug dose on days 1, 6 & 13, were actually drawn 30 minutes ahead of schedule. Plasma concentrations for these determinations were extrapolated to the end of the dosing interval using individual estimates of norfloxacin half-life.

*** Day of active treatment, not study day

Firm's Conclusions:

1. Results indicate that norfloxacin, when administered twice daily to volunteers with normal renal function, produces similar (0.15 - 0.18 g/ml) serum levels 12 hours after dosing on the 2nd, 7th, and 14th day of administration. Steady state is established between 2 and 7 days of drug administration (400 mg q 12 hours).
2. Analysis of the safety profile indicated that norfloxacin at a dose of 400 mg q 12 hours is safe and well tolerated.

Study Reference: # 17 ; vol [REDACTED], pg [REDACTED]

Title: A Double -Blind, Multiple Dose, Five-Day Crossover Study to Investigate the Safety and Tolerance of Norfloxacin(MK-366) Versus Placebo

Investigator/Site: Miguel A Zinny, M.D.
Medical and Technical Research Associates, Inc.
408 South Huntington Ave
Jamaica Plain, MA 02194

Objective: 1) To evaluate the safety and tolerability of norfloxacin at the highest daily dosage schedule(1200 mg) used in clinical trials. 2) to determine the serum levels and urinary excretion this dosage regimen would produce in those volunteers sampled(four subjects).

Design: multiple dose, double blind, random crossover

Dosing: oral administration of either A. or B., followed by the other Tx.

- A. 400 mg q 8 hour., norfloxacin X 5 days; Kyorin-B product
- B. placebo X 5 days

A seven day washout period separated treatments. Subjects fasted since midnight of the day prior to initial dosing(AM) and resumed a normal diet at approximately 3-4 hours after the morning dose. No food was consumed from 1 hour before to 1 hour after dosing for subsequent doses.

Hydration: 250 ml of water 1 hour prior to dosing, 250 with administration of the dose, and 250 ml every 2 hours postdosing up to 4 hours after the first dose of the day. Subjects were encouraged to maintain a good fluid intake.

Concurrent Medications: None allowed(including alcohol) from seven days prior to the initiation of the study until its completion.

Subjects: Although 26 healthy male(25) and female(1) volunteers between the ages of 19 and 40 years of age participated in the study, PLASMA SAMPLES FOR PHARMACOKINETIC ANALYSIS WERE OBTAINED IN ONLY FOUR SUBJECTS. Selection criteria included weight within 15% of IBW for age and height(M.I.C.S.B., 1959) and in good health on basis of medical Hx, physical examination and clinical laboratory values. Exclusion criteria: hx of renal, hepatic, cardiac, pulmonary or hepatic disease, hx of epilepsy, neurologic disease, psychiatric disorders, and pregnant or lactating females.

Specimens:

Blood - Days 1, 2 and 5 of both periods

-1, 0(prior to dose), 1, 2, 3, 4, 6 and 8 hours after dosing.

Urine(intervals) - Days 1, 2 and 5 of both periods

-1 to 0(day 1 only), 0-1, 1-2, 2-4, 4-6 and 6-8 hours

Analytical Methods: Plasma and urine samples were analyzed by MSD for norfloxacin by a HPLC method utilizing fluorescence detection. Urine samples were analyzed by HPLC methodology specific for norfloxacin utilizing ultraviolet spectrophotometric detection. A representative standard curve and results of quality controls were provided.

Data Analysis: AUC was estimated using the trapezoid method through 8 hours. Renal clearance of norfloxacin was estimated from corresponding increments of urinary recovery and AUC.

Tables:

Table 17-1: Individual Plasma Concentrations

Table 17-2: Individual Cmax & Tmax values

Table 17-3: Individual AUC Values

Table 17-4: Individual Cmin Values

Table 17-5: Urine Concentrations

Table 17-6: Individual Urinary Recovery

Table 17-7: Individual Renal Clearance

Figure 17-1: Mean Plasma Concentrations

Results:

		Day 1(Dose 1)	Day 2(Dose 4)	Day 5(Dose 13)
Cmax (ug/ml)	mean	1.5	1.73	1.49
	S.D.	0.4	0.33	0.38
	range			
Tmax (hrs)	mean	1.3	1.8	1.5
	S.D.	0.5	1.0	0.6
	range			
AUC(0-8hrs) (ug*hr/ml)	mean	6.34	7.79	7.04
	S.D.	0.88	2.36	1.97
Renal Cl (ml/min)				
Sub # 102		216.9	---	171.3
Sub # 103		---	146.4	161.2

Firm's Pharmacokinetic Conclusions:

1. Too few volunteers (4) participated in the pharmacokinetic phase of this study to demonstrate to what degree norfloxacin accumulation might occur on a 400 mg q8h regimen. It appeared, however, that norfloxacin concentrations in plasma are lowest after the first dose and reach peak concentrations after the second day. Plasma concentrations did not increase thereafter.

Study Reference: #18; vol [REDACTED], pg: [REDACTED], study #13

Title: An Open, Triple Crossover Study to Compare the Bioavailability of Norfloxacin (MK0366) Following Oral Administration of 200 mg and 400 mg Market Image Tablets of MK0366 With a 400 mg Solution of MK0366 Given by Gavage in Healthy Volunteers.

Investigator/Site: Miguel Zinny, M.D.
Medical and Technical Research Assoc., Inc.
Needham, Massachusetts 02194

Objective: The Biopharmaceutic objective of this study was to compare the serum concentrations and urinary excretion profiles of norfloxacin following PO administration of 200 mg and 400 mg market image tablets of MK0366 and 430 mg solution of the drug given by nasogastric intubation. The clinical objectives included determining the effects of norfloxacin on stool Enterobacteriaceae and other gram-negative bacilli as well as determining antimicrobial activity in stool specimens.

Design: Open, single dose, randomized triple-crossover

Dosing: Each of the volunteers received each of the following treatments,

Tx A:

Tx B: 400 mg market image norfloxacin tablet(Kyorin-A formulation)

Tx C: 430 mg norfloxacin solution, given via a nasogastric tube
(The protocol originally specified 400 mg, however, the average assayed solution dose was 430 mg.)

Dosing occurred after a 10 hour fast. Normal meals were resumed 4 hours after each treatment. No other medications(including alcohol) was allowed from 1 week before study start until study completion.

Hydration: 6 ounces(240 ml) of water was given with the dose, followed by 8 ounces at 1, 2, 4, 6 and 8 hours after each treatment.

Subjects: 15 healthy male volunteers 21 years of age or older and within +/- 10% of their IBW for height and age according in the Metropol. Life Insur. Co. Stat Bull No. 40, 1959, participated in the study. Subjects were judged normal on basis of medical history, physical examination and clinical laboratory data. Exclusion Criteria: Hx of renal or hepatic disease, major systemic disorders including cardiac, GI and neurologic disorders, drug taking(including alcohol and salicylates) in the preceding seven days, hx of drug or food allergy and involvement in a drug study during the preceding 3 months.

Specimens:

Blood - 0(before dosing), 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours after dosing.

Urine(intervals) - minus 1 to 0(control), 0 to 1, 1-2, 2-3, 3-4, 4-6, 6-8, 8-12, 12-24 and 24-48 hours.

Rectal Swabs(for bacterial culture and bioassay determination) - before, 12 and 24 hours after dosing.

Stool(in 400 mg tablet group) - prestudy and up to 48 hours after dosing.

Analytical: Serum and urine samples were assayed for MK0366 by MSD Research Laboratories. Serum samples were analyzed by HPLC methodology specific for MK0366 utilizing fluorescence detection. Urine samples were analyzed by HPLC methodology specific for MK0366 utilizing ultraviolet spectrophotometric detection. Antimicrobial activity in stool specimens and rectal swabs were determined by Dr. Sheldon Landsman at The Infectious Disease Laboratory of the SUNY-Downstate Medical School.

Data Analysis: AUC(0-8 hrs) was measured using the trapezoid or sline method and extrapolated to infinity using renal clearance. Renal clearance of norfloxacin was estimated using corresponding increments of urinary recovery and AUC. The relative bioavailability of norfloxacin (tablet vs solution) was calculated using the method of Kwan and Till (submission ref #24) as modified by Hwang and Kwan (submission ref #25). The effective serum half-life was estimated from AUC(0-8) and AUC(0-infinity) as described in submission reference #23.

Results:

Parameter	430 mg SOLN	400 mg TAB
Urin Recov-48 hr-Unadjusted for dose (mg)		
Total		
Mean	121.91	105.14
S.D.	28.96	36.22
N	14	14
% Dose		
Mean	28.38	26.48
S.D.	6.74	9.12
N	14	14
AUC-Dose adjusted up to 430 mg (mcg/ml*hr)		
(0-8 hr)		
Mean	6.04	5.44
S.D.	1.90	2.65
N	15	15
Total Estimated(0-infin)		
Mean	7.58	7.1
S.D.	2.08	3.56
N	14	14
Cmax-Dose adjusted up to 430 mg (mcg/ml)		
Mean	1.87	1.62
S.D.	0.66	0.62
N	15	15
Tmax (hrs)		
Mean	0.70	1.03
S.D.	0.37	0.35
N	15	15
Effective Half-Life (hr) - 8 hour dosing interval		
Harmonic Mean	2.99	3.22
95% C.I.	2.03-3.47	2.92-3.59
Cum. Renal Clearance (ml/min)		
Mean	276.37	299.26
S.D.	71.31	94.96
N	15	15

Relative Bioavailability*

	200 mg Tab/Soln	400 mg Tab/Soln
Mean**	0.89	0.90
95% C.I.	0.70-1.14	0.72-1.13
Power (25% Difference)	0.77	0.78

* Based on the method of Kwan and Till as modified by Hwang & Kwan
submission references #24 & 25)

** Geometric mean

Relative Bioavailability Based on Ratio of Dose Adjusted AUC(0-infin)
400 Tab/400 Soln

Mean Ratio	0.987
S.D. +/-	0.49
C.V.	49.6 %
% w/in 75-125%	38.5% (5/13) 3 Hi, 5 Lo

Tables:

- Table 18-1 : Individual 8 hour AUC
- Table 18-2 : Individual Estimates of Total AUC(0-infin)
- Table 18-3 : Individual Cmax concentrations
- Table 18-4 : Individual Effective Half-Life for Accumulation
- Table 18-5 : Individual 48-hour Urinary Recovery
- Table 18-6 : Bioavailability Parameters
- Table 18-7 : Individual Estimates of Relative Bioavailability
- Table 18-8 : Individual Cumulative Renal Clearance
- Table 18-9 : Summary of Bioavailability Parameters

Firm's Conclusions:

1. Norfloxacin is equally bioavailable from the two tablet strengths studied.
2. Bioavailability from tablet formulations was 90% relative to the solution given by NG tube.

Study: Reference #19; Vol [REDACTED], pg [REDACTED]

Title: An Open Study to Determine the Pharmacokinetics of a Single Dose of Norfloxacin in the Elderly.

Investigator/Site: Dr. K.B. Martin, R.L. Brown
Bios(Consultation & Contract Research) Ltd.
Bagshot, Surrey, England

Objective: To document the safety and to obtain a pharmacokinetic profile of norfloxacin in healthy elderly subjects after a single 400 mg oral dose.

Design: Single oral dose

Dosing: 400 mg MK-366, PO ; film-coated tablet, MK-366;
formulation # 81-54-62, MSD

Drug was administered after an over-night fast. No food was allowed for 2 hours after the dose, at which time a standard breakfast was served. No medicine was allowed for 72 hours prior to the dose and no alcohol for 24 hours prior to the dose.

Hydration: Drug was administered with 150 ml of water, followed by 150 ml of water ("Perrier") at 1, 2, 3, and 4 hours after drug administration. Patients were instructed to consume 150 ml of water upon rising the morning of the study which began at 9:00 a.m.

Subjects: Six, healthy, elderly subjects(2 male, 4 female) between the ages of 67 and 74 years participated in the study. Subjects were reported to be neither grossly overweight nor underweight for their height and build. Basis for determination of normality, inclusion and exclusion criteria were provided. Subjects with a creatinine clearance of greater than or equal to 70 ml/min/1.73 meter squared were included in the study.

Specimens:

Blood - 0(control), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 and 24 hours after the dose.

Urine(intervals) - 0-1, 1-2, 2-3, 3-4, 4-6, 6-8, 8-12, 12-24 hours.

Analytical Methods: Norfloxacin concentration in plasma and urine was assayed at BIOS, LTD. by using HPLC methodology. It is reported that the method is specific and sensitive for norfloxacin and that calibration standards and quality control specimens were processed along with each batch of samples.

Data Analysis: Pharmacokinetic computations were done by Drug Metabolism Department, MSDRL. AUC was estimated using the trapezoid method and extrapolated to infinity using renal clearance. Renal clearance was derived from corresponding increments of urinary recovery and AUC. The effective serum half-life of norfloxacin was estimated according to the method of Kwan, et al(JPS).

Tables/Figures:

Table 19-1 : Individual Urin Recov and Renal Clearance

Table 19-2 : Individual AUC, Cmax, Tmax and Effective T1/2

Table 19-3 : Individual Demographic Data

Figure 19-1 : Mean Plasma Concentration vs Time Curve

Results:

Pharmacokinetic Parameter			
Urin Recov (0-infin)	Mean	90.5 mg	N=6
	S.D.	20.0	
% Dose Recov in Urin		22.3 %	N=6
		6.9	
Renal Clearance		154 ml/min	N=6
		15.7	
AUC(0-infin)		9.8 mcg*hr/ml	N=6
		2.8	
AUC(0-8)		7.5 mcg*hr/ml	N=6
		2.2	
Cmax		2.0 mcg/ml	N=6
		0.8	
Tmax		1.3 hr	N=6
		0.4	
Effective Half-life for Accumulation (8-hour dosing interval)		3.9 hr	N=6
		0.3	

Firm's Conclusions:

1. Pharmacokinetic parameters indicate elimination of norfloxacin may be slightly reduced in the elderly. This results in small increases in plasma levels and may also result in small increases in drug half-life.
2. Changes in norfloxacin disposition appear attributable to the slightly reduced renal function associated with a normal, elderly population.
3. No alteration of dosing regimen appears necessary for elderly subjects whose renal function is normal for this age group (creatinine clearance greater than or equal to 70 ml/min/1.73 meters squared).
4. A single 400 mg dose of norfloxacin appears safe in healthy, elderly subjects.

Study: Reference #20; vol [REDACTED] pg [REDACTED]

Title: An Open Study to Determine Serum Concentrations and Urinary Excretion Profile of a Single Oral Dose of MK-366 in Patients With Varying Degrees of Renal Dysfunction and in Subjects With Normal Renal Function

Investigator/Site: A. William Asscher
Welsch National School of Medicine
Renal Unit-Royal Infirmary
Cardiff, Wales

Objective: 1) To obtain serum concentration and urinary excretion data for a single 400 mg dose of norfloxacin in patients with varying degrees of renal dysfunction and to compare this data with data from subjects with normal renal function. 2) to obtain data for assisting in designing norfloxacin dosage regimens for patients with renal dysfunction. 3) to obtain information on the tolerability and safety of norfloxacin in this patient population.

Design: Open, Single-dose, subjects grouped according to renal function.

Dosing: 400 mg norfloxacin, PO, tablet

- Subject Groups:
- I Healthy subjects with normal renal function
ClCr greater than 100 ml/min/1.73 meters squared
 - II Patients with ClCr 31 to 80 ml/min/1.73 meters squared
 - III Patients with ClCr 10 to 30 ml/min/1.73 meters squared
 - IV Patients with ClCr less than 10 ml/min/1.73 meters squared
(patients not on hemodialysis)

Patients fast 1 for 8 hours prior to dosing. A light snack was allowed 2 hour after the dose followed by lunch 4 hours after the dose.

Hydration: Drug was administered with 250 ml of water, followed by 150 ml at 1, 2, 3, and 4 hours after the dose. Patients were also instructed to consume 250 ml of water upon rising the morning of the study which began at 0800.

Patients: 9 healthy volunteers and 18 patients with varying degrees of renal dysfunction participated in the study. Patients were required to be neither grossly overweight or underweight for height and body build. Criteria for inclusion and exclusion were provided. Subjects with concomitant mild hypertension and stable renal disease were accepted into groups II, III and IV. Subjects were excluded from participating in groups I, III and IV if any of the following conditions were present: 1. A disease, other than renal, which might influence the pharmacokinetics of the study drug, 2. treatment with antibiotics or other drugs which might affect the pharmacokinetics or assay procedure of the study drug.

Specimens:

Blood - 0 (pre-treatment), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, and 48 hours after the dose.

Urine (intervals) - 0 (pre-treatment), 0-1, 1-2, 2-3, 3-4, 4-5, 5-6, 6-8, 8-10, 10-24, 24-48 and 48-72 hours post dosing. It was noted that sampling times and collection intervals varied somewhat that specified in the protocol and above. Occasionally urine collections were made at intervals such as 0-2, 2-4, 4-6, 6-8, 8-10 (or 8-12), 10-24 (or 12-24), 24-48 and 48-72 hours.

Analytical Methods: Serum samples were analyzed for norfloxacin by a HPLC method utilizing fluorescence detection. Urine samples were analyzed for norfloxacin by a HPLC method utilizing an ultraviolet detector. It is reported that both methods are specific for norfloxacin and that standards and quality controls were analyzed with the unknown samples.

Data Analysis: AUC was calculated using the trapezoid or spline method and extrapolated to infinity using renal clearance. Renal clearance was estimated using corresponding increments of urinary recovery and AUC. The effective half-life of norfloxacin was estimated from methods of Kwan, et al (reference # 23).

Tables:

- Table 20-1: Individual Demographic Data
- Table 20-2: Individual and Mean Urin Recov, % Dose Exctd & Renal Cl
- Table 20-3: Individual and Mean AUC
- Table 20-4: Individual and Mean Cmax & Tmax
- Table 20-5: Individual and Mean Effective Half-life
- Figure 20-1: Mean Norfloxacin concentration-time profiles

Results:

Parameters*	ClCr (ml/min/1.73 meters squared)								
		Group I GT 100		Group II 31 - 80		Group III 10 - 30		Group IV LT 10	
			N		N		N		N
AUC(0-8h) mcg*hr/ml	Mean	5.38	8	7.62	5	9.18	4	7.79	4
	S.D.	1.93		2.00		2.41		5.31	
AUC(0-infin)		6.94	8	9.53	5	24.01	4	16.46	4
		2.73		2.47		13.49		14.52	
Cmax (mcg/ml)		1.51	9	1.91	6	1.70	6	1.70	6
		0.56		0.71		0.43		0.92	
Tmax (hr)		1.4	9	1.3	6	1.8	6	1.8	6
		0.4		0.4		1.1		1.2	
Effective T1/2 (hr) (Harmonic Mean); 8 hour dosing interval		3.47	8	3.38	5	6.57	4	6.4	4
Urin Recov(% Dose)		28.2	8	35.3	5	6.7	5	2.4	4
		12.8		9.2		4.1		1.1	
Renal Cl (ml/min)		297.1	8	264.5	5	17.8	4	14.7	5
		117.4		83.2		4.4		8.4	

* data taken from Bioanalytical-Biopharmaceutics Report

Statistical Evaluation

Parameter	Overall	Significant Pairwise Comparisons
Uri Recov(% Dose)	p LT* 0.0001	1,2 vs 3 p = 0.0002 1,2 vs 4 p = 0.0001
Renal Clearance	p LT 0.0001	1,2 vs 3 p = 0.0002 1,2 vs 4 p = 0.0001
C _{max}	NS (p GT* 0.2)	
T _{max}	NS (p GT 0.2)	
AUC(0-8hr)	NS (p GT 0.2)	
AUC(0-infin)	p = 0.03	1 vs 3 p = 0.004 2 vs 3 p = 0.04 1 vs 4 p = 0.06
Effective t _{1/2}	NS (p = 0.10)	

* - LT = less than, GT = greater than

Firm's Conclusions:

1. Based on the renal elimination rate of MK-366, no change is needed in the MK-366 regimen in subjects whose GFR exceeds 30 ml/min/1.73 meters squared.
2. When GFR is less than or equal to 30 ml/min/1.73 meters squared, the regular dose of MK-366 should be given once a day rather than twice a day.
3. The administered dose of norfloxacin appears to be safe in renally impaired patients.

Study: Reference # 21; vol [REDACTED], pg [REDACTED], study #59

Title: An Open, Two-Way Crossover Study to Compare the Bioavailability of Norfloxacin Following Oral Administration of a 400 mg Original Formulation Tablet of MK0366 with a 400 mg New Formulation Tablet of MK0366 in Healthy Volunteers.

Investigator/Site: Miguel Zinny, M.D.
Medical and Technical Research Assoc., Inc.
Boston, Mass 02130

Objective: a) To compare the plasma concentration profile and urinary excretion of norfloxacin following oral administration of a 400 mg new formulation tablet (MSD direct compression process) of MK0366 and a 400 mg old formulation tablet (Kyorin) of MK0366 and b) to determine the antimicrobial activity found in the stool after oral administration of the 400 mg new formulation tablet.

Design: Open, single dose, randomized, two-way crossover

Dosing: Each volunteer will receive,

- A. 400 mg norfloxacin tablet; new formulation (MSD direct compr)
- B. 400 mg norfloxacin tablet; original formulation (Kyorin-B)

Hydration: The dose was given with 8 oz (240cc) of water, followed by another 8 ounces of water at 1, 2, 4, 6, and 8 hours after the dose.

Treatments were separated by a 7 day washout period. Volunteers fasted from 10:00 PM of the night prior to dosing until 4 hours after the dose. No medications were allowed (including alcohol) from one week prior to initiation of the study until its completion.

Subjects: Twenty normal healthy male volunteers between 18 and 40 years of age entered and completed the study. Subjects were to have satisfied inclusion and exclusion criteria.

Specimens:

Blood: 0 (control), 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after dosing.

Urine (intervals): minus 1 to 0 (control), 0-1, 1-2, 2-3, 3-4, 4-6, 6-8, 8-12, 12-24, 24-48 hours.

Stool (only in subjects who received Tx A.): prestudy (control), and all specimens up to 48 hours after drug ingestion.

Analytical Methods: Serum and urine samples were assayed for MK0366 by MSD Research Laboratories. Serum samples were analyzed by HPLC methodology specific for MK0366 utilizing fluorescence detection. Urine samples were analyzed by HPLC methodology specific for MK0366 utilizing ultraviolet spectrophotometric detection. Antimicrobial activity in stool specimens were determined by Dr. Sheldon Landesman at The Infectious Disease Laboratory of the SUNY-Downstate Medical School.

Data Analysis: AUC(0-8 hrs) was measured using the trapezoid or spline method and extrapolated to infinity using renal clearance. Renal clearance of norfloxacin was estimated using corresponding increments of urinary recovery and AUC. The relative bioavailability of norfloxacin (MSD vs Kyorin) was calculated using the method of Kwan and Till (submission ref #24) as modified by Hwang and Kwan (submission ref #25). The effective serum half-life was estimated from AUC(0-8) and AUC(0-infinity) as described in submission reference #23.

Tables:

- Table 21-1 : Individual Plasma concns - Kyorin tablet
- Table 21-2 : Individual Plasma concns - MSD tablet
- Table 21-3 : Individual Cmax concns - Kyorin tablet & MSD tablet
- Table 21-4a : Individual Urine concns - Kyorin tablet
- Table 21-4b : Individual Urine concns - MSD tablet
- Table 21-5 : Individual Total Urin Recov - Kyorin tab & MSD tab
- Table 21-6 : Individual Relative Bioavailability
- Table 21-7 : Individual Cum Renal Cl and Total AUC - Kyorin & MSD Tabs
- Table 21-8 : Mean Pharmacokinetic Parameters - Kyorin & MSD Tabs
- Figure 21-1 : Mean Plasma Conc'n Profiles - Kyorin & MSD Tabs

Results:

Parameter	Kyorin Tab	MSD Tab	ANOVA	POWER
AUC(0-infinity) (mcg/ml*hr)				
Mean	7.82	6.94	NS	85.6
S.D.	2.53	1.69		
N	19	18		
Cmax (mcg/ml)				
Mean	1.56	1.54	NS	75.4
S.D.	0.48	0.42		
N	20	20		
Tmax (hrs)				
Mean	1.35	1.07	Sig(P LT 0.05)	
S.D.	0.43	0.37		
N	20	20		
Urin Recov - % of dose*				
Mean	27.9	27.0		
S.D.	8.9	8.5		
N	19	18		
Renal Clearance (ml/min)				
Mean	261.9	270.0		
S.D.	80.7	63.4		
N	20	18		

* Based on administered doses of 412 and 414 mg for the Kyorin and MSD formulations, respectively. Refer to Assay Content of norfloxacin in table "Dosage Form Characteristics", pg VII-01425, vol. 2.148.

Ratio of AUC(0-infin) MSD/Kyorin

Mean Ratio = 0.967
S.D. +/- 0.31
C.V. 32.4 %

% Within 75-125% -- 10/17 = 58.8 % ; 3 HI, 4 Lo

Relative Bioavailability (New-MSD/Old-Kyorin) as calculated by methods described above.

Geometric Mean	0.94	Power 20% Diff	0.81
N	17	25% Diff	0.99
95% C.I.	0.80 - 1.09		

* values for individual subjects were not provided.

Stool Samples

It is reported that peak norfloxacin activity in the stool occurred approximately 24 hours following ingestion and ranged from 348 to 1916 ug/gm stool.

Firm's Conclusions:

1. The 400 mg norfloxacin tablets formulated by the old Kyorin process and the new MSDRL direct compression process are similarly bioavailable (the new formulation is 94% as bioavailable as the old formulation).
2. Norfloxacin was absorbed faster following the ingestion of tablets manufactured by the new MSDRL process.

Comment: THE MSD PRODUCT UTILIZED IN THIS INVESTIGATION HAS A DIFFERENT COATING THAN THAT OF THE PROPOSED MARKETED TABLET. THE PROPOSED MARKETED TABLET WAS NOT INVESTIGATED IN ANY OF THE BA/PK STUDIES SUBMITTED BY THE FIRM.

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs and Biologics

Review by
1/18/85

action

Attachment I

Thurs
5/18
2:30

Date: April 2, 1985

To: Jerome P. Skelly, Ph.D.
Acting Director, Division of Biopharmaceutics, HFN-220

From: T. Greene Reed, M.D.
Medical Officer, HFN-815

Through: Edward Labor, M.D. *E. Labor 4/3/85*
Director, Division of Anti-Infective Drug Products, HFN-815

Subject: Norfloxacin-induced crystalluria (NDA 19-384)

This request is a follow-up to our Biopharmaceutics Division consultation request regarding norfloxacin, NDA 19-384 from Merck, Sharp and Dohme Research Laboratories which is now under review in this Division. We sent copies of the four volumes which contain pharmacokinetic data, Volumes No. ~~1, 2, 3, and 4~~ to your Division on March 11, 1985.

In your response to our consultation request, please include your comments regarding the possibility that norfloxacin might precipitate into crystals in the human kidney and cause obstruction there or elsewhere in the urinary tract.

Norfloxacin is an orally absorbed member of the quinolone group of antibacterial agents. Crystalluria has been reported in clinical studies of other members of this class. The presence of drug crystals with one member of this class that was never approved for marketing was so troublesome that several products which would acidify urine in an attempt to increase the drug's solubility were given concomitantly during clinical investigations. Later, the pharmaceutical manufacturer suggested that crystallization occurred after voiding while the urine cooled instead of before voiding within the urinary tract.

In animal studies of norfloxacin, crystalluria, consisting of the dihydrate and the magnesium salts of norfloxacin, occurred in rats at 200 and 600 mg/kg/day doses. Crystalluria occurred in beagle dogs given norfloxacin at 50, 150, and 300 mg/kg/day for 26 weeks but not in the 25 mg/kg/day dose group. The incidence was dose related. Three dogs, one in the 150 mg/kg/day and two in the 300 mg/kg/day dose groups, were found dead or were sacrificed due to urinary obstruction from drug crystals. Since emesis occurred in all dose groups in dogs and occurred frequently after dosing, one cannot be sure what proportion of the dose was retained and absorbed. The crystalluria in dogs and rats was attributed to low solubility of the drug in alkaline urine. Crystalluria decreased when urine was acidified by the administration of ammonium chloride. Drug crystals shaped as sea urchins and/or fine needles were occasionally seen in urine from dogs in each of the drug-treated groups.

Norfloxacin is a new drug entity. We are two months into the 180-day new-NDA time period and the application has high priority.

Theresa Greene Reed

cc Orig NDA 19-384, HFN-815, HFN-815/Reed, HFN-815/Buko, HFN-815/CSO 3585b

3/24

Correspondence

Reduced Enteral Absorption of
Ciprofloxacin in the Presence of
Antacids

Sir,

Ciprofloxacin, a new quinolone carboxylic acid derivative, has high in vitro activity against a wide range of pathogens including members of the family *Enterobacteriaceae* and *Pseudomonas aeruginosa* (1). The pharmacokinetics after oral administration of the drug are characterized by rapid absorption, good diffusion into the extracellular space, and elimination by biliary excretion, hepatic metabolism, glomerular filtration and tubular secretion (2).

In a study in fasting volunteers the absolute bioavailability ranged from 0.63 to 0.77, and the cumulative urinary excretion of unmetabolized drug in 24-hour-urine accounted for approximately 35% of the initial oral dose (2). To assess the effect of antacids on intestinal absorption of orally administered ciprofloxacin, we performed a randomized study in ten healthy volunteers (5 females, 5 males, mean age 30 years, mean body weight 67.5 kg) who were given 500 mg ciprofloxacin orally either in a fasting state or 24 h after administration of the antacid 10 x 600 mg Mg-OH + 900 mg Al-OH (Maalox). Serum and urine concentrations were determined by a bioassay and high performance liquid chromatography. The pharmacokinetic parameters were calculated using an open two-compartment model. Administration of the antacid led to a pronounced decrease of the peak serum concentration from a mean of 1.7 mg/l (range 1.3–2.6 mg/l) after ciprofloxacin alone to a mean of 0.1 mg/l (range 0.06–0.2 mg/l) after ciprofloxacin plus antacid ($p < 0.001$). The time after which the serum concentration peaked was only slightly prolonged (73 ± 13 min versus 87 ± 21 min). The cumulative urinary excretion of unmetabolized ciprofloxacin in 24-hour-urine after ciprofloxacin administered alone accounted for 24% (range 19–34%) of the administered dose, as against only 2.1% (range 0.9–4.7%) after prior administration of the antacid.

A possible explanation for the reduced absorption rate of ciprofloxacin administered after the antacid is that Mg^{++} or Al^{+++} chelates form. In fact, chelate complexes of the drug with Mg^{++} have been reported to reduce bactericidal concentrations of ciprofloxacin tested in nutrient broth against *Escherichia coli* K.L.16 (3). In addition, association constants for Mg^{++} complexes of nalidixic and oxolinic acid, analogous substances, were reported to be 3.0 and

3.3 respectively. The diminished absorption of ciprofloxacin seen in our study could be explained by a reduced rate of absorption of the Mg^{++} and Al^{+++} ciprofloxacin chelate complexes. To date it has been difficult to assess the significance of the chelates on absorption. Nevertheless, the pronounced effect of antacids on the bioavailability of ciprofloxacin should be considered if both these drugs are administered to a patient. Furthermore, all other new quinolone derivatives should be tested for such interaction with antacid drugs.

G. Höffken
K. Börner
P. D. Glätzle
P. Koeppe
H. Lode

Section for Chemotherapy and Infectious Diseases, Medical Department Klinikum Steglitz, Hindenburgdamm 10, 1000 Berlin 42, F.R.G.

References

1. Wiegand, W., Graefe, K. H., Gau, W., Förster, O., Beerman, D., Schicht, P.: Pharmacokinetics of ciprofloxacin after oral and intravenous administration in healthy volunteers. *European Journal of Clinical Microbiology* 1984, 3: 355–359.
2. Wise, R., Lockley, M., Webberly, M., Dew, J.: Pharmacokinetics of intravenously administered ciprofloxacin. *Antimicrobial Agents and Chemotherapy* 1984, 26: 208–210.
3. Ratcliffe, N. T., Smith, J. T.: Effects of magnesium on the activity of 4 quinolone antibacterial agents. *Journal of Pharmacy and Pharmacology* 1983, 33: 61.

In Vitro Activity of Ciprofloxacin
against Mycobacteria

Sir,

Ciprofloxacin is a new broad-spectrum quinolone derivative with activity against many gram-positive and gram-negative bacterial species. As little is known about its activity against mycobacteria we decided to investigate the antimycobacterial activity of ciprofloxacin in comparison with enoxacin, another quinolone derivative.

One hundred mycobacteria strains were tested for sensitivity to ciprofloxacin and 30 of these strains were also used for the comparative study with enoxacin. The 100 strains consisted of 69 strains of *Mycobacterium tuberculosis*, 12 of *Mycobacterium*

Appendix B

Tables and Figures

Table 1a

Quantitative Composition of Norfloxacin Tablets and Capsules Used in Clinical Studies of Bioavailability and Efficacy

Ingredient	Amount (mg) per Formulation			
	(A) Kyorin 400- mg Tablet	(B) Kyorin 400- mg Tablet	Merck 400-mg Direct Compression Tablet	Merck 400-mg Market Image Tablet
Core Anhydrous Norfloxacin	400.00	400.00	400.00	400.00

see above
for headings to Cols

Reference #	Study Details	Lot #	002-803	001-003	006-001	020-0017	005-002	
* 18 (Zinny)	SD, Rel BA = Soln study # 13		X	X				
* 21 (Zinny)	SD, BE study # 59				X	X		
* 16 (Zinny)	BD + steady state 400 mg BID (n=23)						X	
* 19 (Martin)	Elderly, SD	} identical formulations, different lot #'s : Most similar to Kyorin-A with the following differences, Made by MSD.					HPCellulose LF	4.5 mg/tab
* 20 (Asscher)	Renal fx, SD						Acrylic Resin	3.6 "
* 9 (Ozaki)	metabolism	formulation not given						
		clinical studies		clinical studies				
		} Most clinical (pivotal) studies appear to have been conducted with Kyorin prepared tablet formulations						
* 12 (Kumasaka)	Food	formulation not given						
* 17 (Zinny)	NO to steady state 400mg TID (n=4) for PK portion of study				X			

Table 1b

Study 59 - Dissolution Profiles

Kyorin 400 mg vs Merck 400 mg NOROXIN Tablets

pH 4 Acetate Buffer, Paddles, 50 RPM

Kyorin Formula - Lot 006-C01 (400 mg)

15 min 30 min 45 min 60 min

$\bar{x}$ = 59% 75% 85% 91%

Merck Formula - Lot 020-C017 (400 mg)

15 min 30 min 45 min 60 min

$\bar{x}$ = 98% 99% 99% 99%

Kyorin

MSD (blue)

Source : Kyorin

Kyorin

Kyorin

MSD-USA

[- "developed for
overseas markets"
- International Blue]

Dissolution Profiles

Merck NOROXIN Tablets 400 mg (Iron Oxide Colors)

pH 4 Acetate Buffer, Paddles, 50 RPM

Lot 029-C010

15 min 30 min 45 min

$\bar{x}$ = 102% 103% 103%

Lot 029-C012

15 min 30 min 45 min

$\bar{x}$ = 99% 100% 101%

MSD (pink)
029-C010

MSD (pink)
029-C012

MSD-USA

MSD-USA

- same composition
- Direct Compression
- "USA-pink"

Table 1b (cont)

~~2011~~

~~2011~~
 NOROXIN Tablets - Final Market Image 400 mg

Lot 0366 FCT 029-C013
 First Production Demonstration Lot

<u>Batch No.</u>	<u>Dissolution (30 minutes) %</u>	<u>Average</u>
850261A		90
850261B		90
850449A		93
850449B		96
850450A		94
850450B		90
850514A		94
850514B		96
850638A		94
850638B		95

% Dissolved

15 Min.

10 Min.

45 Min.

Mean	100	100	100
Rel. Std. Dev.	26	16	26

MSD

Ma

MSD Italy

MSD - USA

Source :

- Direct Compression
 - blue

- Direct Compression
 - USA pink

Table 2

~~XXXXXXXXXX~~
**Identity of All Oral Formulations Used in Clinical Studies of
 Norfloxacin Pharmacokinetics and Bioavailability**

Study Description	Pivotal (P) or Supportive (S)	Type of Formulations Used	Formulation and Batch Number	Batch Size	Number of Subject Studied
Multiple (EID) Dose Study (ref. #16, Study #65)	S	Kyorin Tablets (400 mg)	0366-PCT-005-C02		26
Multiple (TID) Dose Study (ref. #17, Study #66)	S	Kyorin Tablets (400 mg)	0366-PCT-006-C01		26
Tablet Bioavailability vs. Oral Solution (ref. #18, Study #13)	P	Kyorin Tablets (400 mg) Oral Solution	(A)0366-PCT-001-C01 0366-080-001-A01		5
Tablet Bioavailability; Kyorin Tablet vs. Merck Direct Compression Tablet (ref. #21, Study #59)	P	Kyorin Tablets (400 mg) Merck Direct Compression Tablet (400 mg)	0366-PCT-006-C01 0366-PCT-020-C017		20

Tablets from the particular batch of ~~XXXXXX~~ Kyorin tablets identified in Table I were used in pivotal clinical studies in acute uncomplicated urinary tract infections (Study #3, #6, #7) and acute urinary tract infections (Study #8, #10, #12). Likewise, tablets from the largest batch of 400-mg Kyorin tablets were used in key clinical studies in acute urinary tract infection (Study #28) and to suppress aerobic bowel flora in patients with granulocytopenia (Study #15, #19). Similarly prepared batches of Kyorin tablets were used in other key studies to define efficacy in these areas (#2, #5, #11, #9, #314, #505, #543, #521, #16, #17, #37, #39, #27, #25, #36, #40, #35, #554, #545, #535, #539, #549, #538, #565, #542, #564, #530, #518, #551, #534, #533, #541, #528, #537, #532, #519, #555, #548, #53, #24, #507, #508, #52, #509, #512, #509, #510, #511, #568, #567, #693, #573, #694, #574, #692), as well as in pivotal studies in acute bacterial gastroenteritis (#14, #588, #591, #595, #609, #590, #589, #634, #31) and in uncomplicated gonorrhoea (#30, #48, #49).

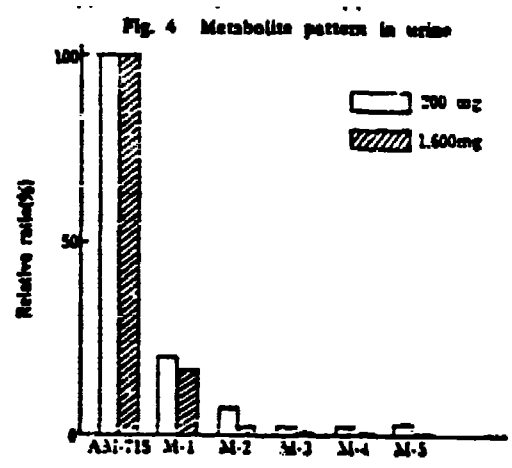
Table 9-4

Table 4 Urinary excretion of AM-715 and its metabolites after oral administration of 200mg of AM-715 to healthy human subjects (mg) -

Name	Time (hr.)	AM-715	M-1	M-2	M-3	M-4	M-5	Total	% of dose
OZ	0-2.5	30.7	4.2	1.3	0.2	<0.2	0.2		
	2.5-5	20.0	4.2	0.6	0.2	<0.1	0.2		
	5-9	11.0	2.2	0.3	0.1	<0.1	0.2		
	9-24	13.0	2.0	0.3	0.2	<0.3	0.4		
	Total	74.7	12.6	2.5	0.8	<0.7	1.0		
	Reduced to AM-715		11.8	2.2	0.3	<0.6	1.3	91.1	45.5
% of dose		37.0	6.0	1.1	0.3	<0.3	0.6		
SU	0-2.5	21.3	3.5	1.0	0.1	<0.2	0.2		
	2.5-5	7.4	2.2	0.6	0.07	<0.1	0.2		
	5-9	6.6	2.0	0.6	0.2	<0.3	0.3		
	9-24	9.2	2.3	1.1	0.4	<0.4	0.4		
	Total	44.5	10.0	3.3	0.8	<1.0	1.1		
	Reduced to AM-715		9.4	3.6	0.4	<0.9	1.4	60.2	30.1
% of dose		22.3	4.7	1.8	0.2	<0.5	0.6		
UC	0-2.5	2.1	0.6	0.1	0.1	0.1	<0.1		
	2.5-5	25.6	5.5	1.5	0.3	0.4	<0.4		
	5-9	9.6	2.0	0.8	0.2	0.2	0.3		
	9-24	3.6	1.6	0.5	0.5	0.5	0.5		
	Total	40.9	9.7	2.9	1.1	1.2	1.3		
	Reduced to AM-715		9.1	3.1	1.0	1.0	1.7	36.8	21.4
% of dose		20.5	4.6	1.6	0.5	0.5	0.8		

$\bar{X} = 26.6$ 5.1 1.5 0.33 ≤ 0.5 0.7 34.7
 S.D. 9.05 0.78 0.36 0.15 0.1 9.4
 range

Figure 9-3



This figure shows the mean ratio of urinary excretion of each metabolite during 24 hours when the ratio of excretion (% of dose) of unchanged form was taken as 100.

Table 9-5

Table 5 Urinary excretion of AM-715 and its metabolites after oral administration of 1,600mg of AM-715 to healthy human subjects (mg)

Name	Time (hr.)	AM-715	M-1	M-2	M-3	M-4	M-5	Total	% of dose
SU	0-2.5	36.1	3.6	0.8	1.3	0.8	0.1		
	2.5-5	116.0	18.2	3.0	0.8	0.3	0.4		
	5-9	67.5	13.1	2.8	1.0	0.2	1.0		
	9-24	68.6	17.6	5.0	0.8	0.4	1.4		
	Total	288.2	52.5	12.6	3.8	1.7	2.9		
	Reduced to AM-715		49.8	13.8	2.7	1.6	3.6	359.7	72.4
	% of dose	18.0	3.1	0.9	0.2	0.01	0.2		
SA	0-2.5	95.3	7.6	0.3	0.3	0.9	0.2		
	2.5-5	308.2	17.2	3.7	1.3	0.9	0.6		
	5-9	35.4	17.8	1.5	0.8	0.2	0.3		
	9-24	98.3	35.4	3.6	0.9	0.4	0.2		
	Total	537.2	78.6	9.1	3.3	2.4	1.3		
	Reduced to AM-715		74.2	10.0	3.8	1.7	1.6	648.5	40.5
	% of dose	34.8	4.6	0.6	0.2	0.1	0.1		
AO	0-2.5	48.6	9.3	0.06	0.2	0.05	0.05		
	2.5-5	62.7	21.9	0.3	0.2	0.09	0.1		
	5-9	130.2	10.1	2.4	0.8	0.2	0.9		
	9-24	101.3	14.9	3.8	1.1	0.4	0.9		
	Total	342.8	56.2	6.6	2.3	0.7	2.0		
	Reduced to AM-715		53.1	7.2	2.2	0.7	2.4	408.4	25.5
	% of dose	21.4	3.3	0.5	0.1	0.04	0.2		
- II	0-2.5	21.1	2.3	1.0	0.1	0.06	0.03		
	2.5-5	96.0	22.8	2.4	0.4	0.2	0.1		
	5-9	75.2	16.6	2.5	0.4	0.1	0.1		
	9-24	94.1	14.8	2.5	0.8	0.4	0.8		
	Total	286.4	56.5	8.4	1.7	0.8	1.0		
	Reduced to AM-715		53.4	4.5	1.6	0.7	1.3	347.9	21.7
	% of dose	17.9	3.3	0.3	0.1	0.05	0.08		

$\bar{X}$ = 23.0 3.6 0.57 0.15 0.05 0.15 27.5
 S.D. 8.0 0.7 0.25 0.06 0.04 0.06 8.8

Fig. 5 Urinary excretion rate of AM-715 and its metabolites after oral administration of 1,600mg of AM-715

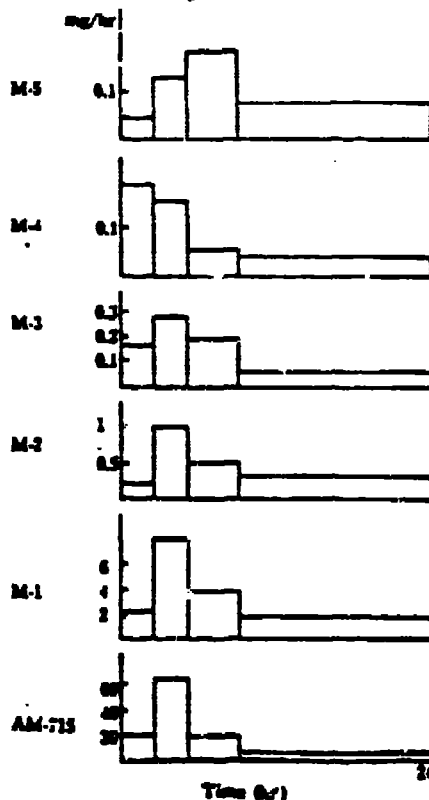


Figure 12-1

Fig-88 Urinary excretion of AM-715 in healthy male adults (200mg/person, p.o. single administration)

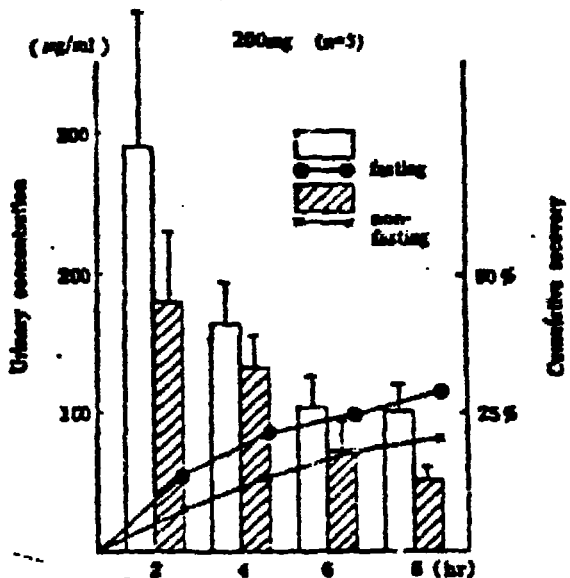


Table 12-1

Group	Volunteer	Urinary excretion				Recovery		
			0-2	2-4h	4-6h		6-8h	
fasting	O.U.35y.M.	(ug/ml)	640	164	80	50	41.1%	
		mg	25.6	8.2	4.8	2.5	20.6%	
	T.O.31y.M.	ug/ml	88	178	66	128	70.6%	
		mg	34.5	34.6	11.9	9.6	35.3%	
	Y.K.28y.M.	ug/ml	84	48	82	156	37.5%	
		mg	10.9	10.6	8.2	7.8	18.7%	
	H.N.26y.M.	ug/ml	480	184	180	78	61.5%	
		mg	36.8	11.0	9.0	4.7	30.7%	
	H.K.26y.M.	ug/ml	300	240	102	108	72.5%	
		mg	25.0	24.0	8.1	8.4	36.2%	
	non-fasting	O.U.35y.M.	ug/ml	240	104	46	88	41.6%
			mg	21.6	8.2	6.0	8.8	20.9%
T.O.31y.M.		ug/ml	36	102	52	30	34.4%	
		mg	10.6	10.2	9.4	4.2	17.2%	
Y.K.28y.M.		ug/ml	312	220	88	64	36.4%	
		mg	8.4	13.2	7.4	6.4	18.2%	
H.N.26y.M.		ug/ml	80	188	142	52	36.4%	
		mg	6.0	15.6	9.9	2.9	18.2%	
A.K.26y.M.		ug/ml	220	82	32	32	30.2%	
		mg	36.4	16.1	4.8	3.2	23.1%	

$\bar{x}$ 181.6 134.8 72 53.2
 S.D. 109.5 53.8 44.2 24.1

$\bar{x}$ = 28.3
 S.D. = 8.19
 CV = 28.9

$\bar{x}$ = 19.9
 S.D. = 3.2
 CV = 16.8%

Table 12-2

Table 1 Plasma levels of AM-715 in healthy male adults
(200mg/po, p.o. single administration)

Group	Volunteer	Serum concentration ($\mu\text{g/ml}$)					
		1/2	1	2	4	6	8 (hr)
fasting	O.U. 35y.M.57kg.	0.60	0.64	0.30	0.16	≤ 0.14	≤ 0.14
	T.O. 31y.M.69kg.	≤ 0.14	0.15	0.44	0.34	0.21	0.20
	Y.K. 28y.M.65kg.	≤ 0.14	0.30	0.52	0.20	0.16	0.15
	H.N. 26y.M.68kg.	0.31	0.40	0.27	≤ 0.14	≤ 0.14	≤ 0.14
	A.K. 27y.M.67kg.	≤ 0.14	0.21	0.29	0.17	≤ 0.14	≤ 0.14
non-fasting	O.U. 35y.M.57kg.	0.43	0.55	0.18	0.15	≤ 0.14	≤ 0.14
	T.O. 31y.M.67kg.	≤ 0.14	≤ 0.14	0.20	≤ 0.14	≤ 0.14	≤ 0.14
	Y.K. 28y.M.65kg.	≤ 0.14	0.30	0.42	0.18	0.17	0.15
	H.N. 26y.M.68kg.	≤ 0.14	0.15	0.23	0.15	≤ 0.14	≤ 0.14
	A.K. 26y.M.67kg.	≤ 0.14	0.21	0.16	≤ 0.14	≤ 0.14	≤ 0.14

Purgand

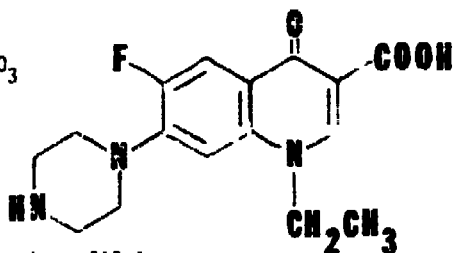
Figure 1

Physical and Chemical Information for Norfloxacin.

Physical and Chemical Information

Structure:

$C_{16}F_1H_{18}N_3O_3$

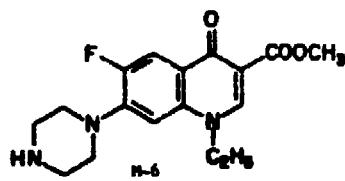
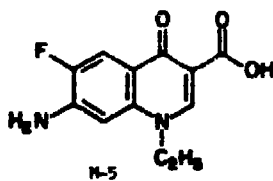
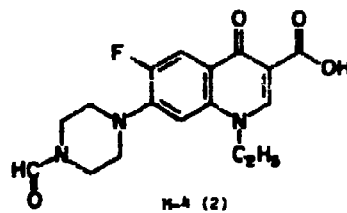
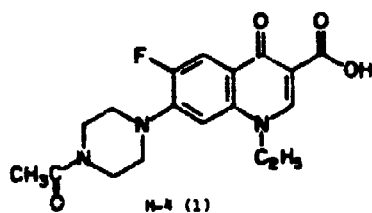
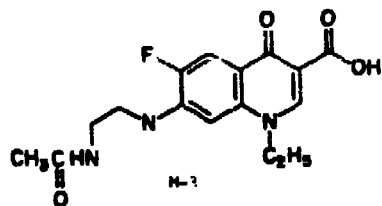
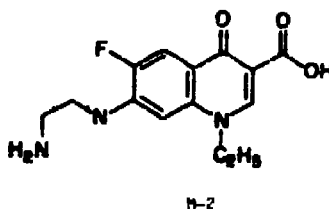
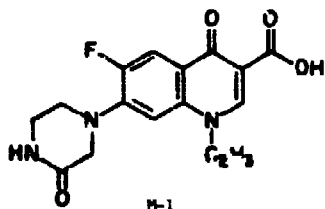


Molecular Weight: 319.3

Description: White odorless powder

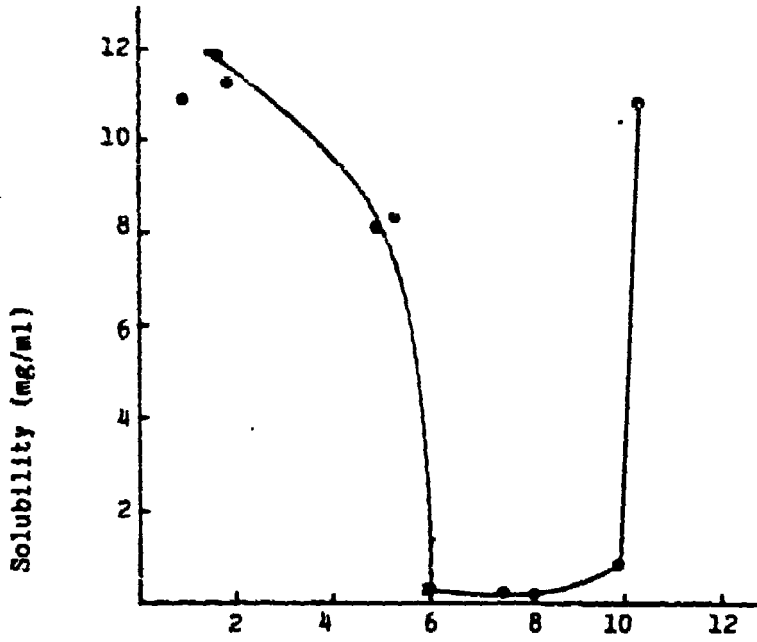
Melting Point: 220-224°C

Metabolites of Norfloxacin.

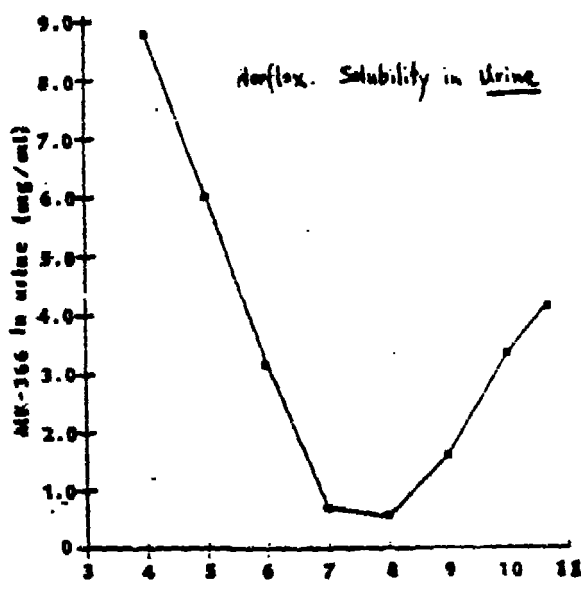


Norfloxacin Solubility in Water (pH 1-10) at 2°C.

Figure 2a

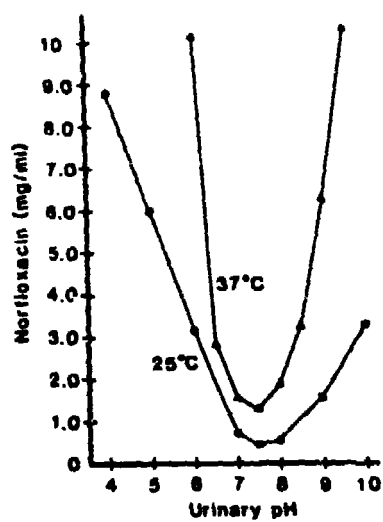


from vol 2.145, pg VII-00148



from vol. 2.146
 pH 25°C
 MK-00532

Figure 2b



Effect of pH and temperature on urinary solubility of norfloxacin.

Figure 2c

Table 3

TABLE 3 Urinary excretion of AM-715 after oral administration of 200 mg of AM-715 in humans

Treatment	Subject no.	Clearance period (h)	Creatinine clearance (ml/min)	AM-715 clearance (ml/min)	Clearance ratio	Urinary recovery (% dose)*
Without probenecid	1	3-5	199.2	290.7	2.7	19.9
		5-7	108.2	190.0	1.8	
		7-9	139.9	301.7	2.2	
	2	3-5	100.1	170.0	1.7	23.8
		5-7	146.7	441.2	3.0	
		7-9	147.0	345.1	2.4	
	3	3-5	121.8	225.5	1.9	33.1
		5-7	154.0	501.3	3.3	
		7-9	117.8	359.3	3.1	
	4	3-5	145.0	363.6	2.5	51.9
		5-7	106.2	524.9	4.9	
		7-9	112.6	398.1	3.5	
	5	3-5	82.1	280.0	3.4	11.2
		5-7	161.6	633.6	3.9	
		7-9	111.8	ND ^b	ND	
Mean ± S.E.	3-5	111.6 ± 10.6	266.0 ± 32.6 (72.1)	2.4 ± 0.3	28.0 ± 6.9 (S.D. = 15.5)	
	5-7	135.3 ± 11.7	387.5 ± 65.3 (146)	3.4 ± 0.5		
	7-9	125.8 ± 7.4	351.1 ± 19.9 (37.6)	2.8 ± 0.3		
				$\bar{x}$ 334.9 ± 62.4 (S.D.)		
With probenecid	1	3-5	146.4	252.6	1.7	10.7
		5-7	140.2	184.2	1.3	
		7-9	131.0	226.9	1.7	
	2	3-5	133.8	160.2	1.2	12.4
		5-7	139.0	141.6	1.0	
		7-9	123.6	216.7	1.8	
	3	3-5	239.1	139.5	0.6	17.4
		5-7	104.0	138.3	1.3	
		7-9	115.7	173.3	1.5	
	4	3-5	101.3	121.6	1.2	20.0
		5-7	104.9	104.0	1.0	
		7-9	102.7	111.5	1.1	
	5	3-5	129.7	150.2	1.2	8.9
		5-7	111.4	153.2	1.4	
		7-9	121.7	187.6	1.5	
Mean ± S.E.	3-5	150.1 ± 23.4	164.5 ± 22.9	1.2 ± 0.2	13.9 ± 2.1 (S.D. = 4.7)	
	5-7	119.9 ± 8.1	144.3 ± 12.9	1.2 ± 0.1		
	7-9	118.9 ± 4.7	181.8 ± 19.7	1.5 ± 0.1		

* Recovery of AM-715 12 h after administration.

^b ND, No detectable serum concentration of AM-715.

$\bar{x}$ 163.6 ± 18.6 (S.D.)

Figure 3

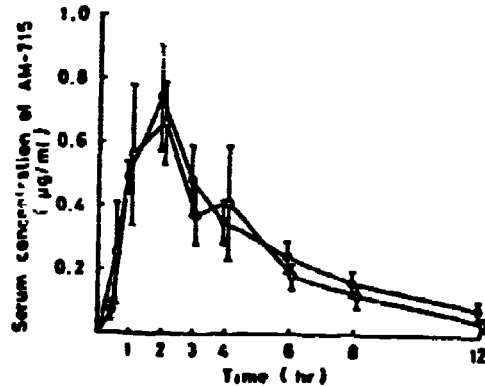
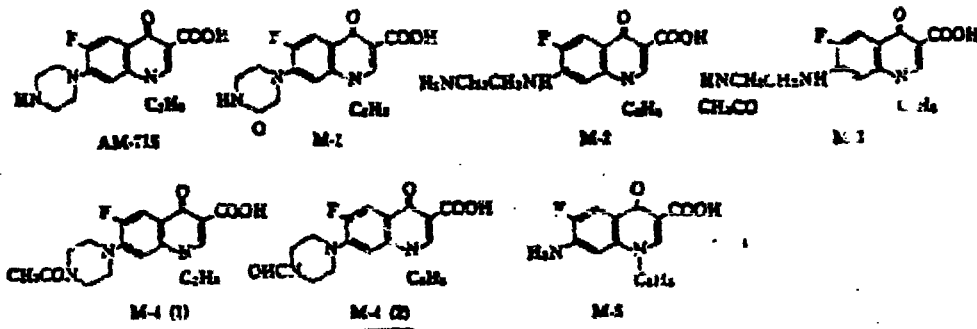


Figure 3. Mean ± standard error serum concentration of AM-715 after oral administration of 200 mg of AM-715 without (O) and with (●) probenecid in human volunteers.

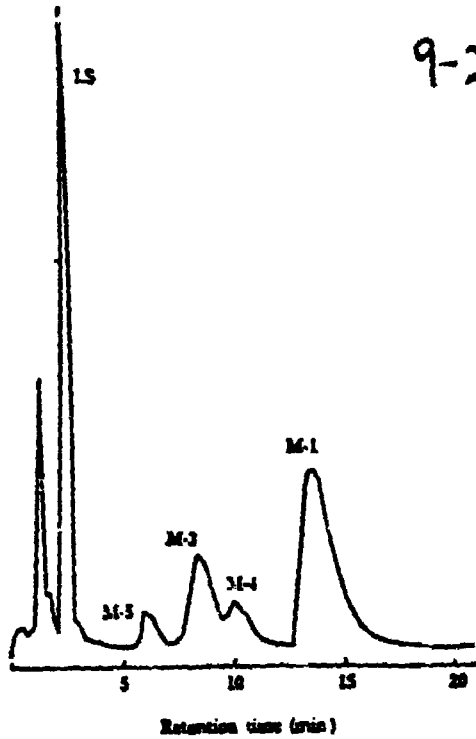
Figure 9-1



Figure

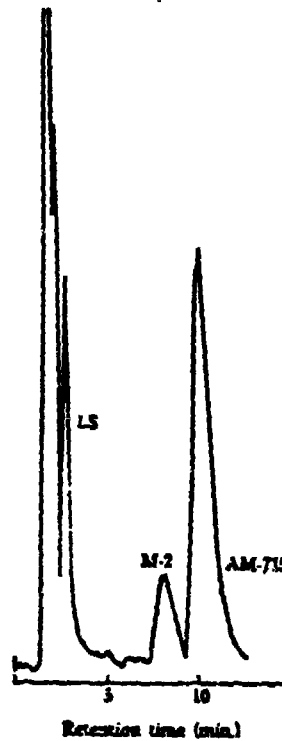
9-2a

Figure 9-2a Chromatogram of M-1, M-3, M-4, M-5 and M-6 in urine sample



9-2b

Figure 9-2b Chromatogram of AM-715 and M-2 in urine sample



9-2c

Figure 9-2c Calibration curve of AM-715 and its metabolites

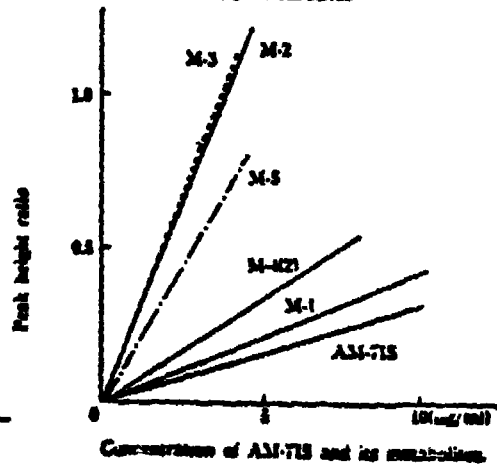


Table 9-1

Table 1 Serum concentration of AM-715 after oral administration of 1,000mg of AM-715 to healthy human subjects (ug/ml)

Name	Time after administration (hr.)							
	0.5	1	2	3	4	6	8	12
SU	--	3	11	13	10	8	5	3
SA	6	11	15	6	6	4	3	3
AO	4	5	8	6	6	4	4	2
IT	--	4	9	7	7	4	4	2
Mean	2.5	6	10.8	8	7.3	5	4	2.5
SD	2.6	3	2.6	2.9	1.7	1.7	0.8	0.5

Table 9-2

Table 2 Urinary concentration of AM-715 and its metabolites after oral administration of 200mg of AM-715 to healthy human subjects (ug/ml)

Name	Time (hr.)	AM-715	M-1	M-2	M-3	M-4	M-5
OZ	0-2.5	192	26	8	1	<1	1
	2.5-5	152	32	5	1	<1	2
	5-9	80	16	2	1	<1	1.4
	9-24	20	3	0.5	0.5	<0.5	0.6
SU	0-2.5	30	8	2	0.3	<0.5	0.4
	2.5-5	32	10	2.5	0.3	<0.5	0.7
	5-9	11	3	1	0.3	<0.5	0.5
	9-24	11	3	1.4	0.5	<0.5	0.5
UC	0-2.5	8	2	0.5	0.5	<0.5	<0.5
	2.5-5	42	9	2.5	0.5	<0.5	<0.6
	5-9	32	7	2.5	0.5	<0.5	0.9
	9-24	4	2	0.5	0.5	<0.5	0.5

Table 9-3

Table 3 Urinary concentration of AM-715 and its metabolites after oral administration of 1,000mg of AM-715 to healthy human subjects (ug/ml)

Name	Time (hr.)	AM-715	M-1	M-2	M-3	M-4	M-5
SU	0-2.5	233	23.2	5	8	5	0.6
	2.5-5	358	36.0	9	3	1	1.2
	5-9	409	79.4	17	6	1	6.0
	9-24	81	20.7	8	1	0.5	1.6
SA	0-2.5	681	34.3	2	2	6	1.3
	2.5-5	717	41.4	9	3	1	1.4
	5-9	205	65.9	6	3	1	0.3
	9-24	139	49.8	5	0.4	0.5	0.3
AO	0-2.5	312	97.9	0.6	2	0.6	0.5
	2.5-5	413	125	2	2	0.6	0.5
	5-9	326	25.3	6	2	0.5	0.6
	9-24	135	19.9	5	1	0.5	1
IT	0-2.5	189	21	9	1	0.5	0.3
	2.5-5	271	64	7	1	0.5	0.3
	5-9	259	37	9	1	0.5	0.4
	9-24	114	17.9	5	1	0.5	1

Purple

Purged

purged

Purple ✓

purged

Purged

Purged

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purged

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Table 16-1

Below is a listing presenting the demographic data of the 27 volunteers at entry into this study.

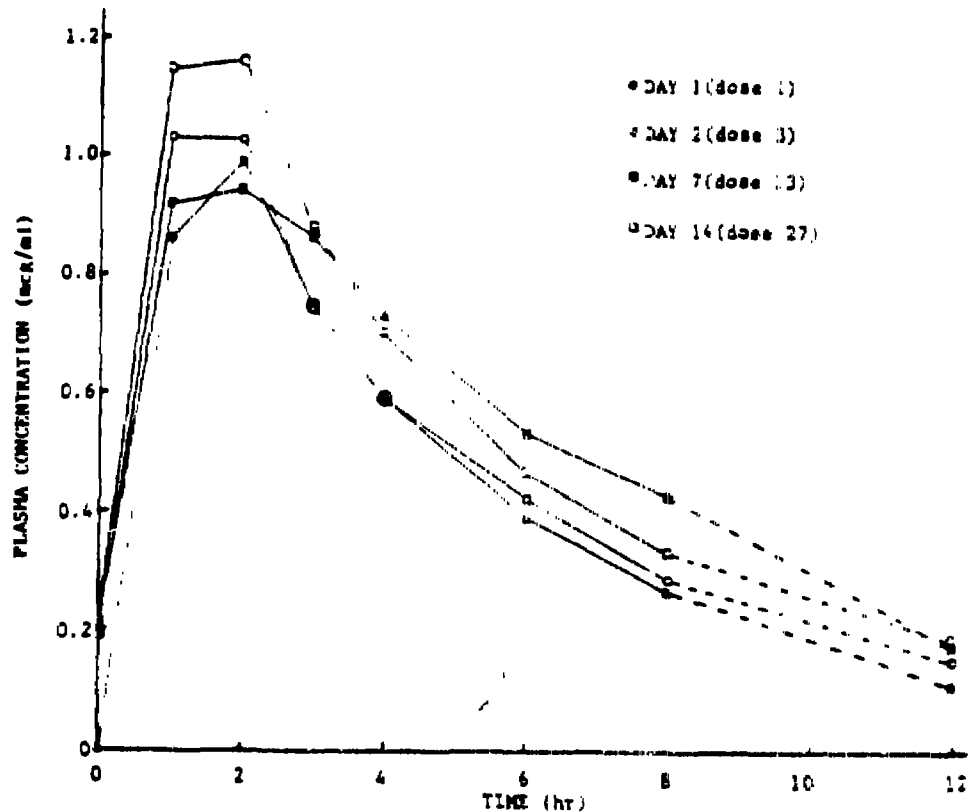
VOLUNTEER DEMOGRAPHIC DATA

Vol. No.	Sex	Age (yrs.)	Height (in.)	Weight (lbs.)	RACE
1	M	41	71	157	Caucasian
2	M	29	69	160	Caucasian
3	M	21	71	155	Caucasian
4	M	21	71	202	Caucasian
5	M	39	70	170	Caucasian
6	M	24	72	179	Caucasian
7	M	31	65	148	Caucasian
8	M	23	70	150	Caucasian
9	M	21	69	166	Caucasian
10	M	44	70	155	Caucasian
11	M	20	76	180	Caucasian
12	M	21	71	155	Caucasian
13	M	45	72	159	Black
14	M	36	72	163	Caucasian
15	M	20	76	190	Caucasian
16	M	34	68	146	Caucasian
17	M	24	74	170	Caucasian
18	M	19	71	150	Caucasian
19	M	31	72	204	Caucasian
20	M	24	71	162	Caucasian
21	F	31	51	124	Caucasian
22	M	24	70	171	Caucasian
23	F	34	68	164	Caucasian
24	F	50	67	164	Black
25	M	21	68	143	Caucasian
26	M	19	66	148	Caucasian
27	M	31	69	155	Caucasian

Ranges: Age - 19 - 50 years
Height - 61-76 inches
Weight - 124-204 pounds

Figure 16-1

Mean Norfloxacin Plasma Concentration Profiles



Purged

Table 16-2

Individual 12-Hour Urinary Excretion (U₀₋₁₂) of Norfloxacin Following Twice Daily Administration

$$\% \text{ of Dose} = \frac{X}{400} = (\quad)$$

U₀₋₁₂ (mg) following 1st Dose on Day . . .

Subject No.	1 (% Dose)	2	7	14
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				

	Day 1	Day 7	Day 14
1	Estimated from cumulative urinary excretion profile.		
	using all data (n=26)	(n=26)	(n=25)
	$\bar{x} = 16.5$	$\bar{x} = 17.75$	$\bar{x} = 18.9$
	S.D. = 6.7	S.D. = 6.2	S.D. = 8.2
	C.V. = 40.6%	C.V. = 34.9%	C.V. = 43.4%
	* Range:	Range:	Range:

Table 16-3

Individual Cumulative Renal Clearance (V_{Cl,R}) of Norfloxacin Following Twice Daily Administration

V_{Cl,R} (ml/min) Following First Dose on Day . . .

Subject No.	1	2	7	14
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
Mean (S.D.)	176.6 (112.0)	330.4 (39.0)	239.6 (34.5)	266.0 (18.6)

Purged

Purged

Table 16-4 cont



Individual Plasma Concentrations (C_p) of Norfloxacin
Following the First Drug Dose on Several Days
During a 14-Day, 400 mg Tablet B.I.D. Regimen

Subj. No. (Period)	Day	C_p (mcg/ml) at . . . hr						AUC(0-12) by Trapezoid Method
		0	1	2	3	6	12	
19 (2)	1							
	2							
	7							
20 (1)	1							
	2							
	7							
	14							
21 (2)	1							
	2							
	7							
	14							
22 (2)	1							
	2							
	7							
	14							
23 (2)	1							
	2							
	7							
	14							
24 (1)	1							
	2							
	7							
	14							
25 (1)	1							
	2							
	7							
	14							

Subj. No. (Period)	Day	C_p (mcg/ml) at . . . hr					
		0	1	2	3	6	12
26 (2)	1						
	2						
	7						
	14						
27 (2)	1						
	2						
	7						
	14						

$\bar{x}$ = 6.71
 S.D. = 2.82
 C.V. = 42 %
 Range =

Purged

Table 16-5

Individual Peak Plasma Concentrations (C_{max}) of Norfloxacin
Following Twice Daily Administration

Subject No.	C_{max} (mcg/ml) Following 1st Dose on Day . . .			
	1	2	7	14
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
Mean (S.D.)	1.15 (0.41)	1.18 (0.55)	1.27 (0.50)	1.35 (0.59)

- 1 No blood samples taken as per protocol.
- 2 Unusually low plasma concentrations.
- 3 Dose not administered.

Table 16-6

Individual Times (T_{max}) that Peak Plasma Concentrations of
Norfloxacin Occurred Following Twice Daily Administration

Subject No.	T_{max} (hr) Following 1st Dose on Day . . .			
	1	2	7	14
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
Mean (S.D.)	1.5 (0.6)	2.2 (1.6)	2.1 (2.0)	1.9 (1.6)

- 1 Blood samples not taken.
- 2 Unusually low plasma concentrations.
- 3 Dose not administered.

Purged

Table 16-7

Individual Minimum Plasma Concentrations (C_{min}) of Norfloxacin Following Twice Daily Administration

Subject No.	C_{min} (mcg/ml) following dose no. . . .							
	Pre	1	2	3	12	13	26	27
1	0							
2	0							
3	0							
4	0							
5	0							
6	0							
7	0							
8	0							
9	0							
10	0							
11	0							
12	0							
13	0							
14	0							
15	0							
17	0							
18	0							
19	0							
20	0							
21	0							
22	0							
23	0							
24	0							
25	0							
26	0							
27	0							
Mean	0	.07	.20	.15	.20	.17	.23	.18
(S.D.)		(.09)	(.11)	(.05)	(.14)	(.11)	(.21)	(.13)

- 1 No blood samples taken as per protocol.
- 2 Dose not administered.
- 3 Unusually low plasma concentrations.

Table 16-8

Individual 12-Hour Area Under the Plasma Concentration-Time Curve, $[AUC]_{12}^{12}$, for Norfloxacin Following Twice Daily Administration

Subject No.	$[AUC]_{12}^{12}$ (mcg-hr/ml) following the first dose on Day . . .			
	1	2	3	4
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
Mean	3.23	3.69	6.57	6.57
(S.D.)	(2.02)	(1.99)	(2.99)	(2.56)

- 1 $[AUC]$ estimated using norfloxacin half-life.
- 2 Drug not detectable at 12 hr. $[AUC]_0^{12}$ only. Excluded from mean.
- 3 Unusually low plasma concentrations. No estimate of $[AUC]$.
- 4 Dose not administered.

APPL #: 019384

FIRM: MSD RES LABS

4 OF 4

TRADE NAME: NOROXIN (NORFLOXACIN) 400MG TABLET

GENERIC NAME: NORFLOXACIN

Table 16-9

LISTING OF VOLUNTEERS WHO RECEIVED MEDICATIONS
OTHER THAN STUDY DRUG

<u>Vol. No.</u>	<u>During Assigned Regimen</u>	<u>Period No.</u>	<u>Medication</u>	<u>Reason for Use</u>
2	Norfloxacin	1	Anusol	Hemorrhoids
	Placebo	2	Haley's MO	Laxative
	Placebo	2	Ducolax	Laxative
10	Placebo	2	Tylenol	Headache
22	Norfloxacin	1	Mylanta	Burning stomach
16	Placebo	1	Penicillin VK	Strep throat
19	Placebo & Norfloxacin	1 & 2	Lortisporin	Boil in external right meatus
	Placebo	1	Tylenol	Headache
20	Post Study	*	Tetracycline	Palpable lymph node
24	Placebo	2	Tylenol	Sore throat & earache

* Seven days after terminating Period 1 and being dropped from study.

Norfloxacin (ME-366)

Table 16-10

Norfloxacin (ME-366) Flame Assay

Validation Data			
Concentration in mcg/ml	Number of Replicates (n)	Coefficient of Variation (CV)	Average Peak Height Ratio
0.05	6	8.0%	0.096
0.10	6	4.7%	0.242
0.25	6	3.9%	0.590
0.50	6	2.9%	1.33
1.0	6	7.5	2.28
2.5	6	4.6%	5.74

Quality Controls			
Actual Concentration (mcg/ml)	Average Concentration (mcg/ml)	Number of Replicates (n)	Coefficient of Variation (CV)
0.50	0.532	12	6.7%
2.0	2.04	12	7.2%

Table 16-11

Norfloxacin (ME-366) Drine Assay

Validation Data*

Concentration in mcg/ml	N	Run I		Run II	
		Coefficient of Variation (CV)	Coefficient of Variation (CV)	Average Peak Height Ratio	Coefficient of Variation (CV)
500	6	1.5%	6.4%	36.1	
250	6	2.1%	1.2%	19.9	
100	6	1.8%	1.3%	7.37	
50	6	4.0%	0.61%	4.10	
25	6	1.9%	0.83%	1.96	
10	6	2.8%	2.3%	0.655	
5	6	2.2%	2.5%	0.470	
1	6	---	9.6%	0.090	

* Samples were received in two shipments 1/3/84 and 3/16/84. A separate validation and quality controls were used for each shipment.

Quality Controls

Run Number	Actual Concentration (mcg/ml)	Calculated Concentration (mcg/ml)	N	Coefficient of Variation (CV)	
				Actual Concentration (mcg/ml)	Calculated Concentration (mcg/ml)
I	90.5	92.1	5	2.3%	
	20.1	21.7	5	9.5%	
II	135.0	133.1	4	2.5%	
	12.0	11.97	4	11.9%	

Purged

Table 17-1

Individual Plasma Concentrations (C_p) of Norfloxacin Following Administration of 400 mg Every 8 Hours for 5 Days

Subj. No. (Period)	Day	C_p (mg/ml) at . . . hr						
		0	1	2	3	4	6	8
101 (1)	1							
	2							
	3							
102 (2)	13							
	14							
	17							
103 (1)	1							
	2							
	5							
126 (1)	1							
	3							
	5							
Mean	1		1.74	1.37	0.994	.746	.533	.364
	2	.622	1.28	1.46	1.29	1.02	.707	.518
	5	.771	1.32	1.41	1.01	.824	.626	.436

Table 17-2

Individual Maximum Plasma Concentrations (C_{max}) and Times These Peaks Occurred (t_{max}) for Norfloxacin Following Administration of 400 mg Every 8 Hours for 5 Days

Subject No.	Day 1 (Dose 1)		Day 2 (Dose 4)		Day 3 (Dose 13)	
	C_{max} (mg/ml)	t_{max} (hr)	C_{max} (mg/ml)	t_{max} (hr)	C_{max} (mg/ml)	t_{max} (hr)
101						
102						
103						
126						
Mean (S.D.)	1.50 (0.40)	1.3 (0.5)	1.73 (0.33)	1.8 (1.0)	1.49 (0.38)	1.5 (0.6)

Table 17-3

Individual 8-Hour Area Under the Plasma Concentration-Time Curve, $[AUC]_0^8$, for Norfloxacin Following Administration of 400 mg Every 8 Hours for 5 Days

Subject No.	$[AUC]_0^8$ (mg·hr/ml) Following First Dose on Day . . .		
	1	2	3
101			
102			
103			
126			
Mean (S.D.)	6.34 (0.88)	7.79 (2.36)	7.04 (1.97)

Figure 17-1

Mean Plasma Concentrations of Norfloxacin

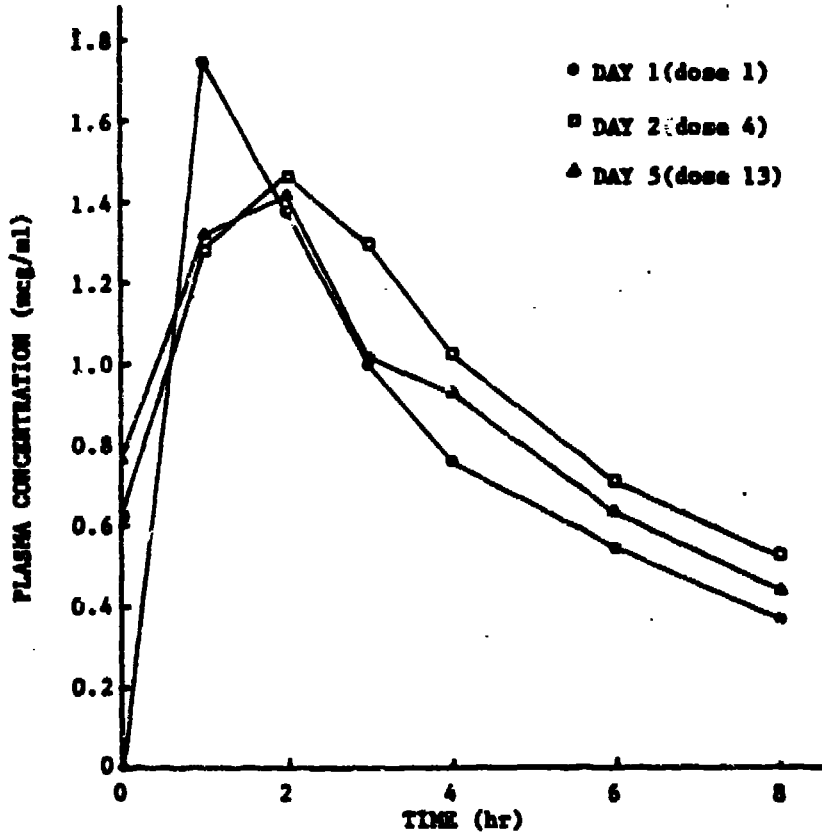


Table 17-4

Individual Minimum Plasma Concentrations (C_{min}) of Norfloxacin Following Administration of 400 mg Every 8 Hours for 5 Days

Subject No.	C_{min} (mcg/ml) Following Dose No. . . .					
	0	1	3	4	12	13
101	0					
102	0					
103	0					
<u>126</u>	<u>0</u>					
Mean (S.D.)	0	.36 (.06)	.62 (.21)	.52 (.29)	.77 (.78)	.44 (.15)

Table 17-5

Individual Urine Concentrations, [U], of Norfloxacin
Following Administration of 400 mg Every 8 Hours for 5 Days

Subject No.	Day	[U] (mcg/ml) during . . . hr				
		0-1	1-2	2-4	4-6	6-8
101	1					
	2					
	5					
102	13					
	14					
	17					
103	1					
	2					
	5					
126	1					
	2					
	5					

NS = No samples. One report form indicates no void.

Table 17-6

Individual Urinary Recovery (U) of Norfloxacin
Following Administration of 400 mg Every 8 Hours for 5 Days

Subject No.	U (mg) Following First Dose on Day . . .		
	1	2	3
101			
102			
103			
126			

¹ Urinary recovery low 1-2 hr. Amount lost estimated from $\dot{V}_{Cl,R}$ and AUC.

Table 17-7

Individual Renal Clearance ($\dot{V}_{Cl,R}$) of Norfloxacin
Following Administration of 400 mg Every 8 Hours for 5 Days

Subject No.	$\dot{V}_{Cl,R}$ (ml/min) Following First Dose on Day . . .		
	1	2	3
101			
102			
103			
126			

Table 18-1

Individual 8-Hour Area Under the Curve, $[AUC]_0^8$, for MK-366 Following Single Oral Doses of Drug

Subject No.	$[AUC]_0^8$, $\mu\text{g}\cdot\text{hr}/\text{ml}$	
	400-mg Tab	430-Soln
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
Mean (SD)	3.02 (± 2.45)	6.04 (± 1.90)

Table 18-2

Individual Estimates of Total Area Under the Curve, $[AUC]_{\infty}$, for MK-366 Following Single Oral Doses of the Drug

Subject No.	$[AUC]_{\infty}$, $\mu\text{g}\cdot\text{hr}/\text{ml}$		400 mg Soln (dose adjustment)
	400-mg Tab	430-mg Soln	
1	-0.88	-6.86	
2	-0.91	-6.73	
3	-0.97	-5.47	
4	-0.64 L	-7.51	
5	-0.41 L	-12.26	
6	-2.26 L	-6.87	
7	-1.34 H	-5.95	
8	-0.54 L	-5.77	
9	-0.61 L	-7.23	
10			
11	-1.34 L	-7.76	
12	-1.11	-9.38	
13		-7.51	
14	-0.67 L	-7.06	
15	-1.15	-3.40	
Mean (SD)	6.30 (± 2.26)	7.38 (± 2.08)	7.05 (± 1.94)
% Within 75-125%	6	5/13 38.5%	

$\frac{400}{430} = 0.93\%$

¹ Incomplete urinary recovery.

with $\bar{X} = 99.8$
(SD ± 0.42)

[CV = 42.1%]

with $\bar{X} = 98.7$
(S.D. ± 0.49)

[CV = 49.6%]

Table 18-3

Individual Peak Serum Concentrations (C_{max}) of NR-366
Following Single Oral Doses of Drug

$\frac{400}{430} = 0.93$

Subject No.	C_{max} (ng/ml)		
	400-mg Tab ^{ts} (Ad.)		430-mg Soln
	In 200 (Ad.)	Sol ^{ns} (Ad.)	(Ad. vs. Tab ^{ts})
1	H	-0.91	-1.72
2	L	-0.97	-2.04
3		-0.59	L -1.80
4	L	-0.79	-2.21
5	L	-0.4	L -2.80
6		-1.29	H -2.06
7	L	-1.60	H -1.12
8		-0.48	L -1.21
9	L	-0.93	-1.6
10	H	-1.52	H -0.58
11		-0.97	-2.11
12	H	-1.62	H -1.34
13	L	-0.24	L -2.73
14	L	-0.70	L -1.72
15		-1.21	-1.07
Mean (±SD)		1.50 (0.58)	1.87 (0.66) $\bar{y} = 1.74$
		38.7%	SD = 0.61
		$\frac{6}{15} = 40.0\%$	CV = 35%

$\% \text{ in } 75-125\%$

Table 18-4

Effective Serum Half-Life ($t_{1/2, \alpha}$) of Norfloxacin
Following Single Oral Doses of Drug

(For 8 hr dosing interval)

Subject No.	$t_{1/2, \alpha}$ (hr)		
	Treatment A	Treatment B	Treatment C
1	— ¹	3.1	2.7
2	3.8	2.9	2.0
3	3.7	2.6	3.5
4	2.8	3.1	2.4
5	3.7	3.4	3.3
6	4.5	4.2	4.0
7	— ¹	4.0	3.4
8	3.3	2.3	4.1
9	2.7	3.9	3.5
10	4.1	3.7	— ¹
11	4.2	3.3	2.7
12	4.4	3.8	4.1
13	2.5	— ¹	3.2
14	2.3	2.9	2.9
15	2.6	3.1	2.2
Mean	3.3	3.2	3.0

¹ No estimate of $[ADC]_0$ because of incomplete urinary recovery of drug

Table 18-5

Individual 48-Hour Urinary Recovery (U_{0-48}) of NK-366
Following Single Oral Doses of Drug

Subject No.	200-mg Tab.		400-mg Tab.		430-mg Soln	
	U_{0-48} (mg)	X Dose ⁴	U_{0-48} (mg)	X Dose ⁴	U_{0-48} (mg)	X Dose ⁴
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
Mean (SD)		35.3 (29.1)		76.3 (49.1)		78.4 (46.7)

- 1 Renal clearance estimates indicate incomplete urinary recovery of drug 1-2 hr and 4-6 hr. Excluded from mean.
- 2 Renal clearance estimates indicate incomplete urinary recovery of drug 0-1 hr. Excluded from mean.
- 3 Renal clearance estimates indicate incomplete urinary recovery of drug 1-2 hr. Excluded from mean.
- 4 For dose estimates see Table 13.

Table 18-6

MEANS OF BIOAVAILABILITY PARAMETERS
NORFLOXACIN STUDY 819-- DR. ZIDON

RELATIVE BIOAVAILABILITY	400 MG TAB/STANDARD
N	13
MEAN (SD)	0.90 (0.90)
95% C.I.	0.78-1.13
POWER (5% DIFFERENCE)	0.70 (0.70)
FURTHERON PRED. (10%)	0.47
(15%)	0.70
(20%)	0.86
(25%)	0.95
(30%)	0.98

(*) - GEOMETRIC MEANS TABULATED.

None of the above ratios is significantly different from unity.

Table 18-7

Individual Estimates of Norfloxacin Relative Bioavailability from 200-mg and 400-mg Market Image Tablets as Compared to Solution Administration of the Drug

Based on the method of Kwan and Till (as modified by Huang & Kwan)

Subject No.	Tab 400 / Soln 400	
	F_B / F_C	
1	0.82	
2	1.02	
3	0.96	
4	0.79	
5	0.47	
6	1.82	
7	1.33	
8	0.55	
9	0.61	
10		
11	1.12	
12	1.14	
13		
14	0.74	
15	1.15	
Geometric Mean	0.90	

Subscripts A, B and C refer respectively to the 200-mg tablet, the 400-mg tablet, and the 400-mg solution treatments.

- 1 Incomplete urinary recovery Treatment A.
- 2 Incomplete urinary recovery Treatment C.
- 3 Based on the ratio of 2-dose urinary recovery.
- 4 Incomplete urinary recovery Treatment B.

Table 18-8

Individual Cumulative Renal Clearance ($\sum_{Cl,R}$) of NK-366 Following Single Oral Doses of the Drug

Subject No.	$\sum_{Cl,R}$ (ml/min)	
	400-mg Tab	400-mg Soln
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
Mean (SD)	399.3 (±93.0)	276.2 (±71.3)

Table 18-9

MEANS OF BIOAVAILABILITY PARAMETERS
MERFLEMICIN STUDY 013-- DR. 2007

40-000 URINARY RECOVERY		TABLETS 430 MG SOL'N (STANDARD)	400 MG TABLET
TOTAL		NO (INDJ)	
N		14	14
MEAN		221.91	188.14
S.D.		22.95	24.22
X DOSE			
N		14	14
MEAN		20.30	26.40
S.D.		6.74	9.12
0-HR AUC		MG-HR/ML (A)	
N		15	15
MEAN		6.34	5.44
S.D.		1.90	2.65
ESTIMATED TOTAL AUC		MG-HR/ML (A)	
N		14	14
MEAN		7.50	7.10
S.D.		2.08	3.36

(A)--DOSE ADJUSTED UP TO 430 MG.

0.01 SIGNIFICANTLY LOWER THAN STANDARD 430 MG SOL., P<0.05, 0.01 RESPECTIVELY.
 0.00 SIGNIFICANTLY LOWER THAN 400 MG TABLET, P<0.05, 0.01 RESPECTIVELY.

CON. RENAL CLEARANCE		TABLETS 430 MG SOL'N (STANDARD)	400 MG TABLET
		ML/MIN	
N		15	15
MEAN		270.37	279.26
S.D.		71.22	91.95
PEAK SERUM CONC--C _{MAX}		MG/ML (A)	
N		15	15
MEAN		1.87	1.62
S.D.		0.60	0.62
TIME TO PEAK SERUM CONC--T _{MAX} HR			
N		15	15
MEAN		0.70	1.05
S.D.		0.27	0.28
HALF-LIFE		HR	
N		14	14
MEAN (B)		2.09	2.22
95% C.I.		2.63-3.07	2.98-3.09

(A) - DOSE ADJUSTED UP TO 430 MG.

(B) - GEOMETRIC MEAN TABULATED.

0.05 - SIGNIFICANTLY DIFFERENT FROM STANDARD 430 MG SOL., P<0.05, 0.01, RESPECTIVELY.
 NO SIGNIFICANT DIFFERENCES WERE FOUND BETWEEN THE TWO TABLETS.

Table 19-1

INDIVIDUAL 24-HOUR URINARY RECOVERY (U_{0-24}) TOTAL URINARY RECOVERY (U_{∞}), AND RENAL CLEARANCE ($V_{Cl,R}$) OF NORFLOXACIN IN HEALTHY ELDERLY VOLUNTEERS

SUBJECT NUMBER	URINARY RECOVERY			$V_{Cl,R}$ (ML/MIN)
	U_{0-24} (MG)	U_{∞} (MG)	% OF DOSE ¹	
1				
2				
3				
4				
5				
6				
Mean (S.D.)			22.3 (6.9)	154.0 (15.7)

1 Assay content was 405 mg of norfloxacin per tablet

2 Questionable urinary recovery three to twelve hours; U_{0-24} estimated from renal clearance (zero to three hours) and AUC_{0-12} plus U_{12-24}

Table 19-2

INDIVIDUAL PHARMACOKINETIC PARAMETERS FOR NORFLOXACIN IN PLASMA OF HEALTHY, ELDERLY VOLUNTEERS*

SUBJECT NUMBER	$[AUC]_0^8$	$[AUC]_{\infty}$	C_{max}	T_{max}	$t_{1/2, \eta}$
	(MCG.HR/ML)	(MCG.HR/ML)	(MCG/ML)	(HR)	(HR)
1					
2					
3					
4					
5					
6					
Mean (S.D.)	7.48 (2.24)	9.80 (2.83)	2.02 (0.77)	1.3 (0.4)	3.9 (0.3) (harmonic mean)

(q 8^h dosing interval)

* Plasma parameters:

$[AUC]$ = Area under the plasma concentration-time curve

C_{max} = Maximum plasma concentration

T_{max} = Time to peak, (C_{max})

$t_{1/2, \eta}$ = Effective plasma half-life

Figure

19-2

MEAN NORFLOXACIN PLASMA CONCENTRATION IN HEALTHY ELDERLY SUBJECTS GIVEN A SINGLE 400 MG TABLET

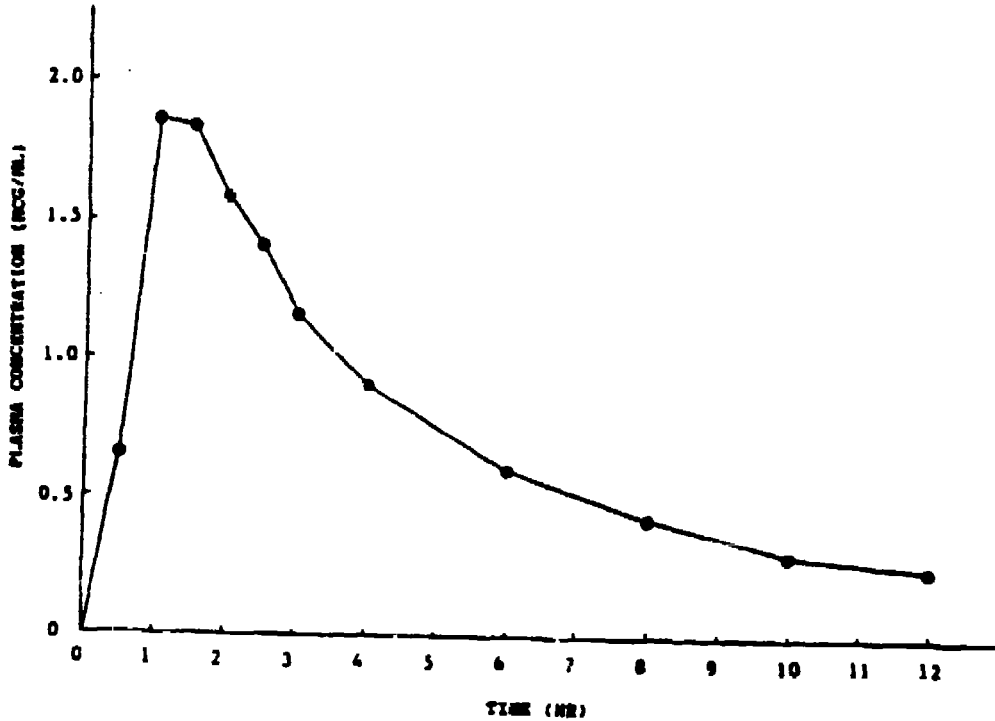


Table 19-3

DEMOGRAPHIC DATA FOR SUBJECT POPULATION

SUBJECT NUMBER	SEX	AGE, YR	WEIGHT, KG	HEIGHT, IN.	CREATININE CLEARANCE ML/MIN/1.73 m ²
<u>Individual Data</u>					
1	F	69	56.8	64	86
2	F	68	69.1	68	115
3	M	69	60.9	65	95
4	M	72	69.5	66	72
5	F	67	60.0	62	88
6	F	68	58.2	63	90
<u>Averages By Sex</u>					
1,2,5,6	F	68.0	61.0	64.3	94.8
3,4	M	71.5	69.2	65.5	83.5
<u>Overall Average (S.D.)</u>					
1 to 6	4F,2M	69.2 (2.5)	62.4 (5.5)	64.7 (2.2)	91 (14.1)

Table 20-1

Individual Demographic Data

Subject No.	Sex	Age (Yr)	Wt (Kg)	GFR (ml/min/1.73m ²)	Other Medication
Group I					
1	M	51	72	96 ¹	None
2	M	35	74	117 ²	None
7	M	23	103	131 ⁴	None
9	M	27	53	115	None
10	M	16	63	125 ²	None
14	M	27	70	110 ²	None
20	M	31	73	111	None
8	M	49	89	148 ³	Warfarin, Pimozide
21	M	21	65	94	Hydroxychloroquine, Prednisolone
Group II					
5	M	60	62	60 ⁴	Furosemide, Slow K
6	M	51	88	31	Mixard, Furosemide, Spironolactone
12	M	56	64	46	Atenolol
25	F	55	75	56	Atenolol, Moduretic
26	F	45	43	60 ³	Captopril, Nifedipine, Diazide, Nitrazepam
27	M	53	73	74 ³	None
$\bar{x} = 54.5$ S.D. 19.6 <i>subject excluded from analysis due to low GFR (see text)</i>					
Group III					
3	M	69	62	12 ⁶	Aminophylline, Salbutamol
11	M	52	78	28 ¹	Furosemide, Aludrox
13	F	52	64	13	Chlorpropamide, Prednisolone, Furosemide
15	M	65	57	17	Flurbiprofen, Slow K Insulin, Vit. E
17	M	72	55	12	Captopril, Hydralazine, Furosemide, Ampicillin, Erythromycin
18	M	51	80	10	Allopurinol, Lactulose, Alucaps, Tenaxpan
					Alfacalcidol, Aluminum hydroxide

Individual Demographic Data (Continued)

Subject No.	Sex	Age (Yr)	Wt (Kg)	GFR (ml/min/1.73m ²)	Other Medication
Group IV					
19	F	23	54	9.2	Atenolol, Bendroflumazide
23	F	69	68	7.5	Nifedipine, Hydralazine
16	M	54	53	6.6	Prednisolone, Isosorbide dinitrate, Allopurinol, Furosemide, Slow K
4	F	54	49	8.0 ³	Ferrous sulphate, Prazosin, Furosemide, Alucaps
22	M	43	77	7.6	Furosemide, Aludrox, Slow sodium
24	F	62	61	9.1	Aluminum hydroxide, Thyroxine

GFR = Glomerular Filtration Rate as determined on study days by Cr⁵¹-EDTA clearance unless otherwise noted.

1 ¹³¹I/¹²⁵I Hippuran clearance (assuming a filtration factor of 0.2)

2 Creatinine Clearance

3 Determined 2 months after the study

4 Determined 1 month after the study

5 Determined 1 month before the study

6 ⁵¹Cr-EDTA clearance determined 2 months after the study. Creatinine clearance was 4 ml/min 3 days before the study.

Table 20-2

Individual Total Urinary Recovery (U_m) and Cumulative Renal Clearance ($\dot{V}_{CL,R}$) of Norfloxacin In Renal Insufficiency Study

Subject No.	U_m (mg)	Dose	$\dot{V}_{CL,R}$ (ml/min)
Group I			
1	60.3	14.7	94.2
2	191.2	46.6	467.5
7			
8 ⁴			
9			
10			
14			
20			
21 ⁵			
Mean		28.2	297.1
(± S.D.)		(12.8)	(117.4)
Group II			
5 ⁴			
6 ³			
12			
25			
25			
27			
Mean		35.3	264.3
(± S.D.)		(9.2)	(83.2)
Group III			
5			
11 ¹			
13			
15 ²			
17 ³			
18			
Mean		6.7	17.8
(± S.D.)		(4.1)	(4.4)

Individual Total Urinary Recovery (U_m) and Cumulative Renal Clearance ($\dot{V}_{CL,R}$) of Norfloxacin In Renal Insufficiency Study
(Continued)

Subject No.	U_m (mg)	Dose	$\dot{V}_{CL,R}$ (ml/min)
Group IV			
4			
16			
19 ⁴			
22 ³			
23			
24			
Mean		2.4	16.7
(± S. D.)		(1.1)	(8.4)
1	Questionable urinary recovery 0-2 hr. No estimate of $\dot{V}_{CL,R}$ possible. Excluded from mean.		
2	Questionable urinary recovery 4-8 hr. Urinary recovery 4-6 estimated from $\dot{V}_{CL,R}$ and AUC.		
3	No drug detectable in urine.		
4	Questionable urinary recovery 0-2 hr. Urinary recovery estimated from $\dot{V}_{CL,R}$ and AUC.		
5	Questionable urinary recovery. Excluded from mean.		
6	Questionable urinary recovery. No drug detectable in urine after 12 hr but serum levels detectable through 24 hr. Excluded from mean.		

Table 20-3

Individual Area Under the Serum Concentration-Time Curve, [AUC],
for Norfloxacin in the Renal Insufficiency Study

Subject No.	[AUC] ₀ ⁸ (mcg ⁸ hr/ml)	[AUC] ₀ ¹ (mcg ¹ hr/ml)
<u>Group I</u>		
1		
2		
7		
8		
9		
10		
14		
20		
21		
Mean	5.38	6.94
(±S.D.)	(1.93)	(2.73)
<u>Group II</u>		
3		
6		
12		
25		
26		
27		
Mean	7.62	9.53
(±S.D.)	(2.00)	(2.47)
<u>Group III</u>		
3		
11		
13		
15		
17		
18		
Mean	9.18	24.01
(±S.D.)	(2.41)	(13.49)
<u>Group IV</u>		
4		
16		
19		
22		
23		
24		
Mean	7.79	16.46
(±S.D.)	(3.31)	(14.52)

¹ See Table 20-2.

² Excluded from mean.

Table 20-4

Individual Maximum Serum Concentration (C_{MAX}) of Norfloxacin and the Time that Maximum Occurred (T_{MAX}) in the Renal Insufficiency Study

Subject No.	C_{MAX} (mcg/ml)	T_{MAX} (hr)
<u>Group I</u>		
1		
2		
7		
8		
9		
10		
14		
20		
21		
Mean (±S.D.)	1.91 (0.56)	1.4 (0.4)
<u>Group II</u>		
5		
6		
12		
23		
26		
27		
Mean (±S.D.)	1.91 (0.72)	1.3 (0.4)
<u>Group III</u>		
3		
11		
13		
15		
17		
18		
Mean (±S.D.)	1.70 (0.43)	1.8 (1.1)
<u>Group IV</u>		
4		
16		
19		
22		
23		
24		
Mean (±S.D.)	1.70 (0.92)	1.8 (1.2)

Table 20-5

Individual Effective Serum Half-life ($t_{1/2, n}$) of Norfloxacin in the Renal Insufficiency Study

Subject No.	$t_{1/2, n}$ (hr)	Subject No.	$t_{1/2, n}$ (hr)
<u>Group I</u>		<u>Group III</u>	
1		3	
2		11	
7		13	
8		15	
9		17	
10		18	
14		Mean ¹	6.57
20			
21		<u>Group IV</u>	
Mean ¹	1.67	4	
		16	
<u>Group II</u>		19	
5		22	
6		23	
12		24	
25		Mean ¹	6.40
26			
27			
Mean ¹	1.38		

¹ Harmonic Mean

² See Table 9.

Figure 20-1

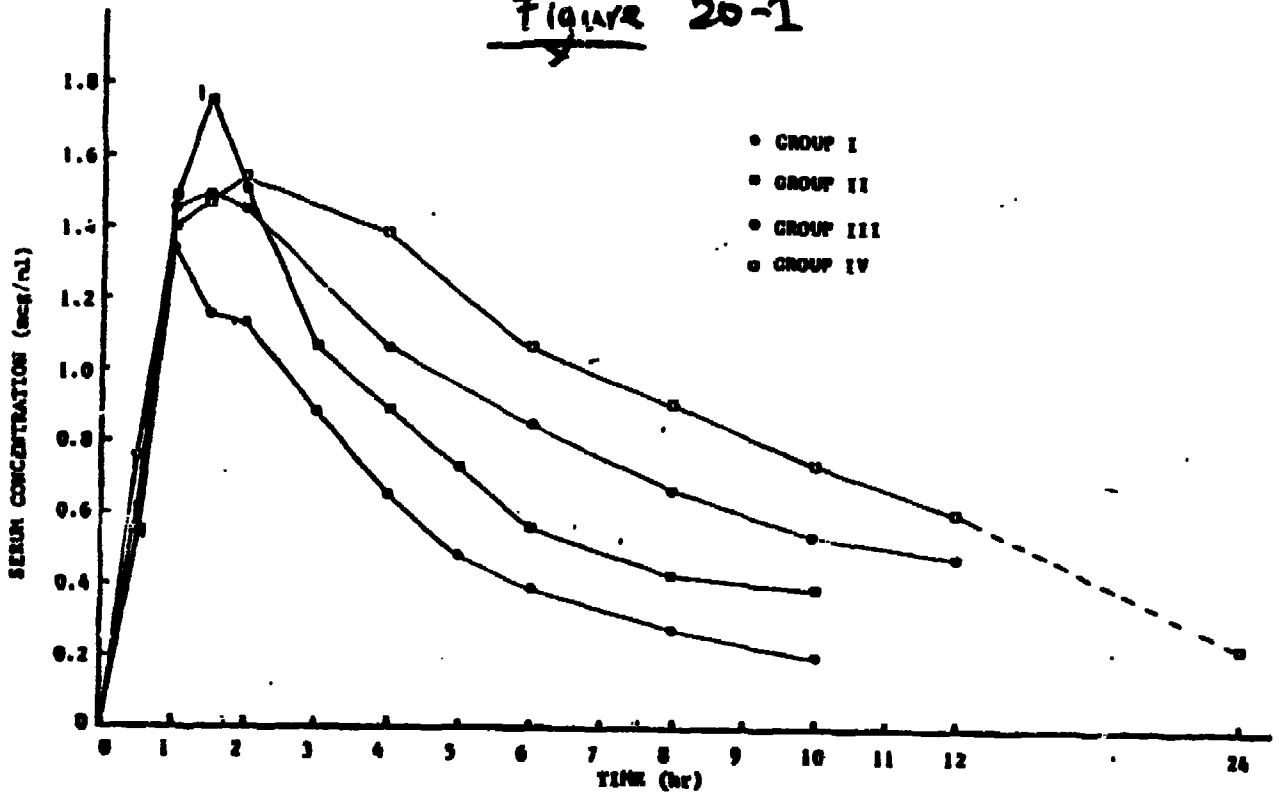


Figure 5. Mean norfloxacin serum concentration profiles.

Table: 21-1

Individual Plasma Concentrations (C_p) of Norfloxacin Following Administration of One 400-mg Tablet (Old Formulation)

Subject No.	C_p (µg/ml) at ...hr.									
	0	0.5	1.0	1.5	2	3	4	6	8	12
51										
52										
53										
54										
55										
56										
57										
58										
59										
60										
61										
62										
63										
64										
65										
66										
67										
68										
69										
70										
Mean	-	0.48	1.17	1.35	1.29	0.96	0.78	0.53	0.40	0.23

Table: 21-2

Individual Plasma Concentrations (C_p) of Norfloxacin Following Administration of One 400-mg Tablet (New Formulation)

Subject No.	C_p (µg/ml) at ... hr									
	0	0.5	1.0	1.5	2	3	4	6	8	12
51										
52										
53										
54										
55										
56										
57										
58										
59										
60										
61										
62										
63										
64										
65										
66										
67										
68										
69										
70										
Mean	-	0.94	1.48	1.29	1.05	0.80	0.67	0.48	0.36	0.23

C_{max}
75-125

Table 21-3

Ratio Eval (MSD/Kyorin)

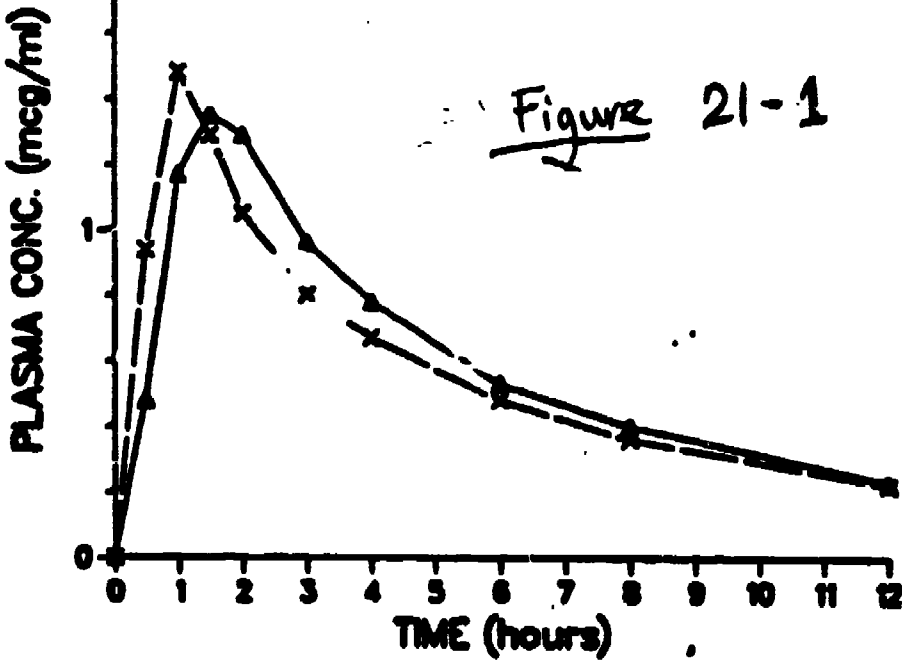
Individual Peak Plasma Concentration (C_{max}) of Norfloxacin and Time that Peak Occurred (T_{max}) After Tablet Administration

Sub ⁿ	Ratio Eval	MSD/Kyorin
1	1.17	
2	1.03	
3	1.44*	H
4	0.77	
5	1.28*	H
6	1.03	
7	0.45*	L
8	0.81	
9	0.97	
10	1.19	
11	0.67*	L
12	1.21 (1.2056)	
13	0.90	
14	1.05	
15	1.78*	H
16	1.40*	H
17	1.43*	H
18	1.08	
19	0.90	
20	0.48*	L

Subject No.	(kyorin)		(MSD)		T _{max}	Ratio Eval	MSD Eye
	C _{max} (μg/ml)	T _{max} (hr)	C _{max} (μg/ml)	T _{max} (hr)			
1-51						0.25*	+
2-52						1.0	-
33						1.0	-
54						0.5*	+
55						1.0	-
56						0.75	+
57						0.5*	+
58						2.0*	-
58/						1.0	+
60						1.0	-
61						0.7*	+
62						1.0	-
63						1.0	-
64						0.7*	+
65						2.0*	-
66						0.7*	+
67						0.5*	+
68						1.0	-
69						1.0	-
70						0.3*	+
Mean (S.D.)	1.56 (0.48)	1.7 (0.4)	1.56 (0.42)	1.1 (0.4)			% w/in 75-125
CV (%)	(30.8%)	(28.6%)	(27.3%)	(36.4%)			10/20

% w/in 75-125 $\frac{12}{20}$ (0.62)

5 Hi
3 L



Legend
 ▲ OLD FORM.
 × NEW FORM.

Table 21-4a

Individual Urine Concentration, [U], of Norfloxacin Following Administration of One 400-mg Tablet (Old Formulation)

Subject No.	[U] (µg/ml) at ...hr								
	0-1	1-2	2-3	3-4	4-6	6-8	8-12	12-24	24-48
51									
52									
53									
54									
55									
56									
57									
58									
59									
60									
61									
62									
63									
64									
65									
66									
67									
68									
69									
70									

Table 21-4b

Individual Urine Concentration, [U], of Norfloxacin Following Administration of One 400-mg Tablet (New Formulation)

Subject No.	[U] (µg/ml) at ...hr.								
	0-1	1-2	2-3	3-4	4-6	6-8	8-12	12-24	24-48
51									
52									
53									
54									
55									
56									
57									
58									
59									
60									
61									
61									
63									
64									
65									
66									
67									
68									
69									
70									

Legend applies to both tables, a + b

- NS - No sample
- ED - Below detection limits of assay
- NV - Sample received; no volume recorded

NOTE: Multiple entries represent more than one urine collection during the specified interval. A single value can not be reported because of the problem indicated.

Table 21-5

Individual Total Urinary Recovery (U) of Norfloxacin Following Single-Dose Administration of Old and New Tablet Formulations

Subject No.	Kyorin - 412mg		MSD - 414mg		Patic Niss
	Old Formulation		New Formulation		
	U (mg)	%-Dose	U (mg)	%-Dose	
51					0.72
52					1.16
53					1.21
54					
55					1.18
56					8.11
57					—
58					—
59					—
60					—
61					1.78
62					0.79
63					0.98
64					—
65					—
66					0.56
67					1.37
68					—
69					—
70					0.57
Mean (±S.D.)		27.9 (8.9) (CV 31.9%)	—	27.0 (8.5) (CV 31.5%)	

- 1 No sample or no void 1-2, and 6-8 hr. Excluded from mean.
- 2 No void 0-1 hr. Renal clearance indicates drug retrieved in 1-2 and 2-3 hr collection.
- 3 No sample or no void 4-6 hr.
- 4 No sample or no void 8-12 hr. Urinary excretion estimated from $V_{Cl, R}$ and AUC.
- 5 No void 1-2 and 3-4 hr. Renal clearance indicates drug recovered in 2-3 hr collection.
- 6 No sample 12-24 hr. Excluded from mean.
- 7 No sample or no void 8-12 and 24-48 hr. Urinary excretion 8-12 estimated from $V_{Cl, R}$ and AUC. Later sample assumed insignificant.
- 8 Five urine collections covered the interval 24-48 hr. One sample missing or no volume recorded.
- 9 Three and 7 urine collections covered the interval 12-24 and 24-48 hr., respectively. No volume given for 1 sample 12-24 and 2 samples missing 24-48 hr.
- 10 Four urine collections covered the interval 24-48 hr. No volume given for 1 sample or 1 sample missing.
- 11 No sample or no void 2-3 hr. Excluded from mean.

Table 21-6

Individual Estimates of Norfloxacin Relative Bioavailability
From 400-mg New Formulation Tablets (F_{NEW}) as Compared to
Old Formulation Tablets (F_{OLD})

Subject No.	F_{NEW}/F_{OLD}
1	0.79
2	0.98
3	1.09
4	<u>1</u>
5	1.31
6	1.05
7	0.50
8	0.90
9	0.79
10	<u>1</u>
11	0.70
12	1.02
13	0.91
14	1.11
15	1.61
16	0.96
17	1.38
18	<u>1</u>
19	0.94
20	<u>0.54</u>
Geometric Mean	0.94

¹ Incomplete urinary recovery

Unit g

REL. BIOAVAILABILITY	NEW FORM/OLD FORM
N	27
GEOMETRIC MEAN	0.94
95% C.I.	0.80-1.09
90% (10% DIFFERENCE)	0.87
80% (20% DIFFERENCE)	0.84
70% (30% DIFFERENCE)	0.81
60% (40% DIFFERENCE)	0.79
POSTERIOR PROB. (10%)	.68
(20%)	.69
(30%)	.97
(40%)	.99

NOTE: PATIENTS 8, 14, 68 AND 69 WERE EXCLUDED FROM BIOAVAILABILITY CALCULATIONS.
ALL INCLUSIONS/EXCLUSIONS WERE CARRIED OUT IN ACCORDANCE WITH THE PHARMACEUTICS REPORT.

Table 21-7

Individual Cumulative Renal Clearances ($\dot{V}_{CL,R}$) and Total Area Under the Plasma Concentration-Time Curve, [AUC]_{0-∞}, for Meclofenacin

Subject No.	Kyojin		MSD		Ratio	MSD/Kyojin
	Old Formulation	New Formulation	Old Formulation	New Formulation		
	$\dot{V}_{CL,R}$ (ml/min)	[AUC] _{0-∞} (mcg.hr/ml)	$\dot{V}_{CL,R}$ (ml/min)	[AUC] _{0-∞} (mcg.hr/ml)		
51					0.84	
52					0.90	
53					1.04	
54					1.40 - Hi	
55					1.03	
56					0.48 - Lo	
57					0.77	
58					0.71 - Lo	
59					0.68 - Lo	
60					1.11	
61					0.89	
62					1.11	
63					1.69 - Hi	
64					0.99	
65					1.32 - Hi	
66					0.88	
67					1.11	
68					0.88	
69					0.54 - Lo	
70					0.54	
Mean	261.9	7.82	270.0	6.94		
(±S.D.)	(80.7)	(2.53)	(63.4)	(1.69)		
CV (%)	30.5	32.3	23.3	24.3		

$\bar{x} = 0.967$
 $S.D. = 0.313$
 $CV \bar{x} = 32.4\%$

412 / 414 = 0.995 → 1
 402 / 402 = 1.000 → 1

75-125 = 10 / 17 = 58.8% within

Incomplete urine collection

Table 21-8

Means of Pharmacokinetic Parameters

BASED ON SUBJECTS WITH COMPLETE URINARY RECOVERY ON BOTH FORMULATIONS

PARAMETER	N	OLD FORMULATION		NEW FORMULATION		CHANGE (NEW-OLD)	
		MEAN	S.D.	MEAN	S.D.	MEAN	S.D.
PEAK SERUM CONC.--MC/ML	20	1.56	0.40	1.54	0.42	-0.02	0.50 NS
TIME TO PEAK CONC.--HR	20	1.30	0.43	1.07	0.37	-0.27	0.57 *
AUC--MC/ML X HR	17	7.71	0.50	6.90	1.73	-0.82	2.10 NS
RENAL CLEARANCE--ML/MIN	16	266.10	83.90	269.90	63.00	3.80	61.1 NS
URINARY RECOVERY--% (UMBJ)	23	117.43	37.70	106.55	36.94	-10.88	36.74 N/A
URINARY RECOVERY--% DOSE (A)	17	27.74	0.90	26.72	0.62	-1.02	7.00 NS

NOTE: BASED ON 412 AND 414 MG FOR THE OLD AND NEW FORMULATIONS RESPECTIVELY.

NOTE: SUBJECT 049 WAS EXCLUDED FROM MEAN OF UR-X DOSE BECAUSE OF INCOMPLETE URINARY RECOVERY FOLLOWING TREATMENT A (OLD FORMULATION). SUBJECTS 054 AND 045 WERE EXCLUDED FROM MEAN OF UR-X DOSE BECAUSE OF INCOMPLETE URINARY RECOVERY FOLLOWING TREATMENT B (NEW FORMULATION). RENAL CLEARANCE CALCULATIONS WERE AVAILABLE FOR SUBJECT 049 BUT NOT FOR SUBJECTS 054 & 045. ALL THREE SUBJECTS WERE EXCLUDED FROM AND ANALYSES ON AUC AND RELATIVE BIOAVAILABILITY.

ALL EXCLUSIONS WERE CARRIED OUT IN ACCORDANCE WITH THE BIOPHARMACEUTICS REPORT.

NS-- NOT STATISTICALLY SIGNIFICANT.

N/A--NOT ANALYSED.

*--DIFFERENCE IS STATISTICALLY SIGNIFICANT, P<0.05

ANALYSES ADJUSTED FOR PERIOD.

MEMORANDUM OF A MEETING

DATE: March 13, 1986

BETWEEN: Division of Biopharmaceutics (HFN-226)
Gene D. Mason, Pharm.D.
John Hunt, B.S.
C.T. Viswanathan, Ph.D.

AND: Division of Anti-Infective Drug Products (HFN-815)
Theresa Reed, M.D.
Edward Tabor, M.D.
John Taylor, Ph.D.
Armand Cascla, Ph.D.
Richard Norton

DRUG: Norfloxacin, N-19384, Merck, Sharp & Dohme (400 mg tablets)

PURPOSE: 1) to discuss Norfloxacin crystallization in urine
2) to discuss bioavailability issues (Dissolution,
Food/Anticids)

The following is a summary of the discussion.

1. Crystalluria

With lower doses and adequate water loading to maintain sufficient urine flow, crystallization of norfloxacin is probably less likely to occur (see attachment notes). However, there is no guarantee that crystallization would not occur in some patients taking this drug because a variety of factors could potentially lead to some crystal formation (i.e. pH changes, decreased urine output, etc.). Crystalluria is a medical safety issue and not a biopharmaceutics factor and therefore should be appropriately considered with benefit/risk in patients.

It was pointed out that should this drug be approved by HFN-815, strict labeling with warnings for possible crystalluria should be included.

2. Dissolution

It was pointed out that the 400 mg tablet (and also the 200 mg tablet) that is to be actually marketed has not been tested in a well controlled bio-study to establish either its bioavailability or bioequivalence to clinically tested formulations. Even though the actual formulation to be marketed has a small change in its coating as compared to the 400 mg MSD Direct Compression tablet that was tested in one bioequivalence study conducted by Zinny (#59) (i.e. was

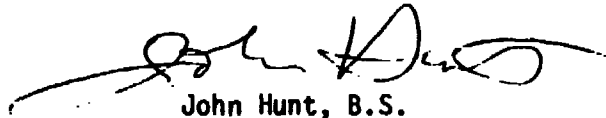
compared to a clinical tested formulation), as a minimum requirement prior to approval, it was agreed that the sponsor should do some comparative in vitro dissolution testing (e.g. at different media pH's) on its proposed marketed formulation as well as the tablet lots that were used in the above described bioequivalence study. The Division of Biopharmaceutics was to contact the sponsor regarding this.

The Division of Biopharmaceutics plans to request from the firm in-vitro dissolution profiles for individual tablets under the following conditions:

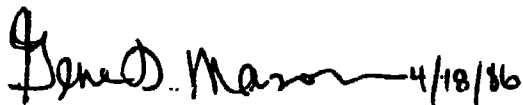
1. Employ lots used in Zinny study #59 (ref #21) representing the Kyorin Formulation (B) and MSD Direct Compression Tablet (1 lot for each formulation) and 3 different lots of the Merch Market Image Tablet at [redacted] and 400 mg.
2. Repeat the profiles under conditions of simulated gastric juice (pH 1.2), pH 4 (proposed by firm), and pH 6.
3. Sampling times should include 15, 20, 30, 45 and 60 minutes
4. Twelve (12) tablets from each lot should be included

3. Food and Antacids

Pointed out were concerns of the possible influence of food and antacids on this drug's systemic absorption, especially knowing that this drug's solubility is highly pH sensitive. It was decided that labeling in the package insert could handle these issues at this time but well controlled studies would be desirable to address these concerns.



John Hunt, B.S.



Gene D. Mason, Pharm.D.

cc: HFN-226(Mason, Hunt, Viswanathan), HFN-815(Tabor, Reed), Chron, and Drug Files

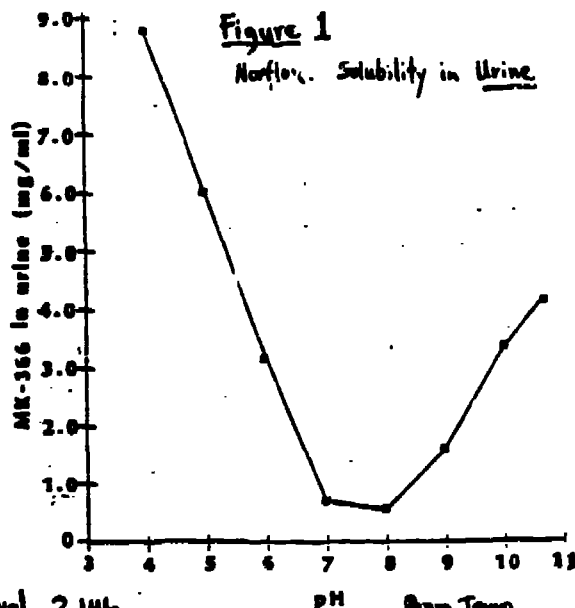
GDM/JH:lyf:smj [redacted]:4/16/86

NOTES ON THE ANALYSIS OF CRYSTALLURIA WITH NORFLOXACIN

A Solubility

As shown in Figures 1 and 2, the solubility of norfloxacin in urine varies greatly with pH, being lowest between 6 and 10. Because urinary pH normally ranges from pH 6-8, the solubility of norfloxacin over this range will be the focus of the discussion. Figure 2 shows the relative solubility of norfloxacin in urine at 25 and 37 degrees centigrade.

In animal studies of norfloxacin, crystalluria consisted of the dihydrate, magnesium and covalent salts of norfloxacin. It is unclear at this time whether the parent compound and/or the above salts should be the focus of discussion of the possibility of crystallization in humans. Swanson, et al(1), observed "drug crystals" in freshly voided urine specimens collected after administering single oral 1200 and 1600 mg doses to human volunteers. Crystals were not found at lower doses(200-800 mg). Urine pH of specimens with crystals was between 7 and 7.8. Drug was administered with only 250 ml of water under fasting conditions.



from Vol. 2.146

p VII-00532

pH Room Temp
25°C

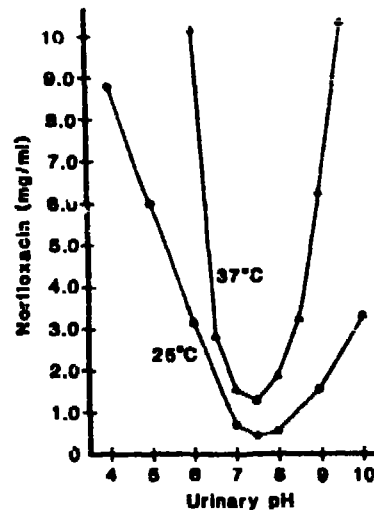


FIG. 2 Effect of pH and temperature on urinary solubility of norfloxacin.

(from Swanson, et al)

B Pharmacokinetic Predictions

Using data in the Ferguson(ref #15) and Zirny(ref #16) studies, it is possible to do calculations to determine if, on a theoretical basis, drug crystals of the parent compound norfloxacin are likely to be formed.

Assumptions/Conditions;

1. a worst case scenario
2. high single doses and/or the recommended multiple dose
3. a constant plasma concentration
4. solubility of norfloxacin in urine at 25 and 37 degrees C.

I. Using the urinary excretion rate, compare the concentration of drug in the kidney with the solubility of the drug.

The ratio, (A) drug excretion rate / (B) rate of urine formation, estimates the concentration of drug in the kidney tubules.

The solubility of norfloxacin was obtained from the pH solubility profile in urine.

A. Single dose evaluation

1600 mg PO

$$Cl_{renal} \times C_{max} = \frac{\text{maximum excretion rate}}{\text{(introduction of drug to kidney)}}$$

$$300 \text{ ml/min} \times 4.0 \text{ ug/ml} = 1200 \text{ ug/min} (1.7 \text{ mg/min})$$

(Consistent with actual values reported by the firm in table 13-14 of the BA review)

In normal individuals, the rate of urine formation (B) is approximately 1 ml/min (Guyton, Textbook of Medical Physiology, 6th Ed., 1981).

$$\frac{A}{B} = \frac{1200 \text{ ug/min}}{1 \text{ ml/min}} = 1200 \text{ ug/ml} (1.2 \text{ mg/ml})$$

1200 mg PO - $C_{max} = 3.0 \text{ ug/ml}$,
Excretion rate = 900 ug/min (0.9 mg/min)

Ratio A/B = 0.9 mg/ml

B. Multiple dose regimen,

	<u>C_{max}</u>	<u>Est'd Drug Exct'n Rate</u>	<u>Ratio A/B</u>
400 mg BID	2.0 ug/ml	600 ug/min (0.6 mg/min)	0.6 mg/ml
400 mg TID	3.0 ug/ml*	900 ug/min (0.9 mg/min)	0.9 mg/ml

* predicted value (actual value in 4 subjects was approx. 2.0 ug/ml)

COMPARISONS WITH SOLUBILITY OF NORFLOXACIN IN URINE

Regimen	Ratio A/B	Solubility (mg/ml)				
		25 ° C		37 ° C		
3600 mg SD	1.2 mg/ml	pH 6 :	3.2	OK	10.0	OK
		pH 7 :	0.75	Exceeded	1.5	OK
		pH 8 :	0.6	Exceeded	1.9	OK
1200 mg SD	0.9 mg/ml	pH 6 :	3.2	OK	10.0	OK
		pH 7 :	0.75	Exceeded	1.5	OK
		pH 8 :	0.6	Exceeded	1.9	OK
400 mg BID	0.6 mg/ml	pH 6 :	3.2	OK	10.0	OK
		pH 7 :	0.75	OK	1.5	OK
		pH 8 :	0.6	Borderline OK	1.9	OK
400 mg TID	0.9 mg/ml	pH 6 :	3.2	OK	10.0	OK
		pH 7 :	0.75	Exceeded	1.5	OK
		pH 8 :	0.6	Exceeded	1.9	OK

II. It is well documented that the crystalluria can be avoided by assuring an adequate rate of urine flow (Gibaldi, Biopharmaceutics and Clinical Pharmacokinetics, 3rd Ed., 1984). Thus, the minimum rate of urine flow may be calculated by dividing the excretion rate of drug by its solubility at a given pH. (cont' next page)

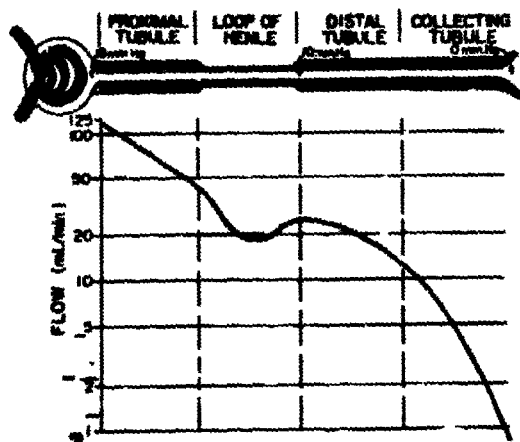


Figure 3. Volume flow of fluid in each segment of the tubular system per minute. Note that the flow is plotted on a semi-logarithmic scale, illustrating the tremendous difference in flow between the earlier and later segments of the tubules.

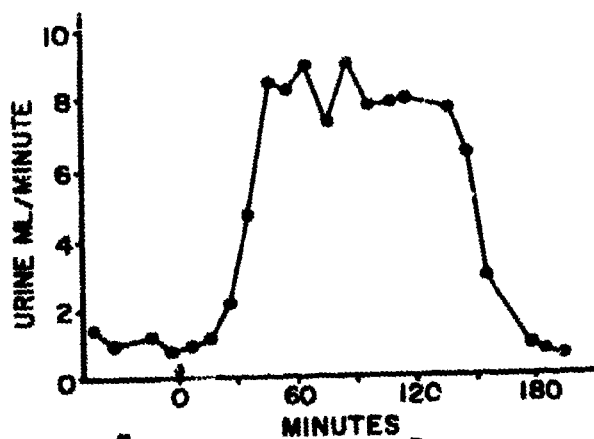


Figure 4. Water diuresis in a human being following ingestion of 1000 ml. of water. (Redrawn from Smith: The Kidney: Structure and Functions in Health and Disease. Oxford University Press, 1951.)

$$\text{Minimum Rate of Urine Flow} = \frac{(\text{A}) \text{Excretion Rate of Drug}}{(\text{B}) \text{Solubility in urine at a given pH}}$$

AT TEMP 25° C

B(solubility)	pH 6 = 3.2 mg/ml	pH 7 = 0.75 mg/ml	pH 8 = 0.6 mg/ml
Ratio	A/B	A/B	A/B
S.D. - 1600 mg C _{max} = 4 ug/ml A* = 1.2 mg/min	0.375 ml/min	1.6 ml/min	2 ml/min
S.D. - 1200 mg C _{max} = 3 ug/ml A = 0.9 mg/min	0.28	1.2	1.5
M.D. - 400 BID C _{max} = 2 ug/ml A = 0.6 mg/min	0.19	0.9	1.0
M.D. - 400 TID C _{max} = 3 ug/ml A = 0.9 mg/min	0.28	1.2	1.5

AT TEMP 37° C

B(solubility)	pH 6 = 10 mg/ml	pH 7 = 1.5 mg/ml	pH 8 = 1.9 mg/ml
Ratio	A/B	A/B	A/B
S.D. - 1600 mg C _{max} = 4 ug/ml A* = 1.2 mg/min	0.12 ml/min	0.8 ml/min	0.63 ml/min
S.D. - 1200 mg C _{max} = 3 ug/ml A = 0.9 mg/min	0.09	0.6	0.47
M.D. - 400 BID C _{max} = 2 ug/ml A = 0.6 mg/min	0.06	0.4	0.31
M.D. - 400 TID C _{max} = 3 ug/ml A = 0.9 mg/min	0.09	0.6	0.47

* Drug Excretion Rate

C. STUDY DOSING CONDITIONS

The possibility of crystalluria decreases if a water diuresis is created. As shown in the above graph, a water diuresis of up to 8 ml/min urine output can occur within 1 hour of ingesting 1000 ml of water. EXAMINATION OF EACH BIOAVAILABILITY STUDY REVIEWED SHOWS THAT PATIENTS WERE FLUID LOADED TO VARIOUS DEGREES. Below is a summary of dosing conditions.

- Ref #15(Ferguson) - 1750 ml of water over a 9 hr period
- Ref #16(Zirny) - 1000 ml of water over a 5 hr period
- Ref #17(Zirny) - 1000 ml of water over a 5 hr period
- Ref #18(Zirny) - 1440 ml of water over an 8 hr period
- Ref #19(Martin) - 750 ml of water over a 4 hr period
- Ref #20(Asscher) - 1100 ml of water over a 5 hr period
- Ref #21(Zirny) - 1440 ml of water over a 9 hr period

It is standard practice that the drug under investigation be administered under conditions identical to those proposed for the general patient population. If conclusions about the safety of norfloxacin are drawn from these investigations then they should be limited to patients with a similar state of hydration. It is recommended that dosing conditions (hydration status) used in clinical studies be evaluated for additional information and consider the need to include in the package insert instructions to patients to ensure a sufficient fluid intake.

D. CONCLUSION

Based on the above pharmacokinetic predictions, it appears that crystallization should not be a problem with the parent compound norfloxacin when using a solubility curve produced at 37 degrees centigrade (body temperature). Mixed results are obtained from a solubility curve produced at 25 degrees centigrade (room temperature). It should be emphasized that the above manipulations are theoretical and their limitations are demonstrated by the observations of crystals after large single doses (i.e. 1200 & 1600 mg) as reported by Swanson(1) et al. These predictions should be used in conjunction with actual clinical data to make conclusions about the safety of this drug with regards to crystalluria. The fluid loaded conditions used in the BA studies complicate interpretation of the clinical results of these studies for resolving safety issues. The above manipulations and conclusions do not apply to the dihydrate, magnesium or oxalate salts of norfloxacin.

Concern is expressed about the potential for formation of crystals under abnormal conditions commonly seen. Some of these conditions are periods of low urine formation (e.g. dehydration), alterations in urine pH which effect renal tubular secretion and the solubility of the drug, and pathological conditions that alter kidney physiology. The labeling should include specific instructions to maintain a good fluid intake in all patients to prevent crystallization of drug in the urinary tract.

Reference

- (1) Swanson B, et al, 1983. Norfloxacin Disposition After Sequentially Increasing Oral Doses. Antimicrob. Agents Chemother. 23(2):284-288.

PHARM

REV

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 19-384 (Original Submission, dated 7/14/85)

Date Review Completed: 2/3/86

Applicant: Merck Sharp & Dohme

Drug: Noroxin™ Coated Tablets

Code Names: Kyorin AM-157; NK-0366

Category: Quinolone urinary antibacterial

Related Drugs: All quinolone urinary antibacterials

PRECLINICAL STUDIES

Labs Performing Studies: Kyorin Pharmaceutical Co., Ltd. Japan; MSD, USA; and various Italian, French, Canadian res. institutes & universities.

Note: "*" is used to designate foreign studies.

ACUTE TOXICITY

These studies follow the order of Vol. 2.43, from page III-00510 on.

Animals Used: Rats; dogs; mice; monkeys

#1. Acute Toxicity [Kyorin]

IV LD₅₀: 220 mpk in mice
Oral LD₅₀: 4000 mpk in rats & mice

#2. Acute Toxicity & Lethality in Rats & Mice [Institute Gen. Path., Italy]

MLD for both species: 3000 mpk, PO; 1500 mpk, SC; 300 mpk, IV

#3. Oral Toxicity of the 6 Metabolites of the Drug [Kyorin]

Oral LD₅₀s: M-1, M-4 (2), M-5: Greater than 2000 mpk
M-2, M-3, M-4 (1): Greater than 4000 mpk

SUBACUTE TOXICITY

#1. 1-Month Oral Toxicity in Rats [Kyorin]

Doses: 250, 500 & 1000 mpk/day. A slight but stat. sig. increase in urinary K excretion was seen in F rats at the MD & HD, but no concurrent decrease in serum K level. Besides enlargement of the cecum at the HD, which is usual in these studies, no toxic signs were seen.

#2. 1-Month Oral Toxicity in Rats [Institute Gen. Path., Italy]

Doses employed were the same as in the previous study. There was no appreciable toxicity; not even potassuria.

#3. 1-Month Oral Toxicity in Dogs [U. of Cagliari, Italy]

Doses: 50, 100 & 200 mpk/day. No drug related changes observed.

#4. Subacute Oral Toxicity Study in Dogs [Kyorin]

Doses: 25, 50 & 100 mpk b.i.d. The only abnormality was slightly increased glucose-6-phosphatase activity in the liver of most drug-treated groups; the biological sig. of this change is not known. No other drug-induced changes were observed.

Reviewer's Comment: Regarding the enzyme changes, I don't know how to interpret this finding either.

5. 14-Week Oral Toxicity in Dogs Receiving NH₄Cl [MSDRL, USA]

This is a repetition of a French study in which, at the same doses as in this study, crystalluria and/or urinary obstruction occurred. Based on the knowledge that in vitro, the solubility of the drug is substantially increased under pH 6, the study was repeated in the USA with simultaneous administration of NH₄Cl (oral). No detailed write-up of that study was provided. Since the MSD study is pivotal, a detailed review will be presented here.

Animals, Doses, Route & Duration: Beagles, 43-45 wks of age; 4 groups, 3/sex/gp - Controls, 50, 150 & 300 mpk/day; oral (gavage); 14 wks, with acidification by adding 1% ammonium chloride to the drinking water.

Results

Mortality: Four in all gps due to aspiration.

Week 3	Week 6	Week 8
T M 0 300mpk	T M 0 150mpk	T F 0 150mpk; 1 F 0 300 mpk

The following dogs had aspiration pneumonia as a result of vomiting and regurgitation: Controls, 2/6; LD, 5/6; MD, 4/6; nD, 4/6. [Reviewer's Comment: Since the controls did not receive the drug, but only the vehicle, apparently the vehicle itself was irritating to the stomach of some control dogs, resulting in this reaction.]

Body Wt: All animals at the MD and several from other gps (including controls) lost body wt. The mean total wt change (kg/gp) was: Controls, +0.2; LD, -0.4; MD, -0.1; nD, -0.8.

Crystalluria: The admin. of ammonium chloride to drinking water was routinely effective in reducing urine pH to an approx. range of 5.5-6.5.

Drug crystals shaped like sea urchins and/or fine needles were occasionally seen in urine from dogs in each drug-treated gp. Those found during Drug Weeks 11, 12 & 13 were shown by high performance liquid chromatography to be MK-366. The severity & incidence of crystalluria was greatest in the HD gp.

No evidence of urinary tract obstruction was observed. Chronic tubulointerstitial nephritis (unilateral, slight-moderate) was present in 1 M each in the MD & HD gps. This lesion is not typical of a toxic change and its association to treatment is unknown.

Other: No other drug-related changes were seen in urinalysis, hematology or serum chemistry determinations.

No dose-related changes were seen in organ wts or on gross exam or histomorphologic exam of tissues.

6. Urinary Drug Disposition Study in Dogs [MSDRL, USA]

An oral study was initiated in beagle dogs with MK-366 to determine whether crystals of MK-366 or its metabolites can be isolated from the urine. The drug was administered to 4 dogs (2/sex) @ 300 mpk/day for 4 days, by oral gavage (as a suspension in aq. methylcellulose). A similar gp of dogs received 0.5% methylcellulose and served as controls. Urine samples were collected 2, 4, 6 & 24 hrs following dosing and were analyzed for undissolved MK-366-related material; 24-hr urine samples were also examined microscopically for crystals & cells. All dogs were killed at termination and both kidneys & urinary bladders removed and samples from each fixed in 10% neutral buffered formalin.

Results: One drug-treated dog showed large numbers of needle-shaped crystals on microscopic exam, suggestive of drug crystals. Three or 4 types of crystals were detected by HPLC in the urine of the dogs. The majority of the crystals seen were MK-366.

#7. Subacute Toxicity Study in Monkeys [Kyorin]

Material Tested: MK-366 administered as oral suspension

Animals, Doses & Duration: *Macaca fascicularis*; 4 groups, 2 M/gp; Controls (sterile dist. water), 25, 50 & 100 mpk b.i.d.; 4 wks

Schedule of Parameters Measured: Food & water intake, daily; body wt prior to treatment and day of sacrifice; hematological & serum biochem. parameters, pretest and after 2 & 4 wks of treatment; urinalysis, at necropsy. The following enzyme activities were determined in all animals at termination: ATP; glucose-6-phosphatase; B-glucuronidase; heart ATP; kidney ATP; bone marrow alkaline phosphatase; skeletal muscle ATP.

Wts of brain, pituitary, submandibular gland, thyroid, thymus, heart, lung, liver, pancreas, cecum, spleen, kidneys, adrenals, testes & epididymides were recorded at necropsy. Various tissues were fixed in

10% formalin. May-Giemsa stained bone marrow smears were prepared from all monkeys. Microscopic exam was done on hematoxylin- & eosin-stained sections from an extensive list of tissues.

Results: No changes attributable to treatment were seen.

8. Subacute Oral Toxicity Study in Immature Rats

Animals, Doses, Route & Duration: Immature (age under puberty) white laboratory rats (strain not specified); 4 groups - Control, 250, 500 & 1000 mpk/day; orally in suspension; 7 days/week for 4 weeks

Schedule of Parameters Measured: Observation of signs of toxicity & body wt gain daily; food & water intake weekly; hema: ogy, serum biochemistry, enzyme activity of kidney, heart & skeletal muscle, urinalys: , organ wt and gross & microscopic exams of various tissues near or at the end of the study.

Results

Body Wt; Food & Water Intake: No drug-related changes.

Hematologic & Serum Biochemical Parameters; Urinalysis: Stat. sig. changes in some of these parameters; however, the differences were small, within the limits of normal variation, and generally not dose-dependent.

Reviewer's Comment: The applicant does not consider these changes treatment-related. This might be true, but where are the reports on the expected arthropathy, at least clinically?

The following is a verbatim quotation from the report. Note: it does not even mention joint involvement.

"An increase of absolute and relative weights of ⁶secum was found in drug-treated males and females. This is not an uncommon finding in animals treated with antibacterial agents for long periods. There were no other organ weight changes or gross or microscopic changes attributable to treatment with MK-366."

CHRONIC TOXICITY

#1. 6-Month Chronic Toxicity Study in Rats [Kyorin]

Animals, Doses, Route & Duration: Laboratory white rats (strain not specified); 4 gps, 10/sex/gp - Controls, 125, 250 & 500 mpk/day; orally in suspension; 7 days/week for 6 mos. The age of the rats was 7 weeks at the start of the study. [Note: Puberty onset is at the end of the 10th wk of life in rats. Thus, for 3 wks this was a study in immature (juvenile) rats. I wonder if arthropathy was experienced during the first 3 wks of the study. However, since it is difficult to observe it clinically in the rat, and since the histopathology at the end of the 6-mo. treatment period might be negative (if they paid any attention to

the articular cartilage of the weight bearing joints), this study might indicate negative results with respect to arthrosis, although it could occur but remain unnoticed clinically during the first 3 wks of treatment.]

Schedule of Parameters Measured: Body wt, prior to the study and weekly thereafter; clinical signs, daily; food & water intake, once/week; ophthalmic exam, at 3 mos. & 6 mos. after start of treatment; hematology & urinalysis on all rats 2, 4 & 6 mos. after initial treatment; serum biochemistry on all rats 6 mos. after start of the study; glucose-6-phosphatase & B-glucuronidase, kidney ATP, bone marrow alkaline phos. activity in 5/sex rats from control & HD gps at study termination. All animals were terminally necropsied, and organ wts (heart, spleen, thymus, pituitary, adrenal, liver, pancreas, lung, brain, kidneys, testes, epididymides, prostate, ovaries & uterus) were recorded. Various tissues were fixed in 10% formalin. Microscopic exam was done on hematoxylin & eosin-stained sections of extensive tissues of all rats. Samples of liver & kidney were examined by using transmission electron microscopy. In addition, cochlea were examined using a scanning electron microscope to determine ototoxic potential.

Results: Slight body wt retardation was seen in M rats at the MD & HD. This did not occur in F. Serum albumin/globulin ratio showed tendency to increase in M at all dose levels and in F at the MD & HD. This was considered not to be treatment-related. There were no other changes attributable to treatment, including ototoxicity.

#2. Chronic Toxicity Study in Rats [Institute Gen. Path., Italy]

This study is identical to the previous study, but performed in Italy.

Results: No treatment-related changes in any of the parameters examined.

#3. 26-Week Oral Toxicity Study in Rats [MSD, Chibret, France]

Animals, Doses, Route & Duration: Laboratory white rats, 5 wks of age at study initiation; 4 gps - Controls, 50, 200 & 600 mpk/day; orally (gavage), suspended in aq. methylcellulose; controls received methylcellulose sol'n only.

Results

Signs: Grey feces (unabsorbed drug) in all treated gps; slight salivation occasionally in the HD gp.

Food & Water Intake: No significant effects.

Mortality: None

Body Wt Gain: Slight, but stat. insig. decrease in body wt gain in the HD M which could be treatment-related.

Hematology, Serum Biochemistry & Urinalysis: (weeks 4, 8, 12, 18 & 25) No drug-related hematological changes. Very slight but stat. sig. dec. in serum proteins were observed in M at the HD at all scheduled exams and in M at the MD in drug wks 8 & 12 (significance unknown).

Crystalluria, consisting of needle-shaped and "sea urchin" shaped crystals (dihydrate & magnesium salt of MK-366), occurred in rats from the MD & HD gps. Crystalluria was most common in M at the HD. There was no crystalluria in LD rats. A high incidence (40-100%) of cecal enlargement was seen at all dose levels. This is not an uncommon finding in rats treated with antibiotics for a prolonged periods. There were no other treatment-related changes seen at necropsy including organ wt & histopathology.

#4. 54-Week Oral Toxicity Study in Rats [Bio Research Labs, Ltd., Canada]

Animals, Doses, Route & Duration: Albino rats [Cri:CD (SD) Br strain]; 20/sex - Controls, 50, 200 & 600 mpk/day; orally by gavage as a suspension; up to 54 wks; controls rec'd dist. water. The age of the rats at study initiation was 7 wks. N.B.: This age is one week short of the onset of puberty, i.e., 8 wks.

Schedule of Parameters Measured: Physical exam of all rats, daily; more detailed physical exam of abnormal animals, weekly; body wts twice/week for 2 wks during the pretreatment period, the first 13 wks of feeding, and thereafter once/week & preterminally; ophthalmic exam of all animals prior to treatment and of control & HD rats during drug weeks 27 & 52; hematology, serum biochem. & urinalysis, drug weeks 6, 12, 25 & 51 using the first 10/sex rats of each gp. Necropsy was performed on all rats dead or sacrificed during the course of the study, and on the rest at termination. At necropsy: body wt measurement; histopathology on all dead & sacrificed rats, 10/sex from control & HD gps, and any rat from any group showing gross lesions at necropsy.

Results

Physical Exam: No abnormalities.

Mortality or Sacrifice of Moribund Rats: Total of 19 (controls, 4; LD, 2; MD, 7; HD, 6). None were considered to be treatment-related.

Body Wt: Lower than that of controls in all treated gps at termination; however, it was sig. different in the MD & HD F.

Ophth. Exam: No abnormalities attributable to treatment.

Hematology, Serum Biochem. & Urinalysis: Normal biological variations

Gross Pathology: Findings not indicative of drug treatment (normal abnormalities).

Organ Wt: Stat. sig. dec. in mean abs. wts of liver, spleen, heart & brain of the HD M, compared to controls. "The differences for the liver, spleen and heart were reflected in the organ weight relative to brain weight. Liver and spleen weights relative to body weight were also statistically significantly decreased. These findings are not considered to be biologically significant since all mean values are within the 95% range of controls values and since there were no histomorphological changes that could account for these organ weight changes."

Histopathology: No drug-related changes.

#5. 13-Month Chronic Toxicity Study in Dogs [Kyorin]

Animals, Doses, Route & Duration: Dogs (breed not specified), 6 mos. old; 4 gps, 4/sex/gp - Controls, 25, 50 & 100/200* mpk/day; orally as a coated tablet; 6 days/wk for 13 mos; controls rec'd placebo tablets.

- * "Dogs given 100 mpk/day for 10 months of the study were given 200 mpk/day for the remainder of the study."

Schedule of Parameters Measured: Clinical signs, daily; body wt, weekly; hematology, serum biochemistry, prior to study initiation and 3, 6, 9 & 13 mos. after the initial dose; urinalysis, 13 mos. after initial dose; ECG & ophth. exam, 13 mos. after initial dose. Organ enzymes monitored at termination were: liver ATP, glucose-6-phos. & B-glucuronidase, heart ATP, creatinine phosphokinase, kidney ATP, skeletal muscle ATP, creatinine phosphokinase, bone marrow alkaline phos. Similarly, drug metabolizing enzymes of the liver (cytochrome P-450; aminopyrimidenethylase; aniline hydroxylase) were examined at termination. Sera of all dogs were examined for specific antibodies vs. the drug at termination. All dogs were necropsied at termination and examined histologically.

Results: All of the above parameters remained normal.

Reviewer's Comment: The initial age of the dogs is the minimal age of puberty in this species. This explains the lack of degenerative joint disease.

#6. Chronic Oral Toxicity in Dogs [U. of Cagliari, Italy]

This is a shorter version of the previous (Kyorin) study. However, it lacks the wealth of parameters measured of the Kyorin study. Since this is not a pivotal study, it will be narratively reviewed.

MK-366 was administered orally as a susp. in distilled water, to gps of dogs (1/sex/gp) for 20 wks at dose levels of 25, 50 & 100 mpk/day. A control gp was established and rec'd distilled water. The animals were observed for general condition & behavior. Body wts were recorded weekly. Hematology, blood chemistry & urinalysis were done at the beginning and at the end of treatment. All animals were necropsied and major organs weighed. Histopath. exam of selected organs was performed.

Results: There were no treatment-related changes in any parameter examined. N.B.: No crystalluria.

#7. 21-Week Oral Toxicity Study in Dogs [MSD, Chibret, France]

Animals, Doses, Route & Duration: Beagle dogs, approx. 11 mos. old; 4 gps, 3/sex/gp - Controls, 50, 150 & 300 mpk/day; 7 caps/wk for 26 wks. The drug was suspended in 0.5% methylcellulose and administered in gelatin capsules up to Drug Week 6, and thereafter by oral gavage. Controls were treated with empty gelatin capsules or methylcellulose suspension.

Schedule of Parameters Measured: Clinical signs, daily; body wt, 2x/wk up to week 12, then once/week; ophth. exam, ECG, hematology, serum biochemistry & urinalysis, weeks 3, 8, 12, 17 or 18 & 25. F were sacrificed after receiving 182 doses, M after 183 doses. Routine histologic exam was done on all dogs from the control & HD gps, as well as those that died or were sacrificed prior to scheduled termination. In addition, heart, kidneys, and all gross changes observed were examined microscopically in all dogs.

Results

Mortality: Total of 4; 1 & 3 in the MD & HD, respectively - found dead or sacrificed because of deteriorating physical condition.

Clinical Signs

- dose-related emesis post-dose and salivation pre- & post-dose in all treatment gps; less frequent in the LD gp;
- gray or clay-colored feces (unabsorbed drug) in all treatment gps;
- anorexia in HD dogs that died or were sacrificed during the study;
- dehydration in 2 HD dogs;
- marked wt loss in the same 2 HD dogs;
- slight retardation of body wt gain in surviving MD & HD dogs.

Ophthalmologic Exam; EKG: No changes or abnormalities attributable to treatment.

Hematology; Serum Biochemistry: Treatment-related changes characteristic to uremia & nephropathy, secondary to intra-renal or urethral obstruction (MK-366 crystals). These changes occurred in those dogs that were sacrificed during the study, e.g., (1) neutrophilic leucocytosis & slight lymphopenia; (2) monocytosis & slight lymphopenia.

Biochemical studies in sacrificed dogs showed moderate-marked increases in BUN & creatinine and moderate decreases or increases in serum electrolytes. Slight-moderate increases in activity of SGOT, SGPT, and/or alkaline phos. were also seen in these dogs and were probably secondary to uremia. There was also slight-moderate stress-related inc'd serum glucose in these dogs.

There were very slight transient inc's in BUN & creatinine in one surviving HD dog. Blood was present in the urine of one surviving MD & 2 HD dogs. There were no macroscopic and/or microscopic changes to account for these.

Crystalluria was evident in all treated gps. The crystals were needle-shaped or "sea urchin" shaped and identified as the dihydrate or magnesium salt of MK-366, respectively. Crystalluria was seen in most dogs at the HD & occasionally at the LD & MD. Microscopic changes were seen in the 2 sacrificed MD & HD dogs. Urethral obstruction, as well as hemorrhages in the urinary bladder wall & renal capsule, congestion of renal parenchyma, renal tubular dilatation & hemorrhagic prostatitis were also evident upon gross examination of these dogs. Acute pyelitis, pyelonephritis & nephrocalcinosis were also seen in one of these dogs. The 3rd dog sacrificed, a HD F, had no sig. gross changes in the urinary tract. Renal tubular dilatation, pyelonephritis and very slight unilateral papillary necrosis were apparent in this dog and were considered secondary to obstruction of the ducts of Bellini. Other microscopic changes occurring in the GI tract of one dog, also considered secondary to uremia, included gastritis & a pyloric ulcer. Marked lymphoid depletion in the thymus was apparent in all HD dogs that died or were sacrificed during the study and was considered related to stress.

One HD dog found dead at Week 12, showed no renal or urinary tract changes, but did show slight lymphoid cell depletion related to stress. The changes were present in the lymph node, spleen & Peyer's patches. There were no signs of toxicity in dogs given the MK-366 LD. Crystalluria was seen occasionally in this group.

Reviewer's Comment: Except for occasional crystalluria, the LD appears to be safe. Since crystalluria is an inherent toxic effect of this group of drugs, the final answer should come from human clinical experience. However, in the HD, a new effect surfaced which has not previously been found to be part of the spectrum of toxicity of drugs of this class. This is the lymphoid depletion induction. The sponsor interprets this as a stress-induced change. I question this, since during a 6-month stress period, the adrenal cortex is either exhausted or undergoes hypertrophy. None of these are mentioned in the report. I suspect a peculiar endocrine related effect inherent to the drug or its metabolite(s), since the drug has another endocrine related effect on pregnant Cynomolgus monkeys. The lymphoid depletion, at least of the thymus, can be experimentally accomplished by parenteral admin. of either estrogens or progesterone & its synthetic derivatives, by simultaneous administration of both, or by testosterone alone in F rats. It is also well known that the admin. of exogenous glucocorticoids leads to the same effect, without stress. The importance of this lymphoid-depleting effect of the drug is that it may indicate an, as yet unsurfaced, potentially hazardous effect of this class of drugs. If the lymphoid depletion is a nonspecific stress-related effect, then any carcinogenicity study in laboratory animals should start with a report on "stress-related immunosuppression." Indeed, this is sometimes the case. However, I don't know if, from a sample statement on the presence of "allegedly

indirect immunosuppression" anyone can say that it is strictly stress related. A xenobiotic alone could be directly immunosuppressive, and at the same time, be responsible for the "treatment-induced chronic stress." Who can estimate the rate of contribution of the 2 factors from a simple histologic recognition of lymphoid depression? I wonder what a stress expert would say about this?

#8. 53-Week Oral Toxicity Study in Dogs [Bio Research Labs, Ltd., Canada]

Animals, Doses, Route & Duration: Beagle dogs (avg. age = 24-28 wks; age of replacement = 30-32 wks; the 24-28 wks of age coincides with the minimal age of puberty; the replacement dogs were already post-pubertal); 4 groups, 4/sex/gp - Controls, 50, 100 & 150 mpk/day of MK-366; gavage in aq. suspension; 7 days/week for 53 wks; controls rec'd distilled water.

Schedule of Parameters Measured: Physical exam of all dogs, daily; more detailed physical exam of abnormal dogs, weekly; body wt, pretest & weekly during treatment & just before sacrifice; food intake, daily prior to & during treatment; ophth. exam & EKG on all dogs, prior to treatment and at wks 12, 24 & 51; hematology, serum biochem. & urinalysis on all dogs, prior to treatment in at drug wks 6, 12, 23 & 50. At completion of the treatment period, all surviving dogs (except 5, fed by oversight) were fasted overnight, then killed by IV overdose of pentobarbital Na followed by exsanguination via incision of the axillary arteries. In dogs killed at study termination, the adrenals, brain, heart, kidneys, liver & testes were weighed. In addition, a necropsy was performed on all dogs sacrificed during the study. Hematoxylin & eosin-stained sections of tissues from all dogs were prepared for histopathological exams. Oil red O-stained frozen sections of liver & kidney from the same dogs were examined histopathologically by the applicant. Prepared & stained femoral bone marrow smears and reticulocyte counts for all sacrificed dogs were not evaluated, since hematological findings did not warrant these examinations.

Results

Clinical Signs: Silver-gray colored feces (unabsorbed drug) daily in the HD M & F, from wk 27 to termination.

Mortality: One HD M at wk 7, attributed to intussusception of cecum into the colon; one control F at wk 5, [dermatitis (demodicosis), undefined pulmonary pathology (abnormal respiratory sounds & congestion)].

Body Wt Gain: The HD dogs had lower wt gain than controls; wt gain in the LD & MD dogs was comparable to controls.

Food Intake: No adverse effect in any gp.

Ophth.; EKG; Hematology; Serum Biochem.; Urinalysis: No treatment-related effects.

Gross Path.; Organ Wts; Histopath.: No treatment-related findings.

Reviewer's Comment: This study contradicts the French study. The dose levels, except for the 300 mpk dose of that study (French), are identical.

The duration of treatment in this study is approx. double that of the French study and the age range of the animals is the same; yet this study is incredibly clean. Where is the crystalluria, nephropathology, lymphoid depletion, at least at 150 mpk? The applicant should explain this. [Is the French dog (whichever breed) reacting differently than the Canadian dog? Where is the stress effect?]

I also wish to note that, in my experience, the final outcome of a toxic effect depends not only on the dose, but on the duration of treatment. In other words, toxicity is the result of a multiplication of the daily dose with the no. of the days of admin. In this case, 300 mpk for 26 wks should result in the same sort & severity of toxicity as 150 mpk for 53 wks (in terms of lymphoid depletion). Lymphoid depletion (immunosuppression) is particularly bad for an antimicrobial drug. Although this cosmetic mistake is not severe enough to hold up approval of this drug, an acceptable explanation should be submitted by the applicant. The 50 mpk/day "no effect dose level" is high enough for the calculation of an acceptable and efficacious human dose.

SPECIAL STUDIES

These studies follow the order in Vol. 2.51.

Arthropathy Studies

#1. Effect on the Diarthroidal Joint of Immature Dogs [Kyorin]

Animals, Doses, Route & Duration: Beagle & mongrel dogs, 3-5 mos. of age; 2/group and a neg. control gp. The treated dogs received orally:

- MK-366 @ 30, 60, 100, 250 & 500 mpk/day for 7 days, recovery study - 200 mpk/day for 99 days;
- Pipemidic Acid @ 30, 60, 100, 250 & 500 mpk/day for 7 days;
- Nalidixic acid: 30, 60 & 100 mpk/day.

Results: This is the best report I have ever seen on this subject. The summary is excellent and worthy of a verbatim quote. [At the end, I will make some comments on certain aspects of this study; however, is there any study which cannot be made better or more comprehensive?]

"Clinical signs of lameness appeared from the second day of treatment in dogs given doses of MK-0366 greater than 60 mpk/day which persisted through the duration of the study (7 days). In the 99-day study there was recovery from clinical signs within 6-8 weeks after initiation of the study. The degree of lameness was related to dose administered. In dogs administered PPA (pipemidic acid) and NA (nalidixic acid), similar dose related lameness was seen at dose levels greater the 30 mpk/day.

An increased amount of synovial fluid was found at necropsy in dogs at doses at 100 mpk/day or greater for all three compounds in the 7-day study. The synovial fluid was sometimes yellow & semiopaque with white suspended matter. The abnormality in the synovial fluid was dose dependent for all three compounds. No abnormality was seen in the synovial fluid of dogs in the 99-day study at the time of necropsy.

The joint lesions were characterized by blister formation in the articular cartilage. At higher doses ruptured blisters (erosions) were common. The chondrocytes adjacent to the blisters and erosions were hypertrophied. Although there was recovery from clinical signs in dogs in the 99-day study, gross and microscopic changes were evident in the articular cartilage at termination. Synovial membranes and epiphyseal plates were not affected by any of the three compounds tested.

No abnormalities related to treatment were detected in the hematologic and serum biochemical parameters, urinalysis or tissue enzymes."

Reviewer's Conclusions

- a) The study shows that the very left-hand ring of the quinolone, which is a fused substituted benzene in MK-366, could be modified by exchanging 1 carbon of the ring with a N-atom (NA) or 2 carbons with 2 nitrogen atoms (PPA) without losing the arthrotoxicity of the drug.
- b) The molar conc'n of the same dose is higher for NA (m.w. 232.23), less for PPA (m.w. 303.33) and even less for norfloxacin. Though the minimal arthropathogenic dose is not known for any of the drugs, from the available data, a conclusion based on the ratio of molecular size (no. of moles) and severity of the lesions cannot be drawn.
- c) No other organs or systems were affected by MK-366 from a 500 mpk/day dose for 7 days, or from 200 mpk/day for 99 days.
- d) Conspicuous is the finding in the synovial fluid at 100 mpk/day and higher. Unfortunately, it is not stated that this change included increased viscosity; cloudiness was due to inflammatory cellular exudate and/or increased protein content. The most important aspect of protein content would be its enzyme activity, which was not investigated.
- e) It is also interesting that minor lesions in the articular cartilage are present, in the case of all these drugs, at doses not inducing changes in the synovial fluid; therefore, it is safe to assume that the synovial fluid change is not essential in the pathogenesis and that it appears to be secondary.
- f) The hypertrophy of the chondrocytes adjacent to blebs & fissures indicates something. Is this a desperate tendency to regenerate, or do these cells only appear to be hypertrophied since, in the neighborhood of the "lakes", they are not compressed as tightly as in normal cartilage?

- g) It is still not clear from this study (or any study) whether or not the chondrocytes or the matrix are primarily affected by the drug or vice versa. From one single photograph of Dr. Margett's, I am unable to conclude that the drug is deposited only in the chondrocytes in the case of NA in the rat.
- h) The drug does not appear to be an enzyme inhibitor in a general sense, since it did not show these effects in a number of visceral enzymes. The 3 enzymes that might play a crucial role in the articular toxicity of these drugs might be Mg-dependent topoisomerase, the Mg-dependent GPI-ase, and the group of lysosomalytic (proteoglycan) enzymes of the chondrocytes, which were not investigated.
- i) This study also proved that only the juvenile cartilage is sensitive to the arthrotoxic effects of the drug. Prior to this study, they tested mature rats & dogs for this purpose, with negative results.
- j) Finally, the study shows that MK-366 is less arthrotoxic (with a factor of 2) than the world-wide (USA involved) marketed NA, and the world-wide (except USA) marketed PPA.
- k) Although the applicant rightly determined the acute toxicity of the individual metabolites, it is unknown whether or not the drug per se, or one or several of the metabolites, with or without the drug in concert, are responsible for the arthrosis.
- l) This study does not identify any objection to the approval of the drug.

#2. Study in Immature Rabbits [Kyorin]

Animals, Doses & Duration: Japanese white rabbits, 8-10 wks old; 250 & 300 mpk/day of MK-0366 for one week or 100 & 300 mpk/day for 21 days; groups of 5-11 rabbits; 4 other groups were treated with NA (150 mpk) & PPA (250 mpk/day) for 7 days, as pos. controls.

Results: No gait abnormalities, hematologic, serum biochemical, urinary or tissue enzyme changes related to treatment in any group.

Pathology: Gross blisters were seen on the articular cartilage of the stifle, hip or elbow joints or some of the rabbits treated with NA, PPA & MK-366 for 7 days. The rabbits given MK-366 for 21 days had no blisters on the articular cartilage. However, 1/5 control rabbits also had blisters on the articular surface of the stifle joint. Histopathologically, activation was seen at the intermediate zone of the cartilage with matrix rarefaction & fibrillation in the immediately surrounding cartilage.

Reviewer's Comment: The study does not indicate the no-arthropathogenic-effect dose level in rabbits.

#3. Antigenicity Studies [Kyorin]

- MK-366 elicited no delayed hypersensitivity reaction on the skin of guinea pigs, whereas under the same conditions, 2,4-dinitrochlorobenzene elicited a positive response.
- Anaphylactic reaction was not observed in guinea pigs sensitized with MK-366 alone or in a mixture with Freund's complete adjuvant (FCA).
- Serum from guinea pigs sensitized with MK-366 induced no passive cutaneous anaphylaxis in recipient guinea pigs.
- Specific antibodies vs. MK-366 were not detected in sera of rabbits immunized with MK-366-BGG conjugate & FCA.

#4. Guinea Pig Skin Maximization Test [Kyorin]

There was no evidence (gross or microscopic) of sensitization in the MK-366 treated groups. On the other hand, the challenge sites of all animals in the DNCB group showed, as expected, characteristic sensitization reactions consisting of slight-marked dermal inflammation and slight-moderate epidermal thickening.

#5. Influence on the Retina of Cats [Kyorin]

Retinal toxicity of MK-366 was evaluated in cats by electroretinogram (ERG) & histopathological exam. NA was used as a reference substance. MK-366 or NA was infused IV (0.8 ml/min) at a dose of 40 mpk and ERGs were recorded during & after dosing. There were no sig. changes in latent times or amplitude of ERG waves during or up to 60 min. after dosing with MK-366, when compared with those before admin. NA, on the other hand, caused a prolongation of latency as early as 15 min. after the start of dosing, followed by complete loss of op- & b-waves of ERG.

In another experiment, MK-366 was administered orally at doses of 50, 100 & 200 mpk/day for 2 wks. NA was administered orally @ 100 & 200 mpk dose levels (varied doses, based on the presence or absence of toxicity) for 2 wks. ERGs were recorded at termination under anesthesia or while the animal was immobilized by a muscle relaxant. All animals were killed after recording of ERG and eyes were collected for histopathology. Results of histopathologic exam were negative.

#6. Auditory Toxicity in Rats [Kyorin]

Schedule: A daily dose of 500 mpk of the drug was given orally to Wistar rats for 7 mos. Other groups of rats were given 200 mpk b.i.d. of kanamycin & 400 mpk b.i.d. of streptomycin for 27 days (pos. controls). All groups were tested for auditory & vestibular function at the end of their period of treatment.

Upon completion of auditory & vestibular function tests, the animals were killed and cochleae were resected & processed for scanning electron microscopic exam.

There were no treatment-related changes in auditory or vestibular function in rats given MK-366 @ 500 mpk/day for 6 wks. There were also no histopathological changes in the organ of Corti.

The rats given streptomycin showed changes in vestibular function characterized by tremor, tilting of the head & decreased ability to balance on a bar; there were no abnormal auditory functions or histopath. changes in the organ of Corti. The rats treated with kanamycin showed auditory dysfunction, but no vestibular dysfunction. Histologically, there were dec's in the number, reaction & size of cilia of the inner hair cells and complete loss of cilia in the outer hair cells.

7. Acute Phototoxicity in Female Mice [Method of E.S. Copeland, et al., J. Invest. Dermatol. 64: 349-356, 1975]

In this study, chlorpromazine was used as a positive control. Oral admin. of MK-366 at doses of 625, 1250 & 2500 mpk produced no perceptible erythema in F mice after 20 hrs of exposure to long wave UV light. However, oral admin. of chlorpromazine, a known phototoxic agent, produced definite erythema of the ears at a dose of 120 mpk. All 6 animals in this group showed moderate erythema 3 hrs following exposure. By the 7th day, 4 of these had slight or no erythema, while the remaining 2 had marked erythema with scarring. Negative control animals (water) showed no evidence of erythema.

8. Ocular Irritation Study in Rabbits (Draize Method)

All rabbits showed a normal body wt gain during the study. Instillation of MK-366 powder into conjunctival sac produced a very slight conjunctival injection & moderate cloudy discharge at 15 min. The severity of ocular effects increased by 24 hrs with a moderate injection & discharge and a marked amount of chemosis; 2/4 eyes had corneal opacification & circumcorneal hemorrhage by the 4th day; 3/4 eyes appeared normal after 10 days; the remaining eye continued to show severe ocular irritation at day 14.

Applicant's Conclusion: MK-366 was found to be severely irritating to the rabbit eyes in a primary eye irritation study.

9. Drug Deposition Study in Dogs

Purpose of the Study: To determine in Beagle dogs (3 gps, 3/sex/gp), the conc'n of MK-366 in the plasma, aq. humor & lens of dogs after 1 & 21 oral doses of 7 days after cessation of treatment.

Conclusions

- a) Once daily oral admin. of 150 mpk of MK-366 for 21 days to dogs resulted in a small, though stat. sig., increase in aq. humor levels, ranging from 0.06-0.11 ug/ml.
- b) Three-week admin. of MK-366 resulted in a small, but stat. sig. inc.

in the lens content of the product. Such an observation would not be unexpected, as the product is present in low conc'ns in the aq. humor. What is clear is that the avidity of the lens for MK-366 is negligible as reflected by the very low value of 0.24 ug/g. The presence of low conc'ns of MK-366 in the lens most probably result from simple diffusion.

- c) The lack of sequestration of MK-366 by the lens is clearly shown by the rapidity of washout following cessation of treatment, conc'ns declining from 0.24 to 0.08 ug/g at 7 days.
- d) Once daily admin. of 150 mpk of MK-366 does not result in a marked, persistent accumulation of the compound in the dog lens.

REPRODUCTION STUDIES

#1. Effect of MK-366 on Fertility in M & F Mice [Kyorin]

Animals, Doses, Route & Duration: White laboratory mice (SLC:ICR strain); 4 gps, 21 sex/gp - Controls, 125, 250 & 500 mpk; oral; Days 6-15 of gestation. Prior to this an equal no. of M & F were kept together (1:1/cage) until the appearance of a vaginal plug (= day 1 of pregnancy).

Parameters observed were: maternal toxicity, embryotoxicity & lethality, functional & behavioral tests of newborn F₁ & F₂ generations and reproduction performance of F₁ & F₂ generations.

Results: No abnormalities were observed in any parameter.

#2. Teratogenic Effects in Mice [Institute of Gen. Path., Italy]

Animals, Doses, Route & Duration: Laboratory F white mice; 4 groups, 20/gp - Controls, 100, 200 or 400 mpk/day; oral; Days 5-16 of pregnancy.

Results: There were no drug-induced effects on the dams. There were also no treatment-related differences in gestation period, no. of corpora lutea, no. of implants, no. of resorptions, no. of live or dead fetuses, wts of fetuses or external malformations.

#3. Effects of Oral Admin. on Pregnancy in the Rat (Dose-Range-Finding Study) [Life Sciences Res., U.K.]

Animals, Doses, Route & Duration: Charles River CD rats; 5 groups, 20 F/gp - Controls, 200, 400, 600 & 800 mpk; oral; Days 6-17 of pregnancy.

Results: Treatment with MK-366 had no effect on the general condition of the animals or upon body wt gain during gestation. MK-366 had no adverse effect on pregnancy, as assessed by external exam of the uterine horns. It was concluded from this preliminary study that dose levels up to 800 mpk/day should be suitable for use in a main teratology study in rats.

#4. Effects of Oral Admin. on Pregnancy in Rats [Life Science Res., U.K.]

Animals, Doses, Route & Duration: Pregnant F SD/CD rats; 4 groups, 25/gp - Controls, 50, 200 & 800 mg/kg b.i.d.; oral; Days 6-17 of pregnancy.

Results: The general condition & body wt gain of treated animals were similar to those of the controls throughout the study.

At termination on Day 20 of gestation, there were no changes or trends in the nos. of implantations and viable young or in the extent of pre- & post-implantation losses that could be attributed to treatment. Fetal & placental wts were similar in all gps.

Fetal exam at necropsy, by free-hand serial sectioning or following skeletal processing, revealed a small no. of anomalies in all gps, including 4 abnormal fetuses, but no indication of any adverse effects could be related to treatment with MK-366.

#5. Teratogenicity Study of AM-715 in Rats [Kyorin]

AM-715 Chemical Formula: 1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-Piperazinyl)-3-quinolinecarboxylic acid

Animals, Doses, Route & Duration: JCL-SD rats (pregnant F only); 30/gp - Controls, 125, 250 & 500 mpk/day; oral; Days 7-17 of pregnancy. [Max. dose equiv. to 41.7x the proposed clinical dose (12 mpk/day)].

Results: AM-175 showed no undesirable effect on pregnant rats. In the F₁ fetuses of the treated gps, it was determined that the gross malformations, visceral & skeletal abnormalities and variations observed were within the limit of spontaneous occurrence.

AM-715 produced no serious effect on growth, differentiation, functions, behavior or reproductive performance of the newborns. The drug showed no toxicity or any effect on F₂ fetuses.

From the above, it was concluded that admin. of AM-175 to rats during organogenesis, at the doses used in this study, had no adverse effect. Therefore, 500 mpk/day was assumed to be the maximum dose producing no overt teratological effect in rats.

#6. Effects of Oral Admin. on Pregnancy in Rabbits (Dose-Range-Finding Study) [Life Sci. Res., U.K.]

Animals, Doses, Route & Duration: Japanese white domestic rabbits (pregnant F only), 8/group; Controls, 50, 100 & 200 mpk; oral; Days 6-18 of gestation. All surviving rabbits were sacrificed on 2 days before expected parturition.

Results: Body wt loss or dec'd body wt gain and premature births or abortions were observed in all dosage gps.

Applicant's Comments: In view of the sensitivity of MK-366, the rabbit was considered unsuitable for use in a full teratology study. This sensitivity is due to the disturbance of the GI flora.

7. Teratology Study in Rabbits [Kyorin]

Animals, Doses, Route & Duration: White domestic pregnant F rabbits; 4 groups, 12-13/gp; Controls, 25 & 100 mpk/day; oral; Days 6-18 of gestation. On day 29 of gestation, all dams were sacrificed for examination of uterine contents.

Results: Only at the HD, slight dec. in spontaneous movement, sig. reduction of appetite, diarrhea & reduction of body temp. were noted. Sig. wt gain reduction also in the same gp. One dam of this gp aborted dead fetuses on the 27th day of gestation.

Embryotoxicity: Noted in the HD only: inc'd no. of dead embryos and resultant dec. in the no. of surviving fetuses. There were no external, visceral or skeletal malformations that were considered related to the admin. of MK-0366.

8. Exploratory Plasma Profile Study in Rabbits [MSDRL, USA]

Reason for Study: As was suggested in the earlier rabbit studies, the oral route for teratogenicity studies in rabbits is not appropriate. Therefore, it was decided to determine the drug's toxicity in the absence of an effect on intestinal flora by administering the drug parenterally.

A comparative plasma profile study (oral vs. SC) was performed in rabbits, in order to aid in the selection of doses for parenteral admin.

Animals, Doses, Route & Duration: Nonpregnant F NZ albino rabbits; 2 groups, 3/gp; 100 mpk, once, orally; 20 mpk once, SC. Plasma was collected 0.5, 1, 2, 3, 4, 5, 6 & 24 hrs post-dose. Determination of plasma levels were done by microbiological assay. N.B.: This might indicate that in the case of oral admin., a great deal of microbiologically nonactive metabolites entered the blood stream (intestinal microbiological metabolism); but since they don't have antimicrobial effects, the assay does not indicate their presence.

Results: Plasma level of MK-366 peaked at 0.6-1.3 ug/ml within 3 hrs following oral admin. and at 6.8-6.9 ug/ml within 0.5 hr follow SC admin. At 24 hrs post-dose, there was no detectable amount of drug in plasma in either gp of animals.

Based on these results, 20 mpk/day SC is judged to be a more than adequate dose to attain blood levels as high & prolonged as 100 mpk/day orally.

9. Exploratory Biliary Excretion Study in Rabbits [MSDRL, USA]

Reason for Study: As is evident from earlier rabbits studies, oral MK-366 appears to be much more toxic to rabbits than to other laboratory animals (rats, mice). It appears that for teratogenicity studies, the parenteral route is the only available way for the rabbit. To avoid disturbing interference by enterohepatic circulation of the drug, its

biliary excretion had to be explored. The SC route is valuable only if biliary excretion is minimal; therefore, a substantial amount of the SC-administered dose does not enter the intestines, and after being metabolized by the GI bacteria, does not enter the blood stream as a highly toxic metabolite. (Urinary excretion is predominant in most species.)

Animals, Doses, Route & Duration: NZ albino rabbits; 4 groups (1/group) anesthetized; SC; 20 mpk of MK-366. Bile was collected continuously via a cannula in the common bile duct; blood samples were collected periodically for 4-6 hrs after dosing; determinations were done by microbiological assay.

Results: Plasma levels of MK-366 peaked at 3.84-14.4 ug/ml between 10 & 60 min. post-dose. Levels of MK-366 in the bile peaked at 33.3-93.5 ug/ml between 30 & 90 min. post-dose and inc'd & dec'd approx. in parallel with plasma levels. The total amount of drug excreted in bile during the 4-6 hr post-dose period represented 1.2-2.4% of the SC dose. By extrapolating from the decreasing rate of biliary excretion at the end of the collection period, it can be estimated that the total amount excreted in bile would have been 2-4%.

Applicant's Remarks: "The low rate of biliary excretion of MK-0366 in the rabbit makes it possible to design a study to test the hypothesis that the toxicity and fetotoxicity associated with oral dosing may be due to an effect on the intestinal flora."

10. Exploratory Toxicity Study in Nonpregnant Rabbits [MSDRL, USA]

Reason for Study: To prove the hypothesis that the maternotoxicity of MK-366 was secondary to an antibiotic effect on the GI flora, it was decided to administer the drug parenterally, and thereby determine its toxicity in the absence of an antibiotic effect on the intestinal flora. The results of the previous study proved that the biliary excretion rate is low (2-4%); therefore, the potential interference by that portion of the drug that re-enters the circulation after being excreted in the bile is negligible.

Study Objective: To determine whether SC admin. of MK-366 for 13 days at doses up to 20 mpk/day is tolerated in rabbits.

Methods: In this study, which used NZ albino rabbits, MK-366 was given SC to 3 groups of 5 F, at dosage levels of 5, 10 & 20 mpk/day. A 4th group of 5 F received 100 mpk/day of MK-366 orally by rubber catheter in 4 ml/kg of 0.1% methylcellulose. A 5th group of 5 F received 0.9% saline SC and served as controls. The drug (factor = 1.00) or control article was administered once/day for 13 days (day of 1st dose = Day 1). The dosing volume for the SC gps was 0.5 ml/kg. At the beginning of the study, the F were approx. 5-6 mos. of age & weighed 3680-4370 gm.

At the end of the 13-day dosing period, the F were observed for an additional 7 days. Body wts were recorded on Days 1, 4, 7, 10, 13, 14,

17 & 20. Food intake, at 24-hr intervals, was measured the day before the 1st dose and every 3rd day beginning at Day 1. At 0.5 & 3 hrs after the 1st & 13th doses, the rabbits were bled for determination of plasma levels of MK-366 by microbiological assay. On day 14, they were bled for determination of serum levels of urea nitrogen, creatinine, Na, K & Cl. On Day 20, they were sacrificed and discarded without further examination.

Results: There were no deaths. Toxicity was apparent @ 100 mpk/day PO as a mean body wt loss of 354 gm during the dosing period compared to a wt gain of 132 gm in controls. The wt loss was accompanied by dec's in food & water intake. Mean food intake @ 100 mpk/day PO dec'd during the dosing period to 20-30% of controls levels, then inc'd during the post-dose period, but remained below that of controls. Also, on Day 14, there were slight but sig. inc's (Day 14) in serum creatinine (up to 2.0 mg/dl) & urea nitrogen (up to 24.4 mg/dl) levels in the 100 mpk/day orally-treated gp. There was no evidence of toxicity with the SC route.

Orally dosed F had orange urine as early as Day 10 and as late as Day 20. There was no discolored urine in the SC-treated gp.

At 0.5 hr following the 1st dose, plasma levels of MK-366 in the 100 mpk/day PO gp (mean = 1.02 ug/ml) were much lower than those in the 5, 10 & 20 mpk/day SC gps (means = 2.25, 5.33 & 9.25 ug/ml, respectively). Following the 13th dose, however, the oral plasma levels had inc'd compared to those after the 1st dose. At 0.5 hr post-dose (PD), the oral levels (mean = 1.77 ug/ml) were almost as great as those @ 5 mpk/day SC (mean = 2.45 ug/ml). At 3 hrs post-dose, the oral levels (mean = 1.5 ug/ml) were greater than both the 5 & 10 mpk/day SC levels (means = 0.59 & 1.24 ug/ml, respectively). Only the 20 mpk/day SC gp had plasma levels (3.76 & 1.94 ug/ml @ 0.5 & 3 hrs after 13th dose) which exceeded those in the oral gp at all time points tested.

Applicant's Conclusion: "Since the toxicity seen with oral dosing was not seen with SC dosing, even though blood levels of drug were higher following SC dosing, it seems likely that the toxicity seen with oral administration of high doses is not due to a systemic effect of the drug but rather to an effect on the intestinal flora."

11. Exploratory Blood Level Study in Nonpregnant Rabbits

Study Objective: To determine plasma drug levels at many time points after the 1st & 13th doses in order to better define the kinetics of the plasma levels of the drug. In addition, the effect of dec'd food intake on plasma levels of MK-366 was examined in a 2nd gp of F.

Method:

Group A: 5 F NZ albino rabbits received 13 daily oral doses (= Days 1-13) of 100 mpk/day, and were provided with the normal daily allotment of 150 gm/day of food.

Group B: Received a single oral dose of 100 mpk on Day 13 and were provided with an amount of food approx. equal to the max. level consumed

by a gp identical to Group A in a previous study (130 gm, Day 1; 100 gm, Day 2; 70 gm, Day 3; 40 gm, Days 4-13). The base compound of the drug (factor = 1.0) was suspended in 0.1% aq. methylcellulose and administered orally via rubber catheter at a dose volume of 4 ml/kg. At the beginning of the study, the animals were approx. 5-6.5 mos. of age and weighed 3620-4180 gm. Body wts were recorded on Days, 1, 4, 7, 10, 13 & 14. Food intake was measured at 24-hr intervals beginning on Day 1. On Days 1 & 13 (Gp A) & Day 13 (Gp B), the F were bled at 0.5, 1, 2, 3, 4, 6, 8 & 24 hrs PD for plasma drug level determination by a microbiological bioassay procedure. Plasma drug levels were also determined for samples collected from Gp A just before dosing on Day 13. On Day 14, the animals were sacrificed and discarded without further examination.

Results: There were no deaths. Toxicity was apparent in the gp receiving multiple doses (Gp A) as dec'd food & water intake and a mean body wt loss of 266 gm. Some F in Gp A had dark or orange urine as early as Day 9 and as late as Day 13. F in the pair-fed Gp B consumed all food provided and had inc'd water intake, but had approx. the same overall body wt loss (mean = 304 gm) as F in Gp A.

Following the 1st dose, the highest plasma level in Gp A occurred at 0.5 & 1 hr PD (mean levels = 1.25 & 1.24 ug/ml, respectively). No drug was detected at 8 hrs PD. Following the 13th dose, the peak plasma level (mean = 3.5 ug/ml), occurring at 1 hr PD, was approx. 3-fold higher than that following the 1st dose. The drug had not been cleared from plasma, even at 24 hrs after the 12th & 13th doses (mean levels = 0.34 & 0.36 ug/ml, respectively).

In the pair-fed gp B, the highest plasma levels following the single dose on Day 13 occurred at 0.5 & 1 hr PD (mean = 0.92 & 0.89 ug/ml, respectively). The drug had been cleared from plasma by 6 hrs PD. Thus, a low level of food intake for 12 days did not cause inc'd plasma levels of MK-366 in Gp B and is not an explanation for the inc'd plasma level following the 13th dose in Gp A.

Other possible explanations which have not been tested include the following:

- MK-366 may be broken down in the gut to a greater extent with the normal flora than with the antibiotic-altered flora.
- The drug may be bound to intestinal contents to a greater extent with the normal gut flora compared to the antibiotic-altered flora.
- Transit time in the gut may be inc'd in MK-366-treated rabbits.
- The drug may cause an inc'd absorption rate or a dec'd excretion rate.
- The drug may inhibit its own metabolism in the liver.

12. SC/Oral Teratology Study in Rabbits [MSDRL]

Objectives: To determine if the fetal wastage observed with oral MK-366 dosing is also specific to the oral route and not correlated with drug plasma levels, a combined oral/SC teratology study was conducted.

Methods: MK-366 was administered to NZ albino rabbits orally at a dose of 100 mpk/day to a gp of 20 artificially inseminated F and SC @ 20 mpk/day to a 2nd gp of 20 inseminated F. A 3rd gp of 20 F received saline SC and served as controls. For oral dosing, the drug was suspended in 0.1% aq. methylcellulose and administered at a dose volume of 4 ml/kg. For SC dosing, the drug was dissolved in saline. The dose vol. for both SC gps was 0.5 ml/kg. The drug (factor = 1.00) or control article was given once/day on gestational Days 6 thru 18. At the beginning of the study the F were approx. 6-6.5 mos. of age and weighed 3870-4840 gm. Body wts were recorded on Days 0, 6, 8, 10, 12, 14, 16, 18, 19 & 28 of gest. Food intake was measured at 24-hr intervals every 3rd day beginning on Day 3 of gest. At 1, 4, 7 & 24 hrs after the 1st dose on Day 6 of gest., 5/gp were bled for drug plasma level determination. The same F (except for 1 orally dosed F that died after an intubation accident) were bled again for this purpose just prior to the last dose on Day 18 of gest. and at 0.5, 1, 2, 3, 4, 8 & 24 hrs after the last dose. Because of the possibly complicating effects of the bleedings, these F were sacrificed after the last bleeding on Day 19 of gest., then examined grossly. On Day 28 of gestation, the remaining F were sacrificed & evaluated.

Results: There were no treatment-related deaths or abortions. One F at 100 mpk/day PO was found dead on Day 14 of gest. following an intubation accident. There were 2 abortions @ 100 mpk/day PO on Days 26 & 27 of gest. The F @ 100 mpk PO that aborted on Day 27 of gest. had a small amount of blood stained fluid in the thoracic cavity and associated pulmonary telectaxis? At termination on Day 28 of gest., 4 F at 100 mpk PO had varying amounts of clear fluid in the thoracic and/or abdominal cavities compared to one in controls. The applicant feels that this was due to malnutrition.

In the gp dosed orally, maternotoxicity was seen as mean wt loss during the dosing period and inc'd wt gain at the end of dosing. Embryotoxicity was apparent @ 100 mpk/day PO, as evidenced by inc'd resorption, dec'd fetal wt & delayed ossification. There was no maternotoxicity or embryotoxicity in the SC-dosed group.

Applicant's Comment: Since embryotoxicity occurred in the gp with maternotoxicity & lower peak blood levels (100 mpk PO), it is concluded that embryotoxicity is not a direct effect of the drug on the embryo, but rather secondary to maternotoxicity.

Reviewer's Comment: The above explanation is acceptable.

14. Fertility Study in Mice [Kyorin]

MK-366 was administered orally as a suspension in sterile distilled water at dose levels of 125, 250 or 500 mpk/day to ICR M mice (20/gp) for 61 days before mating & during mating, and to ICR F mice (20/gp) daily for 15 days before mating until the 6th day of pregnancy.

Two similar gps of mice served as controls and received distilled water.

The mice were examined daily for their general condition. Body wts were taken daily. Food & water intake were measured once/week for M and 2x/wk for F prior to mating. All M mice were sacrificed & necropsied after mating, and their reproductive organs weighed. On Day 18 of pregnancy, the F were sacrificed, and after fetuses were removed, the corpora lutea & no. of implantation sites were counted. The no. of surviving fetuses, dead fetuses & resorption sites were also counted. The body wts of surviving fetuses & placental wts were also counted. The fetuses were examined for external, visceral & skeletal abnormalities.

Results: No treatment-related effects on reproductive performance or differences in growth & differentiation of the fetuses were observed.

15. Peri/Postnatal Study in Mice

MK-366 was administered orally, suspended in distilled water to F mice (21/gp) from Day 15 of gest. to Day 21 postpartum at dose levels of 0, 125, 250 & 500 mpk/day. The purpose of this study was to determine the effect of the test compound on growth, function, behavior & reproductive performance of F₁ & F₂ offspring. General symptoms & body wt were checked daily during gest. and the nursing period. All pregnant F were allowed to deliver. The length of gest., the no. & sex of newborns and their external abnormalities were determined. The newborns (F₁) were tested for growth & various physiological functions, including reproduction. Major organs were weighed. F₂ offspring were treated in the same manner as the F₁ newborn.

Results: No abnormal signs induced by MK-366 were observed in dams. The body wt of the treated gps was similar to that of controls at all times except on day 18 of gest. in the 500 mpk gp. This was not considered biologically sig.

No sig. differences were observed in the newborns in treated gps compared to controls, in gestation length, sex ratio, birth rate & weaning rate. There was no difference in the no. of implantation sites. There were no external or skeletal abnormalities related to treatment in the F₁ or F₂ newborns. There was also normal body wt gain. Also, there were no abnormalities in function, behavior or reproductive performance of the F₁ or F₂ offspring that were considered related to treatment.

Addendum: In the presently ongoing teratology study in cynomolgus monkeys, preliminary evidence indicates embryoletality at relatively high doses (200 mpk). There is, however, no evidence of teratogenicity. The study is continuing to establish a no-effect level.

Reviewer's Comment: Among all the reproductive & teratology studies, the rabbit & the cynomolgus monkey studies are troublesome. The studies elucidating the maternal-toxicity-dependent embryotoxicity of MK-366 are convincing. By learning about this phenomenon, we are introduced to a new concept in teratology. The rabbit studies do not affect the approval of the drug.

Much more important are the results of the cynomolgus monkey studies which are only briefly mentioned in the NDA and therefore not reviewed above. We have discussed the findings with the applicant. In the present submission, the summary indicates that the drug decreases the serum progesterone level in this species so drastically that dead and/or aborted feti will be delivered by a sizeable portion of the treated group, or if the embryolysis happens quite early, the uterus appears empty at study termination in monkeys which, prior to study initiation, were definitely pregnant.

Since I do not have the final report of the study, I cannot commit myself to anything at this time. However, as I already mentioned, the serum progesterone level reducing effect of the drug should be tested in nonpregnant women. I understand that the progesterone level during pregnancy is much higher than before pregnancy, and that a female body might react differently during pregnancy. I cannot imagine the testing of the effect of the drug in pregnant women, unless it could be done in such cases where the woman is determined to have an abortion anyway. Without saying more about the medical problem, I leave the decision to the medical fora. I anticipate that the monkey findings will call for Pregnancy Category "C", but I cannot offer a final decision on labeling until all the monkey data are submitted (and/or the drug is tested in pregnant women, if this is determined to be ethically feasible by the reviewing MD.)

MUTAGENICITY

MK-366 was tested for mutagenicity in the following tests:

In Vivo Studies: Dominant Lethal Test; Chromosomal Test

In Vitro Studies: V-79 Mammalian Cell Mutagenesis; Rec-Assay; Ames Test; Cytotoxicity Test; Chromosomal Aberration Test, Sister Chromatid Exchange; Unscheduled DNA Synthesis in Rat Hepatocytes; Autoradiographic Assay.

Results: Only the Rec-Assay was weakly positive. In view of this single positive finding, the applicant decided to run a special rat carcinogenicity study, using Fisher rats, 5 wks of age; 3 groups, 50/sex/gp - Controls, 0.05% & 0.2% MK-366 in the diet. Feeding period was 19 mos. followed by withdrawal period of 12-14 wks. Results: No evidence of carcinogenic effect has been observed thus far.

PHARMACOLOGY

MK-366 appears to be without marked pharmacological action in the central & peripheral nervous, GI, and cardiovascular systems. In general, activity was only observed at doses well in excess of those necessary for antimicrobial activity. Therefore, these results suggest that MK-366 is a well-tolerated antibacterial agent.

METABOLIC & PHARMACOKINETIC STUDIES

These subjects were already discussed during the review of the original IND. The spectrum of the metabolites (7) is very similar in various species to those of man. The toxicity of the mixture of the metabolites gives the same LD₅₀ value as the parent drug.

CONCLUSIONS & RECOMMENDATION

This drug appears the least troublesome of all in its group. The total lack of functional & morphological eye toxicity is an encouraging quality. The enigmatic studies are the rabbit & cynomolgus monkey teratogenicity studies. The answer is easy for the rabbit, since the peculiarity of the GI tract flora and its unexpected reaction to the drug make this species unfit as an animal model.

The study which aroused my concern with respect to its abortifacient effects in the cynomolgus monkey, implicitly expresses the great hazard for pregnant women. The final report of this study has not been submitted to us yet. I will recommend a Pregnancy Category only after seeing the final report.


Lorant Buko, D.V.M., M.Sc.

cc: ~~Orig.~~ NDA

~~HFN-815~~

HFN-815/MO

CSO

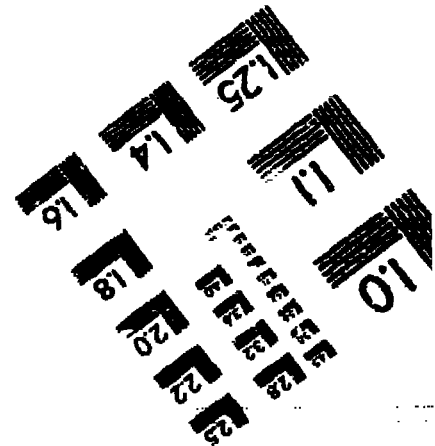
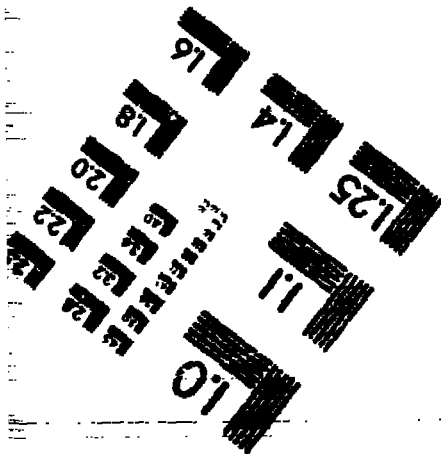
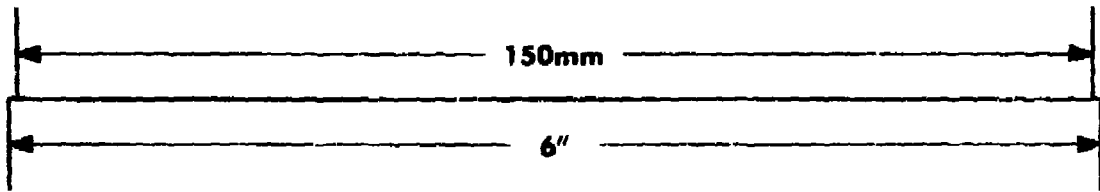
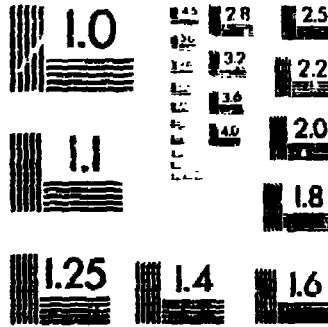
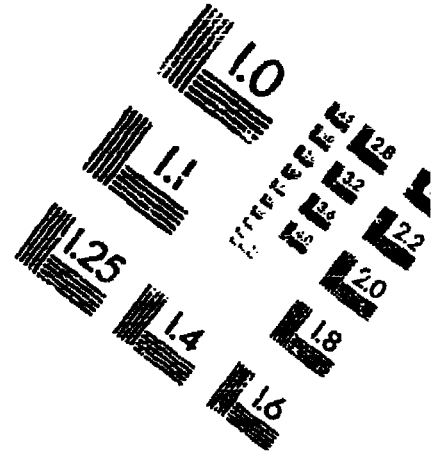
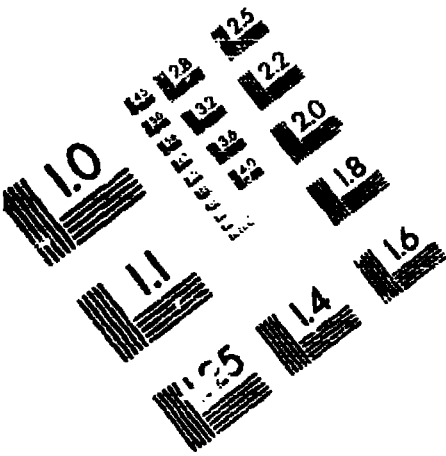
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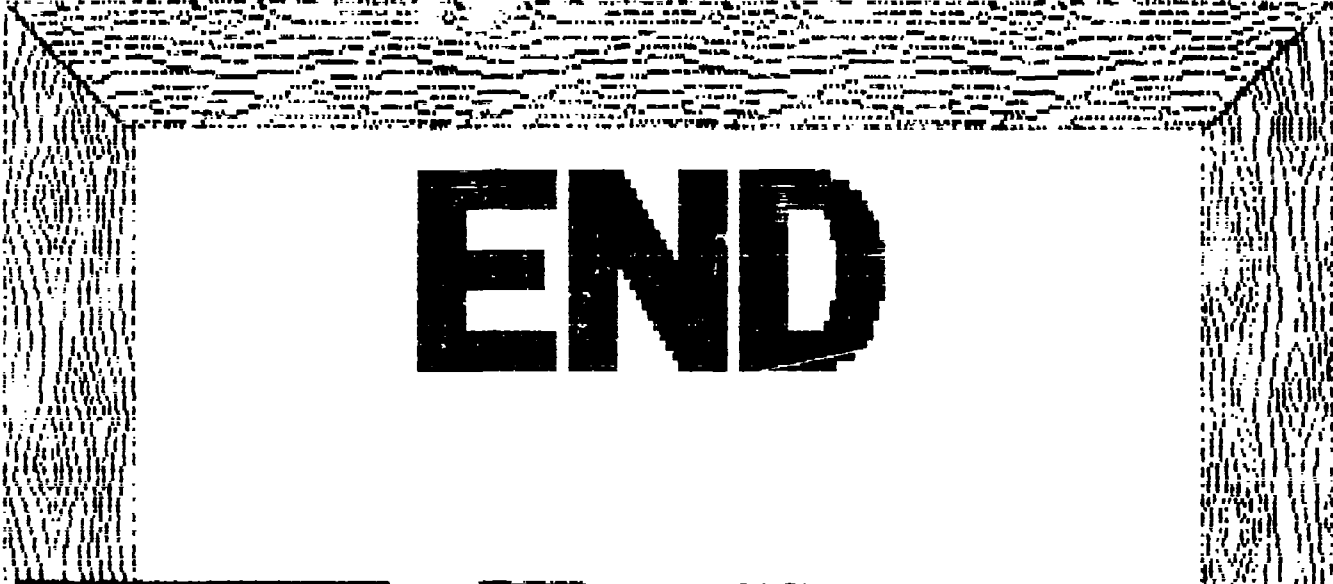
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TEST TARGET (MT-3)



APPLIED IMAGE
 1853 E. MAIN STREET
 ROCHESTER, NY 14609
 TEL. (716) 492-0300
 FAX (716) 299-5888

Precision IMAGING Products & Services



END

END



END

APPL #: 919384

TRADE
GENERIC

FIRM:
NAME:
NAME:

MERCK
NOROXIN TABLETS
NORFLOXACIN

Summary Basis of Approval
Cover Form

Appl #: 019384

Firm: MERCK
Reviewing Div: 520
Trade Name: NOROXIN TABLETS
Generic Name:

NORFLOXACIN

Approval Letter: Y	Statistician Review: N
SBA Form: N	Bio/Dissolution Review: Y
Final Printed Labeling: Y	Microbiologist Review: N
Medical Officer Review: Y	NAS/NRC Review: N
Chemist Review: Y	Pharmacologist Review: Y
Federal Register Notice: N	Completion Date: 09-SEP-93

BIO/DISSOLUTION

REVIEW

Norfloxacin
Noroxin[®] Tablet
400 mg tablet
NDA 19-384
Reviewer: Gene D. Mason, Pharm.D.

Merck Sharp & Dohme
Research Laboratories
West Point, PA 19486
Submissions Dated:
March 14, & July 18, 1985
Feb 14, 24 & March 28, 1986

Review of an NDA

MAY 6 1986

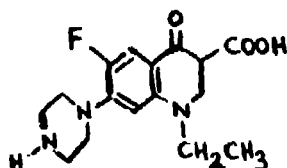
I BACKGROUND

Norfloxacin is a quinoline carboxylic acid antibacterial agent structurally related to compounds such as nalidixic, oxolinic, and pipemidic acids. The proposed indications are for the treatment of infections caused by susceptible strains of micro-organisms, in complicated and uncomplicated cystitis, gonococcal urethritis, acute gastroenteritis and prophylactically in profound neutropenia.

There is no record of any previous submissions to the Division of Biopharmaceutics concerning norfloxacin, the subject of NDA 19-384. Norfloxacin is licensed by Merck from Kyorin Pharmaceutical Co., Ltd. (Japan).

Attachment I of this review is a memo from HFN-815(Dr. Reed) requesting comments on the possibility of crystallization of norfloxacin in the urinary tract based on pharmacokinetic data.

II CHEMISTRY



Structure:

Chemical Name: 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazonyl)-3-quinoline carboxylic acid

Molecular Formula: $C_{16}H_{18}FN_3O_3$ Mol. Wt.: 319.3 Daltons

pKa: 6.3 and 8.8

Solubility: pH solubility profiles in water and urine are given in figures 2a, b, & c of this submission, respectively.

Practically insoluble in water and methyl ether; freely soluble in glacial acetic acid; slightly soluble in methanol, ethanol, ethyl acetate and benzene.

Generic Name: Norfloxacin

Merck Sharp & Dohme Code Names: MK-366, MK0366, AM-715

It is stated by the sponsor that there are no known polymorphs of norfloxacin.

III FORMULATION

Because norfloxacin is licensed by Merck from Kyorin Pharmaceutical Co., Ltd.(Japan) several different formulations have been used in clinical studies prior to the development of the final market image tablet. In addition, different manufacturing processes were utilized by Kyorin Pharmaceutical Co. and Merck Sharp and Dohme. After changing the manufacturing process, MSD subsequently altered the coating formulation. The proposed market image tablet formulation made by direct compression is below. Table 1a of this review compares the proposed formulation to the other formulations used in pivotal bioavailability/pharmacokinetic studies. Table 2 identifies preparations used in pivotal clinical studies. THE FINAL MARKET IMAGE TABLET FORMULATION WAS NOT UTILIZED IN ANY OF THE BIOAVAILABILITY STUDIES OR IN PIVOTAL CLINICAL EFFICACY AND SAFETY STUDIES. THIS ISSUE IS DISCUSSED FURTHER IN SECTION VI-DISSOLUTION.

<u>Ingredient</u>	<u>Merck, 400 mg Market Image Tablet*</u> <u>Amount (mg) per tablet</u>
<u>Core</u>	
Anhydrous Norfloxacin	400.00

* The 200 mg strength tablet is an exact half-size multiple. AT THIS TIME THE SPONSOR DOES NOT SEEK APPROVAL OF THE 200 MG TABLET STRENGTH.

IV PROPOSED DOSING

(taken from proposed circular insert, vol 2.145, pg VII-00186)

Uncomplicated UTI - 400 mg BID X 7-10 days
Complicated UTI - 400 mg BID X 10-60 days
Uncomplicated GC urethritis - 600 mg followed by 600 mg 4 hours later
Acute gastroenteritis - 400 mg BID X 5 days
Prophylaxis in neutropenia - 400 mg TID for duration of neutropenia
(no recommendations available beyond 8 weeks)

One multiple dose study submitted(reference #16, Zinny) utilized the regimen 400 mg BID and submitted relevant pharmacokinetic data in 23 subjects. The regimen of 400 mg TID was used in clinical study #66(Zinny ref #17), however, pharmacokinetic data was obtained in only 4 subjects in this study. A single dose of 1600 mg was administered in study #15(Ferguson).

9 STUDIES REVIEWED

Study Reference #	Title/Location	Objective
7 / Bland, et al, (literature reference)	Vol 2.145, pg VII-00061	Assay
8 / Paulikoudis, et al, (literature reference)	Vol 2.145, pg VII-00065	Assay
8 / Nagatsu, et al, (literature reference)	Vol 2.145, pg VII-00211	Metabolism-Animal
9 / Ozaki, et al, (literature reference)	Vol 2.145, pg VII-234	Metabolism-Human
11 / Nagatsu, et al, (literature reference)	Vol 2.145, pg VII-00272	Metabolism-Animal
12 / Kumasaka, et al, Vol 2.145, pg VII-00309 (literature reference)	?? tab/cap 200 mg PO	Food Effects (SD)
15 / Ferguson(#1) Vol 2.146, pg VII-00450	caps 200 mg 400 mg 800 mg 1200 mg 1600 mg	Dose-propor. (SD)
16 / Zinny(#45) Vol 2.147, pg VII-00627	tabs 400 mg BID	Multi-dose (N=23)
17 / Zinny(#66) Vol 2.147, pg VII-00856	tabs 400 mg TID	Multi-dose (data, N=4)
18 / Zinny(#13) Vol 2.147, pg VII-00993	tabs 200 mg 400 mg soln 400 mg	BA/BE (SD)
19 / Martin(#661) Vol 2.148, pg VII-01142	tabs 400 mg	Elderly (SD)
20 / Asscher(#576) Vol 2.148, pg VII-01293	tabs 400 mg	Renal Failure
21 / Zinny(#59) Vol 2.148, pg VII-01421	tabs 400 mg (old vs new formulation)	BE
26 / Anon, Vol 2.148, pg VII-01590		Assay

SECTION VII OF THIS REVIEW CONTAINS THE SUMMARY AND CONCLUSIONS FROM THE ABOVE STUDIES. APPENDIX A CONTAINS A DETAILED DESCRIPTION OF EACH OF THE STUDIES AND THEIR INDIVIDUAL RESULTS. ALL CORRESPONDING TABLES AND GRAPHS ARE ATTACHED IN APPENDIX B.

VI. DISCUSSION

The following dissolution methods and specifications were proposed by the firm. Table 1b of this review contains dissolution information.

HSP Apparatus 1, 50 rpm

750 ml of 0.05 M sodium acetate buffer (pH 4.0), 37 degrees centigrade,

Q specification of [REDACTED]
Assay via HPLC methodology

The firm provided the following,

1. individual dissolution characteristics of 12 tablets in the final market image,
2. justification/data to support the above dissolution method and specification, and
3. individual in vitro dissolution profiles for various lots used in the bioavailability studies utilizing the proposed methodology for the purpose of comparing the dissolution characteristics of the different formulations.

Inspection of table 1a shows that the MSD-direct compression tablet utilized in study reference #21(Zinny study #59) and the MSD-final market image tablet are identical in core components and differ slightly in amounts of coating constituents(excluding coloring). The amounts of [REDACTED] in the coating on the MSD-final market image product were each decreased by [REDACTED]. The MSD-final market image tablet was not utilized in any bioavailability study submitted. Because of the magnitude and direction of the changes made, it was decided that the MSD-final market image tablet could be evaluated with in-vitro dissolution methods. Several discussions with the firm about the appropriate dissolution conditions(i.e. pH, sampling times, lots to study) and the purpose of the investigation occurred on 3/14, 3/24 & 3/27/86. After evaluation of dissolution data submitted by the sponsor with justification of the chosen methodology(submission dated 3/28/86) the Division of Biopharmaceutics agreed that the proposed methodology appears to be discriminating between Kyorin and MSD manufactured products and produces data consistent with the results of in-vivo investigations. Thus, the Division of Biopharmaceutics concluded that it was appropriate to employ in-vitro dissolution methods to evaluate the various formulations and support/justify approving the 400 mg MSD-final market image tablet.

VI. SUMMARY OF RESULTS AND CONCLUSION

Bioavailability

Reference # 10 - Zinn (single dose; 200,400mg-Kyorin A vs 400mg Soln)
 Reference # 11 - Kumasaka (food effects)

Below are the results of the relative bioavailability study conducted by Zinn (#10).

Parameter	ANG/A	Power*	% Ratios w/in /5/5-125		
For all treatments			T200/S200	T400/S400	T400(b)/T200
AUC(a)	NS	50%	3/12=25%	5/13=38.5	7/12=58.3
Cmax(b)	NS	42%	5/15=33.3%	6/15=40.0	5/15=33.3
Tmax	Sig (P LT 0.05)				

? One-Sided Hypothesis

AUC	Tab 200 vs Soln 400(b)	-	Accept Ho: Not BE
	Tab 400 vs Soln 400	-	Accept Ho: Not BE
	Tab 200 vs Tab 400(b)	-	Accept H1: Bioequivalent
Cmax	Tab 200 vs Soln 400(b)	-	Accept Ho: Not BE
	Tab 400 vs Soln 400	-	Accept Ho: Not BE
	Tab 200 vs Tab 400(b)	-	Accept Ho: Not BE

* 20% diff, alpha = 0.05; T = Tablet, S = Solution;
 a - natural log, dose adj'd to 200 mg; b - dose adj'd to 200 mg

The mean time to peak concentration for the 200 mg and 400 mg tablet was significantly longer (P LT 0.05) than that for the reference solution (1.03, 1.03 vs 0.70 hrs). No significant difference was found for the parameter Tmax between the two tablets. The mean (+/- S.D.) relative bioavailability for dose adjusted Cmax, 400 mg tab/200 mg tab, was 1.1(0.52).

Based on the above observations it is concluded that the 200 mg tab and the 400 mg tab have similar rates and extent of absorption. It cannot be concluded that the solution is bioequivalent to the tablets.

The relative bioavailability (using the methods of Kwan & Till) for the comparisons 200 mg tab/soln, 400 mg tab/soln and 200 mg tab/400 mg tab, are 0.89, 0.90 and 1.0, respectively. The power (as determined by firm) to detect a 25% difference for the comparisons 200 mg tab/soln, 400 mg tab/soln and 200 mg tab/400 mg tab, are 0.77, 0.78 and 0.80, respectively. The relative bioavailabilities (mean +/- S.D.) based on dose adjusted AUC (C_{intin}) for the ratios tab 200/soln 400, tab 400/soln 400, tab 400/tab 200 are 1.0 +/- 0.42(42% C.V.), 0.89 +/- 0.49(50% C.V.), 1.0 +/- 0.33(33% C.V.), respectively. At this time the Division of Biopharmaceutics conventionally uses AUC to compare product bioavailability (extent of absorption) and not the methods of Kwan and Till.

The effect of food was investigated by Kumaska(#12) in 5 volunteers. The results are inconclusive because the AUC was measured only for 3 hours after the dose and thus incomplete, and the product utilized was not the proposed marketed tablet. In addition, meal composition and timing relative to dose was not specified. Tmax for both treatments was 1-2 hours. Mean(S.D.) Cmax in plasma for fasting subjects was 0.46(0.13) vs 0.32(0.16) ug/ml for non-fasting subjects. The Cmax in urine was higher in the fasting group(334 vs 206 ug/ml). In one nonfasting subject, norfloxacin could only be detected(ug/ml) 2 hours after the 200 mg single dose. It appears that administration of the product utilized in this study with food can alter the absorption characteristics of the drug. Because the formulation, dosage form(tablet vs capsule) and source(probably manufactured by Kyorin) of the product administered in this study was not provided, extrapolation of the results of this study to the proposed marketed product is not possible. Because of the effect of pH on the solubility of norfloxacin, the effect of food on the proposed marketed product needs investigation.

A correspondence published in the European Journal of Clinical Microbiology, Vol 4, 1985, p 345(see Attachment II), reported reduced enteral absorption of ciprofloxacin(a quinoline carboxylic acid derivative) when coadministered with antacids. Ten healthy fasting volunteers randomly received 500 mg of ciprofloxacin orally either in a fasting state or "24 hours after administration of 10 X 600 mg Mg-OH + 100 mg Al-OH (Maalox)". A pronounced decrease of the peak serum concentration from a mean of 1.7 mg/L(range 1.3-2.6) after ciprofloxacin alone to a mean of 0.1 mg/L(range mg/L) after ciprofloxacin plus antacid(P < 0.001) was reported. Tmax was only slightly prolonged(73 +/- 13 min versus 87 +/- min). The cumulative urinary excretion of parent drug over 24 hours after ciprofloxacin administered alone was 24%(range 19-34%) of the administered dose as compared to 2.1%(range 0.9-4.7%) after prior administration with antacids. It was postulated that the drug forms chelates of Mg++ or Al++ resulting in reduced absorption. The potential for a similar interaction may also exist for norfloxacin, although the reviewer is not aware of any related investigations. Coadministration of norfloxacin and antacids containing magnesium and aluminum(even possibly calcium) should be discouraged until definitive data is available. It should be noted that in the above study the exact time of administration of antacids relative to ciprofloxacin dosing is unclear.

Another concern related to the above is absorption of norfloxacin in the elderly, who characteristically have a higher gastric pH and often are achlorhydric. Based on the pH solubility profile of norfloxacin, it is predicted that dissolution will be retarded in the pH range 6-9. The mean(S.D.) percent of a single dose recovered in the urine over 24 hours in an elderly population(age 67-74 yrs) was 22.3 %(S.D. 6.9) and ranged from 10.8 to 29.4%(ref #19, Martin). This contrasts with mean percents of 27-32 observed in younger subjects reported by other investigators based on urinary recovery to time infinity(#15,18,21). Even if absorption in the elderly differs from that of younger patients the clinical significance of this observation is not known at this time.

Zinniv (single dose)

Reference #21 - Zinniv (single dose x-over, 400 mg Kyorin vs 400 mg MSD)

Because Kyorin and MSD used different manufacturing methods to produce nortriptyline tablets, a bioequivalency study using products produced by both processes was conducted. IT SHOULD BE NOTED THAT THE MSD PRODUCT USED IN THIS STUDY IS DIFFERENT FROM THE PROPOSED MARKET IMAGE TABLET.

The following results were obtained,

	ANOVA	Power*	% w/in 75/75-125	Other
AUC	NS	85.6	----	
Cmax	NS	75.4	12/20 = 60 %	2 1-Sided Hyp Accept H1: Bio Equivalent
Tmax	Sig (P LT 0.05)			2 1-Sided Hyp Accept Ho: Not BE

* 20 % diff, alpha = 0.05

Based on the above results, it is concluded that the MSD and Kyorin tablets have equivalent extents of absorption. The Cmax for the two products were not statistically significantly different (1.56 +/- 0.48-Kyorin, 1.54 +/- 0.42ug/ml-MSD), however, the power for this evaluation was 75.4% and 75/75-125 Ratio Evaluation was 60 % within 75-125% of the reference product (Kyorin). A statistically significant difference (P LT 0.05) in mean Tmax was observed (1.35 +/- 0.43 hrs-Kyorin vs 1.07 +/- 0.37 hrs-MSD). It is concluded that the rate of absorption is similar (but not statistically equivalent) for the MSD and Kyorin products.

AN ACROSS STUDY COMPARISON OF CMAX, TMAX, AUC AND URINARY EXCRETION FROM A 400 MG DOSE FOLLOWS. THIS IS PROVIDED BECAUSE OF THE DIFFERENT FORMULATIONS UTILIZED IN INDIVIDUAL STUDIES.

COMPARISON OF A SINGLE 400 MG DOSE	mean (S.D.) Cmax (ug/ml)	Tmax (hrs)	AUC*(ug/ml*hr)	% Dose Urin Recov
Zinniv (#16) tab (Kyorin-B), n=25	1.15 (0.41)	1.5 (0.6)	6.7 (2.8) (day 14)	18.9 (8.2) (day 14, 0-12hr)
Ferguson (#15) cap, n=14	1.6 (0.45)	1.1 (0.35)	6.2 (1.8)	31.3 (6.7) (0-48hr)
Zinniv (#18) tab (Kyorin-A), n=15	1.5 (0.58)	1.03 (0.35)	7.1 (3.6)	26.5 (9.1) (0-48hr)
Zinniv (#21) tab (MSD), n=18	1.54 (0.42)	1.07 (0.37)	5.9 (1.7)	27.0 (8.5) (0-48)

* AUC(0-12) at steady-state for the Multiple Dose study (#16) and AUC(0-infinity) for the single dose studies (#15, 18, 21);

Note that the C_{max} , T_{max} and Urinary Excretion of norfloxacin in study #16 differs from that in the other studies. The reason for the discrepancy is not apparent. Study #16 lacked a 1.5 hour plasma sampling time that was used in the other 3 studies. This explanation, as well as a decreased rate of absorption, could explain the difference in C_{max} and T_{max} . It could be suggested that the bioavailability (extent of absorption) of Kyronid product is less than that of the other products based on urinary excretion data, however, evaluation of AUC values does not support this conclusion. The data in study #16 should be interpreted with caution.

Dose Proportionality

Reference #15 - Ferguson (single rising dose, 200-1600mg, capsule)

Ferguson(#15) administered doses of 200, 400, 800, 1200 and 1600 mg of norfloxacin to 14 subjects in single rising doses. ANOVA evaluation of the dose adjusted AUC(0-infinity) resulted in no significant difference across dose amounts ($p > 0.05$, estimated Power 76%). The firm reported a linear trend between dose and AUC ($p < 0.05$) and stated that a proportional dose-response relationship was observed. A less than proportional increase in C_{max} occurred with the increase in dose. A comparison of the dose adjusted C_{max} values of norfloxacin showed that the 800, 1200 and 1600 mg doses were significantly different ($p < 0.05$) from the 200 mg dose. The time for the peak concentration to occur increased as the dose increased from 200 to 1600 mg. T_{max} at the 1200 and 1600 mg dose was significantly greater ($p < 0.01$) than that after the lower three doses.

It is concluded that dose proportionality across the recommended daily dose range (200 - 1600 mg) exists for AUC. However, C_{max} increases less than proportionally with the increase in dose above 400 mg and may be due to a slower rate of absorption as evidenced by the greater T_{max} at the higher doses.

Pharmacokinetic Parameters/ Linearity

This drug was not administered intravenously, thus information on pharmacokinetic linearity was gleaned by several methods using the data from the Ferguson study (#15). The similarity in the terminal elimination half-life (about 5 hours) after a single 200 mg and 1600 mg oral dose is consistent with linear elimination of drug at the concentrations observed. Some information is obtained by comparing AUC and dose. Assuming " F " is constant across the single dose range 200 to 1600 mg, the linearity between dose and AUC is consistent with a linear elimination process. Additionally, the percent of the dose administered that is excreted in the urine as parent drug is constant across the single dose range 200-1600 mg. In conclusion, the data is consistent with linear pharmacokinetic disposition up to the observed clinical concentration of approximately 3.5 ug/ml.

Pharmacokinetic Parameters

Adults (#18, 21) See "BIOEQUIVALENCE" Section Above For C_{max}, t_{max}, AUC & Urinary Excretion Comparison.

Adults (#15), capsule, n=14

Parameter	200 mg	400 mg	800 mg	1200 mg	1600 mg
C _{max} Serum (ug/ml)	0.8 0.2	1.6 0.5	2.4 0.5	3.3 1.0	3.8 1.5
T _{pk} - Serum (hr)	1.1 0.4	1.1 0.3	1.4 0.4	2.0 1.0	1.9 0.5
EFFECTIVE T _{1/2} * (hr)	2.2 0.2	2.2 0.2	2.3 0.2	2.4 0.2	2.5 0.2
Renal Cl mean (ml/min)	313.4	319.6	305.8	290.8	308.5
S.D.	55.0	50.0	92.3	50.2	39.8

* This values represents the "effective half-life for accumulation" as determined by the sponsor for a dosing interval of 8 hours.

Elderly (#19), n=6

	Mean	S.D.	Range
Cl Renal(ml/min)	= 154	15.7	127 - 174
Plasma* T 1/2 alpha(hr)	= 1.2	0.32	0.7 - 1.5
T 1/2 beta(hr)	= 5.6	2.1	3.2 - 8.7
Effective T 1/2 (hr) For Accumulation** (harmonic mean)	= 3.9	--	3.5 - 4.4

* based on 2-COM with 1st order absorption and elimination, ESTRIP program. Values for Cl & Vol were not reported.

** for a dosing interval of 8 hours

Protein Binding

It is reported that protein binding measured by ultrafiltration using pooled human serum at a concentration of 2.5 ug/ml was 13.8% (Vol 2, 41, pg III-00327). Negligible binding to serum protein was reported at a drug concentration above 20 ug/ml.

Probenecid Effects

The excretion of norfloxacin with and without coadministration of 1 Gm of probenecid was investigated in 5 healthy volunteers in a crossover designed study (Shimada, et al, Antimicrob. Agents Chemother., 23(1):1-7, 1983). In the presence of probenecid the renal clearance of norfloxacin decreased from a mean (+/- S.D.) of 334.9(62.4) to 163.6(18.8) ml/min. The urinary recovery of unchanged norfloxacin decreased from a mean(S.D.) 28.0(+/- 15.5) % of the dose administered to 13.9(+/- 4.7) % when norfloxacin was given with probenecid as compared to control (Table 3 of this review). The renal clearance of norfloxacin was 2.4-3.4 times greater than the creatinine clearance

when norfloxacin was administered alone, compared to 1.2-1.3 times greater during coadministration of probenecid and norfloxacin. Probenecid had little effect on the mean plasma concentrations of norfloxacin (Figure 3 of this review). Because the data was quite variable and results for individual subjects were not provided any possible trends in plasma concentrations were not observed. It cannot be concluded that coadministration of probenecid does not effect norfloxacin concentrations.

Metabolism/Elimination

Reference # 9 - Ozaki (single dose, 200 or 1600 mg tablet)

Reference # 15 - Ferguson (single rising-dose, 200-1600 mg capsule)

24 hour urinary excretion - Study #9

Dose	Parent	M-1	M-2	M-3	M-4	M-5	Total**
	(% of administered AM-715 units)						
200 mg PO, SD (N=3)	26.6 (9.0)	5.1 (0.8)	1.5 (0.4)	0.33 (0.15)	0.5 ---	0.7 (0.1)	34.7 (9.4)
% of total recovered in urine	76.7	14.7	4.3	0.9	1.4	2.0	
1600 mg PO, SD (N=4)	23.0 (8.0)	3.6 (0.7)	0.57 (0.25)	0.15 (0.06)	0.05 (0.04)	0.14 (0.06)	27.5 (8.8)
% of total recovered in urine	83.6	13.1	2.1	0.5	0.2	0.5	

M-4 consists of M-4(1) & M-4(2) which could not be separated under study conditions.

48 Hr Urine Recovery - Study #15

Unchanged Parent	
Urine Recovery*	29.9 % (1.9)

*(mean of 200, 400, 800, 1200, 1600mg doses; N = 14 at each dose)

It is reported that no conjugates of norfloxacin or its metabolites were detected in urine (Vol 2.145, pg VII-00013, summary)

Fecal Recovery - Study #18(Zinny) & #21(Zinny)

	% Dose
24-48 hrs specimen collection	30.0*

* Based on antimicrobial activity, thus includes parent and metabolite activity

Norfloxacin is recovered in urine and feces after oral administration to humans. Of drug recovered in the urine (parent and metabolites), approximately 80% represents unchanged parent compound. Approximately 30-35% of the dose administered is recovered in the urine over 24-48 hours as parent (25-30%) and metabolites (4-8%). Fecal recovery over 24-48 hours accounts for approximately 30% of the administered dose. Limited evidence suggests that biliary excretion of parent and metabolites also occurs. In a meeting with representatives of the firm on January 10, 1986, it was suggested by the firm that the remaining 35-40% of the drug not accounted for in urinary and fecal recovery is believed to be bound to feces. The firm later indicated that fecal inactivation of norfloxacin is possible and submitted supportive literature references (submission dated 02/14/86). This would cause underestimation of drug recovery from fecal specimens assessed with microbiological assay techniques.

Renal Insufficiency

Reference # 20 - Asscher (single dose, 400 mg MSD tablet)

The disposition of a single, oral, 400 mg dose of norfloxacin was studied in 18 patients with varying degrees of renal dysfunction. A statistically significant difference in AUC(C-infinity) and % Urinary Recovery was observed overall. No significant difference in Cmax and Tmax was observed (P Greater than 0.2). Significant pairwise comparisons of AUC(0-inf) and % Urinary Recovery are below.

Parameter	Overall	Significant Pairwise Comparisons
AUC(0-inf) (ng/ml-hr)	p = 0.0001	I,II vs III p = 0.0002 I,II vs IV p = 0.0001
% Urinary Recovery	p = 0.07	I vs III p = 0.004 II vs III p = 0.04 I vs IV p = 0.06

Group I - CrCl = 30 ml/min/1.73 meters squared
 Group II - CrCl = 15 ml/min/1.73 meters squared
 Group III - CrCl = 10 ml/min/1.73 meters squared
 Group IV - CrCl = 5 ml/min/1.73 meters squared

Generally, the greatest differences in AUC and Urinary Recovery are observed in subjects with ClCr less than 30 ml/min/1.73 meters squared (Groups III & IV). It is recommended by the firm that the regular dose be administered QD rather than BID in patients with ClCr less than 30 ml/min/1.73 meters squared. It should be noted that the lowest ClCr in Group II was 46 ml/min and no subjects between 28 and 46 ml/min/1.73 msqd were enrolled in this study. It is unclear whether the above recommended cutoff for a dose change should include patients in this range. A conservative recommendation is to use approximately 45 ml/min/1.73 meters squared as a cutoff value. In all cases, monitoring of norfloxacin levels is indicated in renal failure patients receiving long term therapy to insure adequate antimicrobial activity without excessive dosing.

Special Population - Elderly

Reference # 19 - Martin

The disposition of a single 400 mg dose of norfloxacin was studied in six, healthy, elderly subjects with a ClCr greater than 70 ml/min/meters squared. The percent of the dose recovered in the urine as parent compound was 22.3 %, a value lower but comparable to that observed in younger subjects (approx. 30 %). The renal clearance of norfloxacin in this group of subjects was 154 ml/min., compared to approximately 300 ml/min in younger subjects (#15). Despite this difference it appears that dose adjustment is not necessary in elderly subjects with ClCr greater than 70 ml/min/1.73 meters squared.

VII ANALYTICAL METHODOLOGY

Assay methodology employed and comments follow each study listed below.

Ref 9(Ozaki) - HPLC with detection via fluor photometric analyzer for urine and plasma samples. This assay lacks adequate sensitivity with plasma samples for use in clinical studies. Limits: 1-2 ug/ml for AN-715 (parent drug) and metabolite M-1, 0.5-1 ug/ml for other metabolites

Ref 12(Kumasaka) - antimicrobial activity measured via paper disc method employing E. Coli. Validation of assay methodology was not provided. Results of the study were not utilized for reasons other than lack of assay documentation.

The following studies employed similar methodology--HPLC with uv detection(urine) and fluorescence detection(plasma). Documentation of assay specificity, sensitivity and reproducibility was provided.

Ref 15(Ferguson) - MSD(plasma) & T Jefferson(urine)

Refs 16 & 17 (Zinny) - MSD

Ref 18(Zinny) - MSD; antimicrobial activity in stool specimens & rectal swabs was quantitated by Dr. S Landsman of SUNY-Downstate Med School.

Ref 19(Martin) - MSD, assay cited in JPS 73(1);99-102, 1983,
"Quantitation of Norfloxacin, a New Antibacterial Agent in Human
Plasma and Urine by Ion-Pair Reverse-Phase Chromatography",
Pauliukonis, et al(Ref # 2, vol 2.145, pg VII-00065).
Ref 21(Zinny) - MSD; antimicrobial activity in stool specimen &
rectal swabs was quantitated by Dr. S Landsman of SUNY-Dowstate Med
School.

The following is a summary of results of a bioassay procedure for
norfloxacin. The procedure is published in Eur J Clin Microbiol,
2(3):249-252, June 1983.

Ref 1(Huber) - MSD(plasma, urine, tissue); A disk-diffusion bioassay
procedure employing *Klebsiella pneumoniae* ATCC 10031 was developed.
The assay sensitivity(when incubated at 28 degrees C) was reported to
be 0.2 ug/ml. Urine and serum standard curves were similar.
Bioassay values in urine were comparable to those obtained by HPLC.

VIII COMMENTS(For Labeling and For Reviewed BA/PK Studies)

1. The following comments pertain to labeling and the proposed package
insert in vol. 2.145, pg VII-00186.

a. pg 3 - "The effective half-life...is 3-4 hours". The
mean(harmonic) values reported by Ferguson(ref # 15) range from
2.2-2.5, and those by Zinny(ref #18) 3.0-3.3. Individual values
exist outside these ranges. Reporting 2-4 hours is probably more
representative of the data, however, 2.5-3.5 is probably more exact.
Whenever effective half-life for accumulation is reported the
corresponding dosing interval used to calculate the effective
half-life should also be reported. Since the value of effective
half-life for accumulation is different for QD, BID and TID dosing,
and each patient will not necessarily receive the same regimen,
several values for effective half-life for accumulation should be
provided in the package insert. The reviewer is concerned that the
concept "effective half-life for accumulation" is unfamiliar to
practitioners and needs an explanation when used. The conventional
"elimination half-life"(about 5 hours) needs to be included in the
package insert.

b. pg 4 - "In healthy elderly...renal function". Criteria for entry
into the Martin study(Ref #19) was CrCl greater than or = to 70
ml/min/1.73 meters squared. This should be the basis of the
recommendation in the labeling rather than normal renal function
based on age.

c. pg 5 - "Disposition of the drug...creatinine clearance greater
than 30 ml/min/1.73 meters squared". Although the limits for GFR
used by Asscher(Ref #20) in Group II were 31 to 80 ml/min, no data
was obtained in subjects with a measured GFR between 31 and 46
ml/min. The mean(+/- S.D.) GFR value in group II was 54.5(14.6).
The drastic difference in AUC and Urinary Recovery observed between
Group II and III may be due to failure to enroll subjects

representative of the entire GFR range in Group II. Thus, extrapolation of the results of this study to the GFR range 31-46 should be done with caution. It is recommended that approximately 45 ml/min be used in the package insert as the critical value for dose adjustment in patients with renal impairment.

d. pg 5 - "Norfloxacin is eliminated...and renal excretion". It is useful to specify the major route of elimination of norfloxacin. The data suggest that renal elimination of parent drug is the major route of elimination and metabolism of norfloxacin is minor. The extent of biliary excretion is unclear, however, a biliary concentration of 5 ug/ml was measured 1-2 hours after a 200 mg single dose. This information should be included in labeling.

e. pg 5 - "Within 24 hours of drug...of lesser antimicrobial potency." Insert 'in the urine' between the words 'recovered' and 'as', to clarify the statement.

f. pg 5 - "Two to three hours...200 mcg/ml or more...in the urine". Inspection of table 15-16 of this review(Ferguson, Ref #15) shows that 8 of 13 subjects(61 %) had urinary concentrations below 200 mcg/ml during the 2-3 hour urinary collection period. However, a concentration of 200 mcg/ml or greater was observed during either the 0-1, 1-2 or 2-3 hour urine collection period after the dose in 9 of 14 subjects(64 %). The data is variable and the information provided should reflect this. If excretion of drug is independent of urine flow, then the concentration of drug in the urine will vary with urine flow. Thus, the urine concentrations observed in fluid loaded subjects will be comparable to urine concentrations in fluid loaded patients.

g. pg. 13 - "Coadministration of probenecid does not...drug diminishes".

Based on the study provided, it cannot be concluded that coadministration of probenecid does not effect norfloxacin concentrations. The data was quite variable and the results for individual subjects were not provided.

h. pg 15 - "When a 200 mg dose...nursing mothers ..in human milk". Additional information obtained in this investigation follows. At various times after administration of a 200 mg single oral dose, norfloxacin was detected in umbilical cord serum(0.1-0.5 ug/ml) at the time of delivery and amniotic fluid samples(0.18-0.92 ug/ml). However, drug concentration in the blood of neonates after delivery was below the limits of detection(approximately 0.1 ug/ml). It should be noted that human milk samples were only obtained from 1 to 6 hours after the dose.

i. pg 20 - "In patents with apparently normal renal function...greater than 30 ml/min/1.73 meters squared". Concern is expressed over the 30 ml/min/1.73 meters squared value used as the critical point for dose adjustment. See comment c. above in this section.

j. Labeling should include a caution against coadministration of norfloxacin with antacids until evidence demonstrating lack of an interaction resulting in decreased absorption is available.

k. Because of the effect of pH on the solubility of norfloxacin, the effect of food on the proposed marketed product needs investigation. For labeling purposes, administration of norfloxacin with food should be discouraged as a precaution until definitive data is available.

l. Labeling should include specific instructions to maintain a good fluid intake in all patients to prevent crystallization of drug in the urinary tract. Even greater emphasis on the potential for developing crystalluria with resulting complications should be stated in the package insert section "Overdosage". Maintaining adequate hydration should be directed toward this potential problem.

2. Each of the following comments pertain to the specific study referenced with the comment.

Reference #9

1. Biliary excretion data was obtained in only 1 patient. Raw data was not provided. The concentration of AM-715 reported in bile was 5 ug/ml. It is unclear how concentrations of metabolites M-3 thru M-5 in bile were determined. Based on the lower limits of quantitative determination reported by the firm, the concentrations implied by the report are lower than the limits given if 5 ug/ml is the highest concentration observed for AM-715. Little can be concluded from the data presented.

2. The less than 100% recovery observed is consistent with incomplete urinary collection, elimination via other routes, incomplete GI absorption of drug and/or incomplete recovery of drug using the stated analytical methods.

3. The formulation and/or lot number of the tablet dosage form utilized in this study was not provided.

4. Age and weight of the patient with gallstone disease was not provided. Exclusion/inclusion criteria for volunteers was not provided.

Reference #12

1. The usefulness of the data in this pilot study is questioned. Urine and blood samples were collected for a period of 8 hours after dosing. It is possible that sample collection was incomplete, as the elimination half-life of norfloxacin is approximately 5 hours. A trend is observed in the data, however, the ability to extrapolate the results to the general population is limited, at best. The formulation and source (Kyorin vs MSD) of the product used in this study was not provided.

2. Validation of assay methodology was not provided.

3. For mean C_{max} in urine, the firm reported a value of 320.0 ug/ml. It appears that 320.0 is the result of using a 0-2hr urine concentration of 320 ug/ml rather than the 6-8hr urine concentration of 320 ug/ml in patient Y.K. If this subject is atypical then none of his values should be used. unacceptable. Total AUC(0-infinity) was used by the reviewer in the comparison of AUC across the dose

strengths. However, it should be pointed out that Total AUC was estimated(not measured directly) using the measured renal clearance. It was concluded by the reviewer that Total AUC was calculated by dividing $X_u(\text{infinity})$ by Renal Clearance.

2. C_{max} of MK0366 in serum dose not increase proportionately with increasing dose across the single-dose range 200 to 1600 mg(see table 15-6 of this review).

3. Subjects were fluid loaded in this study. Subjects received 250 ml of water 1 hour prior to dosing, 250 ml with dose administration, and 250 ml at 1, 2, 4, 6, and 8 hours post-dosing(total of 1750 ml over 9 hours). Fluids were subsequently permitted ad libitum.

4. The firm should have stated the lower limits of the assay for plasma samples and provided data on the specificity in plasma.

Reference #15

1. The usefulness of AUC(0-8) hours is limited because the remaining portion of the total AUC increases from approximately 18% to 31% as the dose increases from 200 mg to 1600 mg. Excluding 30% of the total AUC from the 0 to 8 hour AUC values used in the comparison is unacceptable. Total AUC(0-infinity) was used by the reviewer in the comparison of AUC across the dose strengths. However, it should be pointed out that Total AUC was estimated(not measured directly) using the measured renal clearance.

2. C_{max} of MK0366 in serum does not increase proportionately with increasing dose across the single-dose range 200 to 1600 mg(see table 15-6 of this review).

3. It appears that an increasing trend in the value of "effective half-life for accumulation" occurs with an increase in dose. The firm concluded that the effective half-life is independent of dose.

4. The firm should have stated the lower limits of the assay for plasma samples and provided data on the specificity in plasma.

Reference # 16

1. In general, the data in this study should be used with caution because of the extrapolations and estimations made by the sponsor in the calculation of AUC(0-12), C_{min} values and obtaining urinary excretion data. These issues are discussed below in parts A, B, and C.

A. It is reported that the area under the plasma concentration-time curve(AUC) from 0 to 8 hours was measured directly by the sponsor using the trapezoid method. The remaining area through 12 hours was estimated using renal clearance or the norfloxacin half-life or measured directly using a log-linear trapezoidal approximation. Renal clearance was estimated from corresponding increments of urinary recovery and (AUC) for norfloxacin. It is unclear why the area under the curve from 8 to 12 hours was estimated rather than measured directly when plasma samples were obtained at 12 hours in all subjects and measurable values were reported in almost all of the subjects(see table 16-4 of this review). There is no need to estimate the area from 8 to 12 hours when it can be measured directly. The reviewer calculated AUC(0-12), when used, by the trapezoidal method. AUC values reported by the sponsor should be used with caution.

B. It is reported that blood samples for determination of C_{min} after the second drug dose on days 1, 6 & 13, were actually drawn 30 minutes ahead of schedule. Plasma concentrations for these determinations were extrapolated to the end of the dosing interval using individual estimates of norfloxacin half-life.

C. The urinary excretion data in this study is inconsistent with that observed in other studies reviewed. The percent of the norfloxacin dose administered that was excreted over 12 hours on days 7 & 14 (under steady state conditions) was 17.7 and 18.9 %, respectively, in this study by Zinny (Ref #16). In addition, the mean C_{max} appears to be lower, and T_{max} longer than that in other studies. The urinary excretion data in this study contrasts with 25-30% of a single 400 mg dose excreted in the urine over 48 hours reported in other studies. This discrepancy could suggest reduced bioavailability of the Kyorin-B product utilized by Zinny compared to the other formulations studied. However, this suggestion is not supported by the plasma AUC data for the various studies. An across-study comparison of mean C_{max} and T_{max} (after the first dose of the multiple dose study), AUC and urinary recovery follows. Because of the inconsistencies in the data from this study (#16), the results should be interpreted with caution.

Mean*(S.D.)	C_{max} (ug/ml)	T_{max} (hrs)	AUC**(ug/ml*hr)	% Dose Urin Recov
Zinny(#16) tab(Kyorin-B), n=25	1.15 (0.41)	1.5 (0.6)	6.7 (2.8) (day 14)	18.9 (8.2) (day 14, 0-12hr)
Ferguson(#15) cap, n=14	1.6 (0.45)	1.1 (0.35)	6.2 (1.8)	31.3 (6.7) (0-48hr)
Zinny(#18) tab(Kyorin-A), n=15	1.5 (0.58)	1.03 (0.35)	7.1 (3.6)	26.5 (9.1) (0-48hr)
Zinny(#21) tab(MSD), n=18	1.54 (0.42)	1.07 (0.37)	6.9 (1.7)	27.0 (8.5) (0-48)

* 400 mg dose compared;

** AUC(0-12) at steady-state for the Multiple Dose study(#16) and AUC(0-infin) for the single dose studies(#15,18,21);

2. It is unclear whether or not the timing of meals relative to dosing is consistent for each dose. The protocol on page VII-00739, vol 2.147, says the following; "Volunteers will be fasting since midnight of the day prior to initial dosing (which should take place at approximately 0800 hours) and may resume a normal diet at lunchtime (approximately 3 to 4 hours after dosing...The subsequent dose of medication will be taken at 2000 hours, and no food shall be consumed from 1 hour before dosing until 1 hour after dosing". Ideally, food should be avoided 2 hrs before and 4 hours after the dose is given to satisfy fasting conditions. It is unclear whether or not patients fasted before each 0800 hour dose or only before the first dose of the 14 day treatment period. If subjects fasted only before the first dose, then fast or nonfasting conditions for subsequent 0800 doses is not specified. It appears that subjects

received the first 0800 hour dose under fasting conditions, subsequent 0800 hour doses under unspecified conditions, and the 2000 hour dose regularly under less than ideal conditions. The significance of this depends on whether or not the presence of food affects the absorption characteristics of norfloxacin.

3. Subjects were fluid loaded in this study. Subjects received 250 ml of water 1 hour prior to dosing, followed by 250 ml of water with dose administration. Subjects were instructed to maintain a good fluid intake and to consume 250 ml of water every 2 hours after the dose up to 4 hours after the first dose each day.

Reference #17

1. The data in this study should be interpreted with caution because of the small number of subjects(4).

2. It is unclear whether or not the timing of meals relative to dosing is consistent for each dose. Subjects fasted overnight before starting the study and were instructed to avoid food 1 hour before to 1 hour after subsequent doses. The reviewer recognizes the restraints that TID dosing puts on attempts to ensure fasting conditions. The significance of inconsistent dosing conditions depends on whether or not the presence of food affects the absorption characteristics of norfloxacin.

2. Patients were instructed to drink 250 ml of water 1 hour prior to dosing, 250 ml with administration of the dose, and 250 ml every 2 hours postdosing up to 4 hours after the first dose of the day. Subjects were encouraged to maintain a good fluid intake.

Reference #18

1. It should be noted that patients were fluid loaded during each treatment of the study(1440 ml of water over an 8 hour period).

2. The dosing interval that corresponds to the effective half-life should be stated whenever values for effective half-life are reported.

Reference #19

1. Subjects were fluid loaded in this study. Subjects received 750 ml of water(including 150 ml with the dose) over a 4 hour period after administration of the drug. Subjects also received 150 ml of water several hours prior to dosing.

2. On pg VII-01272(Vol 2,148) of the Biopharmaceutics Report, it is predicted that norfloxacin plasma levels should accumulate by approximately 32% on an 8-hour dosing regimen and by 13% on an 12-hour dosing regimen. The reviewer agrees with the value 32% but not with the 13% reported. The accumulation half-life for 12-hour dosing will differ from that calculated with 8-hour dosing. The accumulation fraction of 1.13 for 12 hour dosing was calculated using the effective half-life calculated for 8 hour dosing. The actual accumulation fraction for 12 hour dosing is probably less than 1.13.

Reference #20

1. Subjects were fluid loaded in this study. Subjects received 850 ml of water over a 4 hour period after dose administration(including 250 ml with the dose). Subjects were also instructed to take 250 ml of water upon rising the morning of the study, which begun at 0800.

2. Most patients in this study were also taking other medications during the study. The effect of these drugs on the disposition of norfloxacin is not known. Thus, the results of this study must be interpreted with caution.

3. Although the stated range of GFR in Group II is 31 to 60 ml/min, 5 of 6 subjects had a GFR greater than 46. The mean (+/- S.D.) GFR for subjects in Group II is 54.5 (14.6). Subject #6 had a GFR of 31 ml/min but was excluded in the evaluation of Renal Clearance, Urinary Recovery and AUC because of "questionable urinary recovery". Thus, no data was obtained in subjects with a measured GFR greater than 28 ml/min and less than 46 ml/min in this study. Extrapolation of the results of this study to this GFR range should be done with caution.

Reference #21

1. It should be noted that patients were fluid loaded (received 1440 ml of water over an 8 hour period) during each treatment of the study.

VII Comments (con't)

3. The following comment pertains to the Biopharmaceutics Summary, section D.(1) Metabolism in volume 2.145.

References 8 and 11 contain supportive metabolism data in animals. The values presented in the summary section are inconsistent with the data in the corresponding reference. It appears as if the individual study results were combined although the two studies measured different parameters. The discrepancy is not large, yet it is recommended that information on drug metabolism in animals be obtained from the individual studies submitted rather than from the Biopharmaceutics Summary section.

4. The following are general comments.

a. The sponsor investigated 400 mg BID in a multiple dose study (ref #16, Zinny). The regimen of 400 mg TID was utilized in clinical study #66 (Zinny ref #17), however, pharmacokinetic data was obtained in only 4 subjects. The extent of accumulation with TID dosing can be predicted using a linear system and basic pharmacokinetic principles (1-COM). Based on an elimination half-life of 5 hours and an 8 hour dosing interval, C_{min} at steady state should be approximately 1.5 times the C_{min} observed after a single dose (Gibaldi M, Biopharmaceutics and Clinical Pharmacokinetics, 3rd Ed, 1984).

IX CRYSTALLURIA ANALYSIS (see attachment I of this review)

The Division of Biopharmaceutics was asked to comment on the possibility that norfloxacin might precipitate into crystals in the human kidney and cause obstruction there or elsewhere in the urinary tract.

A Solubility

As shown in Figures 1 and 2, the solubility of norfloxacin in urine varies greatly with pH, being lowest between 6 and 10. Because urinary pH normally ranges from pH 6-8, the solubility of norfloxacin over this range is the focus of this discussion. Figure 2 shows the relative solubility of norfloxacin in urine at 25 and 37 degrees centigrade.

In animal studies of norfloxacin, crystalluria consisted of the dihydrate and magnesium salts of norfloxacin. It is unclear at this time whether the parent compound and/or the above salts should be the focus of discussion of the possibility of crystallization in humans. Swanson, et al (ref below), observed "drug crystals" in freshly voided urine specimens collected after administering single oral 1200 and 1500 mg doses to human volunteers. Crystals were not found at lower doses (200-800 mg). Urine pH of specimens with crystals was between 7 and 7.8. Drug was administered with only 250 ml of water under fasting conditions.

B Pharmacokinetic Predictions

Using data in the Ferguson (ref #15) and Zinny (ref #16) studies, it is possible to do calculations to determine if, on a theoretical basis, drug crystals of the parent compound norfloxacin are likely to be formed.

Assumptions/Conditions;

1. a worst case scenario is most useful
 2. high single doses and/or the recommended multiple dose regimen
 3. maintenance of a constant plasma concentration
 4. solubility of norfloxacin in urine at 25 and 37 degrees C.
- I. Using the urinary excretion rate, compare the concentration of drug in the kidney with the solubility of the drug.

The ratio, $(A) \text{ drug excretion rate} / (B) \text{ rate of urine formation}$, estimates the concentration of drug in the kidney tubules.

The solubility of norfloxacin was obtained from the pH solubility profile in urine.

Swanson B, et al, 1983. Norfloxacin Disposition After Sequentially Increasing Oral Doses. Antimicrob. Agents Chemother. 23(2):284-288.

A. Single dose evaluation

1600 mg PO

$$Cl_{renal} \times C_{max} = \text{maximum excretion rate} \\ \text{(introduction of drug to kidney)}$$

$$300 \text{ ml/min} \times 4.0 \text{ ug/ml} = 1200 \text{ ug/min (1.2 mg/min)}$$

(Consistent with actual values reported by the firm in table 15-14 of the BA review)

In normal individuals, the rate of urine formation (B) is approximately 1 ml/min (Guyton, Textbook of Medical Physiology, 6th Ed., 1981).

$$\frac{A}{B} = \frac{1200 \text{ ug/min}}{1 \text{ ml/min}} = 1200 \text{ ug/ml (1.2 mg/ml)}$$

1200 mg PO - $C_{max} = 3.0 \text{ ug/ml}$,
Excretion rate = 900 ug/min (0.9 mg/min)

Ratio A/B = 0.9 mg/ml

B. Multiple dose regimen,

	C_{max}	Est'd Dr. Exct'n Rate	Ratio A/B
400 mg BID	2.0 ug/ml	300 ug/min (0.6 mg/min)	0.6 mg/ml
400 mg TID	3.0 ug/ml*	900 ug/min (0.9 mg/min)	0.9 mg/ml

* predicted value (actual value in 4 subjects was approx. 2.0 ug/ml)

COMPARISONS WITH SOLUBILITY OF NORFLOXACIN IN URINE

Regimen	Ratio A/B	Solubility (mg/ml)			
		25 C		37 C	
1600 mg SD	1.2 mg/ml	pH 6 : 3.2	OK	10.0	OK
		pH 7 : 0.75	Exceeded	1.5	OK
		pH 8 : 0.6	Exceeded	1.9	OK
1200 mg SD	0.9 mg/ml	pH 6 : 3.2	OK	10.0	OK
		pH 7 : 0.75	Exceeded	1.5	OK
		pH 8 : 0.6	Exceeded	1.9	OK
400 mg BID	0.6 mg/ml	pH 6 : 3.2	OK	10.0	OK
		pH 7 : 0.75	OK	1.5	OK
		pH 8 : 0.6	Borderline OK	1.9	OK
400 mg TID	0.9 mg/ml	pH 6 : 3.2	OK	10.0	OK
		pH 7 : 0.75	Exceeded	1.5	OK
		pH 8 : 0.6	Exceeded	1.9	OK

11. It is well documented that the crystalluria can be avoided by assuring an adequate rate of urine flow (Gibaldi, Biopharmaceutics and Clinical Pharmacokinetics, 2nd Ed., 1984). Thus, the minimum rate of urine flow may be calculated by dividing the excretion rate of drug by its solubility at a given pH.

Minimum Rate of Urine Flow	(A) Excretion Rate of Drug		
	(B) Solubility in urine at a given pH		
<u>AT TEMP 25 C</u>			
	pH 6 B(solubility) = 3.2 mg/ml	pH 7 = 0.75 mg/ml	pH 8 = 0.6 mg/ml
	Ratio	A/B	A/B
S.D. - 1600 mg C _{max} = 4 ug/ml A* = 1.2 mg/min	0.375 ml/min	1.6 ml/min	2 ml/min
S.D. - 1200 mg C _{max} = 3 ug/ml A = 0.9 mg/min	0.28	1.2	1.5
M.D. - 400 BID C _{max} = 2 ug/ml A = 0.6 mg/min	0.19	0.8	1.0
M.D. - 400 TID C _{max} = 3 ug/ml A = 0.9 mg/min	0.28	1.2	1.5
<u>AT TEMP 37 C</u>			
	pH 6 B(solubility) = 10 mg/ml	pH 7 = 1.5 mg/ml	pH 8 = 1.9 mg/ml
	Ratio	A/B	A/B
S.D. - 1600 mg C _{max} = 4 ug/ml A* = 1.2 mg/min	0.12 ml/min	0.8 ml/min	0.63 ml/min
S.D. - 1200 mg C _{max} = 3 ug/ml A = 0.9 mg/min	0.09	0.6	0.47
M.D. - 400 BID C _{max} = 2 ug/ml A = 0.6 mg/min	0.06	0.4	0.31
M.D. - 400 TID C _{max} = 3 ug/ml A = 0.9 mg/min	0.09	0.6	0.47

* Drug Excretion Rate

C. STUDY DOSING CONDITIONS

The possibility of crystalluria decreases if a water diuresis is created. A water diuresis of up to 8 ml/min urine output can occur within 1 hour of ingesting 1000 ml of water. EXAMINATION OF EACH BIOAVAILABILITY STUDY REVIEWED SHOWS THAT PATIENTS WERE FLUID LOADED TO VARIOUS DEGREES. Below is a summary of dosing conditions.

- Ref #15(Berguson) - 1750 ml of water over a 9 hr period
- Ref #16(Zinny) - 1000 ml of water over a 5 hr period
- Ref #17(Zinny) - 1000 ml of water over a 5 hr period
- Ref #18(Zinny) - 1440 ml of water over an 8 hr period
- Ref #19(Martin) - 750 ml of water over a 4 hr period
- Ref #20(Asscher) - 1100 of water over a 5 hr period
- Ref #21(Zinny) - 1440 ml of water over a 9 hr period

It is standard practice that the drug under investigation be administered under conditions identical to those proposed for the general patient population. If conclusions about the safety of norfloxacin are drawn from these investigations then they should be limited to patients with a similar state of hydration. It is recommended that dosing conditions(hydration status) used in clinical studies be evaluated for additional information and consider the need to include in the package insert instructions to patients to ensure a sufficient fluid intake.

D. CONCLUSION

Based on the above pharmacokinetic predictions, it appears that crystallization should not be a problem with the parent compound norfloxacin when using a solubility curve produced at 37 degrees centigrade(body temperature). Mixed results are obtained from a solubility curve produced at 25 degrees centigrade(room temperature). It should be emphasized that the above manipulations are theoretical and their limitations are demonstrated by the observations of crystals after large single doses(i.e. 1200 & 1600 mg) as reported by Swanson(1) et al. These predictions should be used in conjunction with actual clinical data to make conclusions about the safety of this drug with regards to crystalluria. The fluid loaded conditions used in the BA studies complicate interpretation of the clinical results of these studies for resolving safety issues. The above manipulations and conclusions do not apply to the dihydrate, magnesium or other salts of norfloxacin.

Concern is expressed about the potential for formation of crystals under abnormal conditions commonly seen. Some of these conditions are periods of low urine formation(e.g. dehydration), alterations in urine pH which effect renal tubular secretion and the solubility of the drug, and pathological conditions that alter kidney physiology. The labeling should include specific instructions to maintain a good fluid intake in all patients to prevent crystallization of drug in the urinary tract.

In conclusion, at pH 6, it appears that crystallization should not be a problem with the parent compound norfloxacin. The results are less clear at pH 7 and 8. However, since a worst case scenario was used, crystallization of norfloxacin at pH 7 is possible but unlikely. It should be emphasized that the above manipulations are theoretical, and are likely to favorably change (crystallization less likely) if a norfloxacin solubility curve created at 37 degrees C (body temperature) is used rather than a curve produced at 25 degrees C (room temperature). The fluid loaded conditions used in the BA studies complicate interpretation of the clinical results of these studies for resolving safety issues. The above manipulations and conclusions do not apply to the dihydrate, magnesium or other salts of norfloxacin.

X OVERALL APPLICATION CONCLUSION

The Division of Biopharmaceutics concludes that the data submitted by the sponsor satisfies the requirements set forth in 21 CFR, part 320 describing bioavailability and bioequivalence requirements.

The data is summarized below.

1. Based on AUC, dose proportionality across the single dose range 200-1600 mg exists for norfloxacin. However, the Cmax of norfloxacin does not increase proportionately with the increase in a single dose beyond 800 mg. After a 400 mg single dose (capsule), mean Cmax was approximately 1.6 ug/ml (Tmax about 1 hour), whereas Cmax was approximately 3.8 ug/ml (Tmax occurs at about 2 hours) after a single 1600 mg dose. The mean Cmax observed after a single 400 mg dose (MSD direct compression tablet) was 1.5 ug/ml with a corresponding mean Tmax of about 1 hour.
2. The MSD and clinically tested Kyorin tablet products have equivalent extents of absorption. Based on mean Tmax, the rate of absorption of the MSD formulation is faster than the Kyorin formulation (1.07 vs 1.35 hrs).
3. Relative to a solution, the mean ratio of dose adjusted AUC(0-infinity) for a 400 mg tablet (Kyorin) to a solution administered as a single dose is 0.99 +/- 0.49. Statistical equivalence was not demonstrated.
4. Norfloxacin is recovered in urine and feces after oral administration to humans. About 30-35 % of the dose administered is recovered in the urine over 24-48 hours as parent (25-30 %) and metabolites (4-8 %). Fecal recovery accounts for approximately 30 % of the administered dose but is probably much greater. Fecal recovery is accounted for by incomplete GI absorption, biliary excretion and/or other factors. Thus the fraction of the administered dose absorbed orally is at least about 30-35 %.
5. The elimination half-life of the parent drug norfloxacin is about 5 hours. The "effective half-life for accumulation" for 8 hour dosing intervals is about 3 hours. The renal clearance of norfloxacin measured in adults with normal renal function is about 300 ml/min.
6. Because of the effect of pH on the solubility of norfloxacin, the effect of food on the proposed marketed product needs investigation.
7. Coadministration of norfloxacin and antacids should be discouraged in the labeling because of the possibility of complexation resulting in a decrease in absorption.

8. The dose of norfloxacin needs to be adjusted in the elderly and patients with renal dysfunction. Guidelines provided by the firm need clarification.

9. Protein binding of norfloxacin measured by ultrafiltration is about 14%.

XII. RECOMMENDATION

The Division of Biopharmaceutics recommends that the biopharmaceutic/pharmacokinetic data submitted to support NDA 19-384 (the 400 mg tablet) be accepted.

HFN-815 should consider comment # 1(a-1) of section VIII above (pertaining to labeling) when evaluating the package insert. It is recommended that comment # 1 be forwarded to the sponsor.

The Division of Biopharmaceutics recommends that the proposed dissolution specification be accepted; Q= 80 % in 30 minutes using USP Method II at 50 rpm in 750 ml of 0.05 M sodium acetate buffer (pH 4.0), at 37 degrees C. The sponsor should use the USP Acceptance Table criteria for this specification.

When the sponsor conducts a food-effect study or seeks future approval of the 200 mg norfloxacin tablet, the Division of Biopharmaceutics recommends that the sponsor contact the Division of Biopharmaceutics to discuss the type of in-vivo study required for approval.

Gene D. Mason (handwritten) 4/18/86

Gene D. Mason, Pharm.D.
Pharmacokinetic Evaluation Branch

RD Initialed by John Hunt 4/18/86

FT Initialed by C.T. Viswanathan, Ph.D. CTV 4/28/86

cc: Orig. NDA 19-384, HFN-815(2), HFN-815(Tabor), HFN-226(Mason), Chron, Drug and FOI files

GDM:gdm:6063x: 2/15/86

Appendix A

Individual Study Results

Study Reference: #9; Vol. 2.145, pg VII-234

Title: Study of the Metabolism of AM-715 in Humans by Means of High-Performance Liquid Chromatography

Investigator/Site: Ozaki T, Uchida H, Irikura T
normals - Department of Internal Medicine, Oyama City Hospital
patient - Department of Surgery, Kawasaki Municipal Hospital

Objective: To elucidate the distribution ratio of metabolites of AM-715 in the serum and urine of healthy volunteers and in the bile of one patient with choledocholithiasis following oral administration of AM-715 tablets.

Design:

- I. 7 normal adult(35-45 years old) males, 50 - 75 Kg in body wt.
3 subjects received - 200 mg AM-715 Tablets, with a cup of water (three hours after a "light meal")
4 subjects received - 1,600 mg AM-715 Tablets, with a cup of water (three hours after a "light meal")
- II. 1 patient with choledocholithiasis(?age & wt)
received - 200 mg AM-715 Tablets,

Hydration: Drug was administered with a cup of water

Specimens:

Normals -

- 200 and 1600 mg dose groups
Urine(intervals) - 0 to 2.5, 2.5-5, 5-9 and 9-24 hours after dosing
- 1600 mg group
Blood : 0.5, 1, 2, 3, 4, 6, 8 and 16 hours after dosing

Patient - Bile was collected for one to two hours(after the dose).

Analytical Methods:

Methods used to treat serum, urine and bile were provided. HPLC with fluorophotometric detection was used for separation and detection of parent and metabolites.

Limits of quantitative determination:

AM-715 & M-1 ug/ml
M-2 thru M-5 ug/ml

Tables:

- Table 9-1 -Serum concentrations of AM-715 after PO 1,600 mg
- Table 9-2 -Urine concentrations of AM-715 and metabolites post PO 200 mg
- Table 9-3 -Urine concentrations of AM-715 and metabolites post PO 1,600 mg
- Table 9-4 -Urinary excretion of AM-715 and metabolites post PO 200 mg
- Table 9-5 -Urinary excretion of AM-715 and metabolites post PO 1,600 mg
- Figure 9-3 -Metabolite pattern in urine
- Figure 9-1 -Chemical structure of parent and metabolites
- Figure 9-2a,b,c -Chromatograms and calibration curves

Results.

Serum

With the 1,600 mg dose, only unchanged parent drug could be detected in serum because the serum concentration of metabolites M-1, M-2, M-3, M-4 and M-5 was below the detection limits of the assay.

Urine (% of dose*)

Species	mean (S.D.)	200 mg (N=3)	1,600 mg (N=4)
AM-715 - parent		26.6 (9.0)	23.0 (8.0)
range		20.5 - 37.0	17.9 - 34.8
M-1 metabolite		5.1 (0.8)	3.6 (0.7)
range		4.6 - 6.0	3.1 - 4.6
M-2 metabolite		1.5 (0.4)	0.57 (0.25)
range		1.1 - 1.8	0.3 - 0.9
M-3 metabolite		0.33 (0.15)	0.15 (0.06)
M-4 metabolite		LT** or = 0.5	0.05 (0.04)
M-5 metabolite		0.7 (0.1)	0.14 (0.06)
Total - 24 hours		34.7 (9.4)	27.5 (8.8)
range		28.4 - 45.5	21.7 - 40.5

* % of administered AM-715 units

** LT = less than

It is stated that the results after treatment with beta-glucuronidase-arylsulfatase did not differ from those determined quantitatively in the urine which did not undergo enzyme treatment. It was concluded that the drug and its metabolites were all unconjugated when excreted in the urine.

Bile - The concentration of AM-715 found in the bile one to two hours after a 200 mg dose was reported as 5 ug/ml. It is reported that the concentrations of M-1, M-2, M-3, M-4 and M-5 observed relative to AM-715 are 13%, 10%, 1%, 2% and 2%, respectively. No raw data was provided.

Study Reference: # 12; vol 2,145, pg VII-00309

Title: Fundamental Study of AM-715

Investigator/Site: Kumasaka Y, Nakahata H, Imamura K, Takebe K
The Third Department of Internal Medicine
Hirotsuki University, School of Medicine

Objective: 1) To investigate antibacterial activity and 2) to compare serum and urine levels after a single 200 mg dose.

Design: Single dose, cross-over

5 healthy male adults received (dosage form, formulation & source not identified)

- a. 200 mg non-fasting (meal composition not specified)
- b. 200 mg fasting

Hydration: Administration of drug with water was not stated.

Specimens:

Serum - 0.5, 1, 2, 4, 6 and 8 hours after dosing

Urine(intervals) - 0 to 2, 2-4, 4-6, and 6-8 hours after administration

Analytical Methods: Norfloxacin levels were determined with the paper disc method employing E. Coli NIHJ JC-2 as the test bacterium. Standard curves were prepared with human serum for serum level determination and pH 7.0 M/15 phosphate buffer was used for the urinary level determinations. Validation of assay methodology was not provided.

Tables:

Table 12-1 : Individual urinary excretion and recovery of AM-715

Table 12-2 : Individual concentrations of AM-715

Figure 12-1 : Urinary excretion displayed graphically

Results:

	Urinary Excretion (ug/ml)			% Recovery	
	0 - 2H	2-4H	4-6H	6-8H	(0-8 hrs)
Fasting mean	290	162	102	104	28.3
(N=5) S.D.	250.6	70.3	45.4	41.5	8.19
range					
Non-Fasting	182	135	72	53.2	19.9
(N=5)	109.5	54.8	44.2	24.1	3.2

	Plasma		Urine	
	Cmax	Tmax	Cmax*	Tmax
	ug/ml	hours	ug/ml	hours
Fasting mean (N=5) (S.D.)	0.46 (0.13)	1-2	334.4** (209.2)	mean 0-2hrs(550 ug/ml): 2 subs 2-4hrs(208 ug/ml): 2 subs 6-8hrs(156 ug/ml): 1 sub
Non-Fasting (N=5)	0.32 (0.16)	1-2	206.0 (80.5)	0-2hrs(257 ug/ml): 3 subs 2-4hrs(129 ug/ml): 2 subs

* The value reported represents the mean value of the highest concentration observed for the 4 urine collection periods in each subject.

** The reviewer calculated this value. The firm reported a value of 320.0 ug/ml. It appears that 320.0 is the result of using a 0-2hr urine concentration of 84 ug/ml rather than the 6-8hr urine concentration of 156 ug/ml in patient Y.K. If this subject is atypical then none of his values should be used.

Firm's Conclusion:

1. The levels in serum and urine in the non-fasting state were slightly lower than those in the fasting state, but they are of a sufficient concentration to produce antibacterial activity and should have not influence on the clinical effectiveness.

Study Reference: # 15, vol 2.146, pg VII-00450, study #1

Title: A Double Blind, Single Rising-Dose, Placebo-Controlled Study to Determine the Safety, Tolerability, Serum Profile, and of Doses of Placebo, and 200, 400, 800, 1200, and 1600 mg of MK-366 Administered Orally to Healthy Male Volunteers.

Investigator/Site: Roger Ferguson, M.D., Clinical Pharmacology Unit
Thomas Jefferson University Hospital
Philadelphia, PA 19107

Objectives: 1) to determine the serum profile and urinary excretion of MK0366 when given in single rising doses from 200 to 1600 mg orally in man and 2) to assess the safety and tolerability of the drug when administered under double blind conditions.

Design: Single dose, rising-dose regimen with two placebo treatments randomly interspersed in the scheme, double-blind, volunteers

Dosing: Each volunteer received one treatment per period and each treatment period was separated by a 6 day washout period. Below are the treatments administered in order of increasing dose. Each subject received all treatments. The two placebo treatments were randomly interspersed in the scheme.

Treatment A: 1 x 200 mg MK0366 capsules, 7 x 200 mg placebo
Treatment B: 2 x 200 mg MK0366 capsules, 6 x 200 mg placebo
Treatment C: 4 x 200 mg MK0366 capsules, 4 x 200 mg placebo
Treatment D: 6 x 200 mg MK0366 capsules, 2 x 200 mg placebo
Treatment E: 8 x 200 mg MK0366 capsules
Treatment F: placebo - 8 x 200 mg placebo
Treatment G: placebo - 8 x 200 mg placebo

Subjects will fast from midnight on the day prior to dosing and until 3 hours after dose administration.

Hydration: 250 ml of water 1 hour prior to therapy, 250 ml with dose administration, followed by 250 ml at 1, 2, 4, 6, and 8 hours post-treatment.

Subjects: 14 healthy male volunteers ranging in age from 21 to 31 years participated in the study. Volunteers were required to be within +/- 10 % of IBW for age and height based on Metro Life Ins Co Stat Bull No 40, 1959. Volunteers were judged normal on basis of medical history, physical examination, clinical laboratory data, and standard ECG. Exclusion

Criteria: Hx of renal or hepatic disease, any major systemic disorder including cardiac and GI disorders, ingestion of drugs (including alcohol and salicylates) within 7 days of study, history of drug or food allergy, inclusion in a drug study within 3 months of the present study.

Concurrent Medications: None Allowed from 7 days prior to study until completion of the study.

Specimens:

Blood - 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after dosing.

Urine(intervals) - minus 1 to 0(control), 0-1, 1-2, 2-3, 3-4, 4-6, 6-8, 8-12, 12-24, and 24-48 hours after dosing.

Analytical Methods: Specimens were analyzed via HPLC methodology with fluorescence(plasma) or uv(urine) detection. Representative standard curves and chromatographs for urine and plasma were provided. Urine specimens with a concentration less than 100 ug/ml were reanalyzed using a 5 ml sample volume instead of a 10 ml volume. The lower limit of sensitivity for 5 ml urine samples was 100 ug/ml. Urine specimens with a concentration above 100 ug/ml were diluted 1:10 in water and reanalyzed as before. Specificity of the assay with respect to metabolites was established by comparing the retention time of MK-366 with that of several metabolite standards. Using the methods described to prepare urine samples, it is stated that none of the metabolites of MK-366 interfere with assay of the parent drug.

Results:

Parameter	200 mg	400 mg	800 mg	1200 mg	1600 mg	ANOVA	Power
48 hr Ur Rec (%dose)	32.4 6.2	31.3 6.7	28.7 6.4	29.0 7.3	28.0 9.7	N.S.	0.97
Renal Cl (ml/min)	mean 313.4 S.D. 55.0	319.6 50.0	305.8 92.3	290.8 50.2	308.5 39.8	N.S.	1.0
AUC(0-inf) (ug/ml*hr)	3.4 0.8	6.2 1.8	12.2 2.6	19.1 5.4	24.1 8.0		
Cmax - Serum (ug/ml)	0.8 0.2	1.6 0.5	2.4 0.5	3.3 1.0	3.8 1.2		
Tpk - Serum (hr)	1.1 0.4	1.1 0.3	1.4 0.4	2.0 1.0	1.9 0.5		
EFFECTIVE T1/2* (hr)	2.2 0.2	2.2 0.2	2.3 0.2	2.4 0.2	2.5 0.2		

* This values represents the effective half-life for accumulation as determined by the firm for a dosing interval of 8 hours.

Tables:

- Table 15-1 : Serum concentrations of MK-366 after 200 mg
- Table 15-2 : Serum concentrations of MK-366 after 400 mg
- Table 15-3 : Serum concentrations of MK-366 after 800 mg
- Table 15-4 : Serum concentrations of MK-366 after 1200 mg
- Table 15-5 : Serum concentrations of MK-366 after 1600 mg
- Table 15-6 : Individual Cmax and Tmax values
- Table 15-7 : Individual Effective Half-life values
- Table 15-8 : Individual 8-hour AUC values
- Table 15-9 : Individual Total AUC(0-infin) values
- Table 15-10 : Urinary excretion of MK-366 after 200 mg
- Table 15-11 : Urinary excretion of MK-366 after 400 mg
- Table 15-12 : Urinary excretion of MK-366 after 800 mg
- Table 15-13 : Urinary excretion of MK-366 after 1200 mg
- Table 15-14 : Urinary excretion of MK-366 after 1600 mg

Table 15-15 : Concentration of MK-366 in urine after 200 mg
Table 15-16 : Concentration of MK-366 in urine after 400 mg
Table 15-17 : Concentration of MK-366 in urine after 800 mg
Table 15-18 : Concentration of MK-366 in urine after 1200 mg
Table 15-19 : Concentration of MK-366 in urine after 1600 mg
Table 15-20 : Individual 48-hr Urinary Recovery
Table 15-21 : Individual Cumulative Renal Clearance of MK-366
Table 15-22 : Mean MK-366 Biopharmaceutic Parameters
Figure 15-1 : Mean MK-366 concentrations displayed graphically
Figure 15-2 : Mean Cumulative Urine Excretion

Firm's Conclusions:

1. Increasing the MK-366 dose does not effect the total absorption of the drug although absorption is somewhat delayed at higher dose levels.
2. The effective serum half-life of MK-366 is independent of the dose.
3. The elimination of MK-366 from serum following single oral doses of 200, 400, 800, 1200 and 1600 mg doses is linear.
4. The AUC increases in proportion to the dose.
5. Average renal clearance is 300 ml/min with no apparent change over the range of doses administered.
6. Urinary recovery of unchanged MK-366 is 30% in 48 hours regardless of the dose.
7. MK-366 was well tolerated by the volunteers.

Study Reference: # 16, vol 2, 147, pg VII-0067, study # 44

Title: A Double-blind, Multiple Dose, Crossover Study to Investigate the Safety and Tolerance of Norfloxacin (MK0366) Versus Placebo.

Investigator(s): Miguel A Zinny, M.D.
Medical and Technical Research Associates
Clinical Unit
410 South Huntington Avenue
Jamaica Plain, MA 02194

Objective: 1) to investigate the safety and tolerability of the multiple doses of norfloxacin with respect to clinical, hematologic, neurologic and biochemical parameters and 2) to determine the plasma levels and urinary excretion following multiple oral doses of norfloxacin in healthy adult males and females.

Design: multiple dose, randomly assigned crossover with placebo, double-blind, healthy volunteers

Dosing: Oral administration using the following scheme,

1 x 400 mg norfloxacin tablet(Kyorin-B), q 12 hours x 14 days
1 matching norfloxacin image placebo tablet, q 12 hours x 14 days

Day 1 thru 14 - Treatment Period 1
Day 15 thru 21 - washout
Day 22 thru 35 - Treatment Period 2
Day 37 - Sampling Day

Volunteers fasted since midnight of the day prior to the 0800 hour dose until 3-4 hours after dosing and avoided food 1 hour before until 1 hour after the 2000 hour dose(see comment # 2). Time of dosing is referred to as zero (0) hour.

Hydration: Treatments were given with 250 ml of water, followed by 250 ml every 2 hours up to 4 hours post first dose of the day.

Concurrent Medications: None allowed from 7 days prior to study until its completion. See table 15-9 for a listing of volunteers who received medications other than the study drug and reasons for use.

Subjects: 27 (24 males, 3 females) healthy volunteers entered the study, however, 23 (20 males, 3 females) completed the study. Three volunteers were discontinued because of adverse clinical effects and 1 volunteer did not ingest one placebo dose. Subjects ranged in age from 19-50 years old, were to weigh within 15% of IBW for ages and height according to the Metro Life Ins Co Stat Bull #40, 1959, and judged normal on basis of medical history, physical examination and clinical laboratory screening.

Exclusion Criteria: hx of, or lab evidence of renal, hepatic, cardiac, pulmonary or hematologic disease, hx of epilepsy, neurologic disease, psychiatric disturbance, emotional instability or ophthalmologic conditions, ingestion of drugs of any kind(including alcohol) in the 7 days preceding initiation of the study, pregnant or lactating women, inability to complete the study.

Urine (intervals)

Blood

Days 1 and 22

1 hour prior to dosing

Days 1, 2*, 7, 14, 22, 23*, 28 and 35

(0 prior to dosing), 1, 2, 3, 4, 6, 8, and 12 hours after dosing

Urine (intervals)

Days 1 and 22

collected for a one hour period prior to dosing

Days 1, 2*, 7, 14, 22, 23*, 28 and 35

0-1, 1-2, 2-4, 4-6, 6-8, and 8-12 hours after dosing

* urine and blood collections on Days 2 and 23 were only collected during period 2.

Analytical Methods: Plasma and urine samples were shipped to MSD for analysis by Drug Metabolism Department. Plasma samples were analyzed for norfloxacin by a HPLC method utilizing fluorescence detection. It is reported that this method is specific for norfloxacin and the daily standard curve is linear from a range of [REDACTED] µg/ml of control plasma. The results for the validation of this method for plasma samples, quality controls, and a representative curve is given in Table 16-10 and Figure 16-2. Urine samples were analyzed for norfloxacin by a HPLC chromatographic system utilizing a spectrophotometric ultraviolet detector. It is reported that this method is specific for norfloxacin and the daily standard curve is linear from a range of [REDACTED] µg/ml of control urine. The results for the validation of this method for urine samples, quality controls, and a representative standard curve is given in Tables 16-11 and Figure 16-3.

Tables:

Table 16-1 - Volunteer Demographic Data

Table 16-2 - Individual Urinary Excretion of norfloxacin

Table 16-3 - Individual renal Clearance

Table 16-4 - Individual Plasma concentrations of norfloxacin

Table 16-5 - Individual Peak Plasma concentrations of norfloxacin

Table 16-6 - Individual Tmax values

Table 16-7 - Individual Cmin concentrations

Table 16-8 - Individual AUC(0-12hrs) values

Table 16-9 - Other medications taken by volunteers

Table 16-10 - Assay validation in plasma

Table 16-11 - Assay validation in urine

Figure 16-1 - Mean norfloxacin plasma concentrations displayed graphically

Figure 16-2 - Plasma calibration curve

Figure 16-3 - Urine calibration curve

Results.

(Subject: 1 dose on...)		Day 1	Day 2	Day 7	Day 14
Renal Clearance (ml/min)	mean	276.6	330.4	239.6	281.0
	S.D.	112.0	39.0	39.5	78.6
	(n)	(9)	(3)	(8)	(9)
C _{max} (mcg/ml)	mean	1.15	1.18	1.27	1.35
	S.D.	0.41	0.55	0.50	0.39
	(n)	(25)	(13)	(26)	(25)
t _{max} (hr)	mean	1.5	2.2	2.2	1.4
	S.D.	0.6	1.6	2.0	0.6
	(n)	(25)	(13)	(26)	(25)
AUC(0-12hr) ^a	mean	5.23	5.69	6.57	6.52
	S.D.	2.02	1.99	2.99	2.86
	(n)	(23)	(13)	(25)	(25)

C_{min}** (mcg/ml) following dose number...

Dose #	1 (Day 1) ^{***}	2 (Day 2)	3 (Day 2)	2 (Day 7)	13 (Day 7)	26 (Day 14)	27 (Day 14)
mean	0.12	0.20	0.15	0.20	0.17	0.23	0.18
S.D.	0.09	0.11	0.05	0.14	0.11	0.21	0.13
(n)	(25)	(13)	(13)	(26)	(26)	(25)	(25)

* In the majority of the subjects on each day, a portion of the total AUC(0-12) was estimated (not measured directly) using norfloxacin half-life or renal clearance(see Comments section of this review).

** It is reported that blood samples for determination of C_{min} after the second drug dose on days 1, 6 & 13, were actually drawn 30 minutes ahead of schedule. Plasma concentrations for these determinations were extrapolated to the end of the dosing interval using individual estimates of norfloxacin half-life.

*** Day of active treatment, not study day

Firm's Conclusions:

1. Results indicate that norfloxacin, when administered twice daily to volunteers with normal renal function, produces similar (0.15 - 0.18 g/ml) serum levels 12 hours after dosing on the 2nd, 7th, and 14th day of administration. Steady state is established between 2 and 7 days of drug administration (400 mg q 12 hours).

2. Analysis of the safety profile indicated that norfloxacin at a dose of 400 mg q 12 hours is safe and well tolerated.

Study Reference: # 17 ; vol 2.147, pg VII-00856

Title: A Double-Blind, Multiple Dose, Five-Day Crossover Study to Investigate the Safety and Tolerance of Norfloxacin(MK-366) Versus Placebo

Investigator/Site: Miguel A Zinny, M.D.
Medical and Technical Research Associates, Inc
408 South Huntington Ave
Jamaica Plain, MA 02194

Objective: 1) To evaluate the safety and tolerability of norfloxacin at the highest daily dosage schedule(1200 mg) used in clinical trials. 2) to determine the serum levels and urinary excretion this dosage regimen would produce in those volunteers sampled(four subjects).

Design: multiple dose, double blind, random crossover

Dosing: oral administration of either A. or B., followed by the other Tx.

- A. 400 mg q 8 hours, norfloxacin X 5 days; Kyorin-B product
- B. placebo X 5 days

A seven day washout period separated treatments. Subjects fasted since midnight of the day prior to initial dosing(AM) and resumed a normal diet at approximately 3-4 hours after the morning dose. No food was consumed from 1 hour before to 1 hour after dosing for subsequent doses.

Hydration: 250 ml of water 1 hour prior to dosing, 250 with administration of the dose, and 250 ml every 2 hours postdosing up to 4 hours after the first dose of the day. Subjects were encouraged to maintain a good fluid intake.

Concurrent Medications: None allowed(including alcohol) from seven days prior to the initiation of the study until its completion.

Subjects: Although 26 healthy male(25) and female(1) volunteers between the ages of 19 and 40 years of age participated in the study, PLASMA SAMPLES FOR PHARMACOKINETIC ANALYSIS WERE OBTAINED IN ONLY FOUR SUBJECTS. Selection criteria included weight within 15% of ideal for age and height(M.I.C.S.B, 1959) and in good health on basis of medical Hx, physical examination and clinical laboratory values. Exclusion criteria: hx of renal, hepatic, cardiac, pulmonary or hepatic disease, hx of epilepsy, neurologic disease, psychiatric disorders, and pregnant or lactating females.

Specimens:

Blood - Days 1, 2 and 5 of both periods

-1, 0(prior to dose), 1, 2, 3, 4, 6 and 8 hours after dosing.

Urine(intervals) - Days 1, 2 and 5 of both periods

-1 to 0(day 1 only), 0-1, 1-2, 2-4, 4-6 and 6-8 hours

Analytical Methods: Plasma and urine samples were analyzed by HPLC for norfloxacin by a HPLC method utilizing fluorescence detection. Urine samples were analyzed by HPLC methodology specific for norfloxacin utilizing ultraviolet spectrophotometric detection. A representative standard curve and results of quality controls were provided.

Data Analysis: AUC was estimated using the trapezoid method through 8 hours. Renal clearance of norfloxacin was estimated from corresponding increments of urinary recovery and AUC.

Tables:

- Table 17-1: Individual Plasma Concentrations
- Table 17-2: Individual Cmax & Tmax values
- Table 17-3: Individual AUC Values
- Table 17-4: Individual Cmin Values
- Table 17-5: Urine Concentrations
- Table 17-6: Individual Urinary Recovery
- Table 17-7: Individual Renal Clearance
- Figure 17-1: Mean Plasma Concentrations

Results:

		Day 1 (Dose 1)	Day 2 (Dose 4)	Day 5 (Dose 13)
Cmax (ug/ml)	mean	1.5	1.73	1.49
	S.D.	0.4	0.33	0.38
	range			
Tmax (hrs)	mean	1.3	1.8	1.5
	S.D.	0.5	1.0	0.6
	range			
AUC(0-8hrs) (ug*hr/ml)	mean	6.34	7.79	7.04
	S.D.	0.88	2.36	1.97
Renal Cl (ml/min)				
Sub # 102		216.9	---	171.3
Sub # 103		---	146.4	161.2

Firm's Pharmacokinetic Conclusions:

T. Too few volunteers (4) participated in the pharmacokinetic phase of this study to demonstrate to what degree norfloxacin accumulation might occur on a 400 mg q8h regimen. It appeared, however, that norfloxacin concentrations in plasma are lowest after the first dose and reach peak concentrations after the second day. Plasma concentrations did not increase thereafter.

Study Reference: #18; vol 7, 147, pg VII-00993, study #13

Title: An Open, triple Crossover Study to Compare the Bioavailability of Norfloxacin (MK0366) Following Oral Administration of 200 mg and 400 mg Market Image Tablets of MK0366 With a 400 mg Solution of MK0366 Given by Gavage in Healthy Volunteers.

Investigator/site: Miguel Zinny, M.D.
Medical and Technical Research Assoc., Inc.
Needham, Massachusetts 02194

Objective: The Biopharmaceutic objective of this study was to compare the serum concentrations and urinary excretion profiles of norfloxacin following PO administration of 200 mg and 400 mg market image tablets of MK0366 and 430 mg solution of the drug given by nasogastric intubation. The clinical objectives included determining the effects of norfloxacin on stool Enterobacteriaceae and other gram-negative bacilli as well as determining antimicrobial activity in stool specimens.

Design: Open, single dose, randomized triple-crossover

Dosing: Each of the volunteers received each of the following treatments,

- Tx A: 200 mg market image norfloxacin tablet(Kyorin-A formulation)
- Tx B: 400 mg market image norfloxacin tablet(Kyorin-A formulation)
- Tx C: 430 mg norfloxacin solution, given via a nasogastric tube
(The protocol originally specified 400 mg, however, the average assayed solution dose was 430 mg.)

Dosing occurred after a 10 hour fast. Normal meals were resumed 4 hours after each treatment. No other medications(including alcohol) was allowed from 1 week before study start until study completion.
Hydration: 8 ounces(240 ml) of water was given with the dose, followed by 8 ounces at 1, 2, 4, 6 and 8 hours after each treatment.

Subjects: 15 healthy male volunteers 21 years of age or older and within +/- 10% of their IBW for height and age according in the Metropol. Life Insur. Co. Stat Bull No. 40, 1959, participated in the study. Subjects were judged normal on basis of medical history, physical examination and clinical laboratory data. Exclusion Criteria: Hx of renal or hepatic disease, major systemic disorders including cardiac, GI and neurologic disorders, drug taking(including alcohol and salicylates) in the preceding seven days, hx of drug or food allergy and involvement in a drug study during the preceding 3 months.

Specimens.

Blood - 0(before dosing), 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours after dosing.

Urine(intervals) - minus 1 to 0(control), 0 to 1, 1-2, 2-3, 3-4, 4-6, 6-8, 8-12, 12-24 and 24-48 hours.

Rectal Swabs(for bacterial culture and bioassay determination) - before, 12 and 24 hours after dosing.

Stool(in 400 mg tablet group) - prestudy and up to 48 hours after dosing.

Analytical: Serum and urine samples were assayed for MK0366 by MSD Research Laboratories. Serum samples were analyzed by HPLC methodology specific for MK0366 utilizing fluorescence detection. Urine samples were analyzed by HPLC methodology specific for MK0366 utilizing ultraviolet spectrophotometric detection. Antimicrobial activity in stool specimens and rectal swabs were determined by Dr. Sheldon Landsman at The Infectious Disease Laboratory of the SUNY-Downstate Medical School.

Data Analysis: AUC(0-8 hrs) was measured using the trapezoid or spline method and extrapolated to infinity using renal clearance. Renal clearance of norfloxacin is estimated using corresponding increments of urinary recovery and AUC. The relative bioavailability of norfloxacin (tablet vs solution) was calculated using the method of Kwan and Hill (submission ref #24) as modified by Hwang and Kwan (submission ref #25). The effective serum half-life was estimated from AUC(0-8) and AUC(0-infinity) as described in submission reference #23.

Results:

Parameter		430 mg SOLN	200 mg TAB	400 mg TAB
<u>Urin Recov-48 hr-Unadjusted for dose (mg)</u>				
Total	Mean	121.91	52.15	105.14
	S.D.	28.96	18.63	36.22
	N	14	13	14
% Dose	Mean	28.38	25.45	26.48
	S.D.	6.74	9.08	9.12
	N	14	13	14
<u>AUC-Dose adjusted up to 430 mg (mcg/ml)*hr</u>				
(0-8 hr)	Mean	6.04	5.57	5.44
	S.D.	1.90	2.36	2.65
	N	15	15	15
<u>Total Estimated(0-infin)</u>				
	Mean	7.58	6.96	7.1
	S.D.	2.08	3.23	3.56
	N	14	13	14
<u>C_{max}-Dose adjusted up to 430 mg (mcg/ml)</u>				
	Mean	1.37	1.60	1.62
	S.D.	0.66	0.66	0.62
	N	15	15	15
<u>t_{max} (hrs)</u>				
	Mean	0.70	1.03	1.03
	S.D.	0.37	0.35	0.35
	N	15	15	15
<u>Effective Half-Life (hr) - 8 hour dosing interval</u>				
	Harmonic Mean	2.99	3.26	3.22
	95% C.I.	2.63-3.47	2.85-3.81	2.92-3.59
<u>Cum. Renal Clearance (ml/min)</u>				
	Mean	276.37	263.39	299.26
	S.D.	71.31	76.13	94.96
	N	15	15	15

Relative Bioavailability*			
	200 mg Tab/Soln	400 mg Tab/Soln	200 mg Tab/400mg Tab
Mean**	0.89	0.90	1.00
95% C.I.	0.79-1.14	0.72-1.13	0.79-1.26
Power (25% Difference)	0.77	0.78	0.80

* Based on the method of Kwan and Till as modified by Hwang & Kwan (submission references #24 & 25)

** Geometric mean

Relative Bioavailability Based on Ratio of Dose Adjusted AUC(0-infin)		
	200 Tab/200 Soln	400 Tab/400 Soln
Mean Ratio	0.998	0.987
S.D. +/-	0.42	0.49
C.V.	42.1 %	49.6 %
% w/in 75-125%	25% (3/12) 4 Hi, 5 Lo	38.5% (5/13) 3 Hi, 5 Lo

Tables:

- Table 18-1 : Individual 8 hour AUC
- Table 18-2 : Individual Estimates of Total AUC(0-infin)
- Table 18-3 : Individual Cmax concentrations
- Table 18-4 : Individual Effective Half-Life for Accumulation
- Table 18-5 : Individual 48-hour Urinary Recovery
- Table 18-6 : Bioavailability Parameters
- Table 18-7 : Individual Estimates of Relative Bioavailability
- Table 18-8 : Individual Cumulative Renal Clearance
- Table 18-9 : Summary of Bioavailability Parameters

Firm's Conclusions:

1. Norfloxacin is equally bioavailable from the two tablet strengths studied.
2. Bioavailability from tablet formulations was 90% relative to the solution given by NG tube.

Study: Reference #19: Vol 2.148, pg VII-01142

Title: An Open Study to Determine the Pharmacokinetics of a Single Dose of Norfloxacin in the Elderly.

Investigator/Site: Dr. K.B. Martin, R.L. Brown
Bios(Consultation & Contract Research) Ltd.
Bagshot, Surrey, England

Objective: To document the safety and to obtain a pharmacokinetic profile of norfloxacin in healthy elderly subjects after a single 400 mg oral dose.

Design: Single oral dose

Dosing: 400 mg MK-366, PO ; film-coated tablet, MK-366;
formulation # 81-54-62, MSD

Drug was administered after an over-night fast. No food was allowed for 2 hours after the dose, at which time a standard breakfast was served. No medicine was allowed for 72 hours prior to the dose and no alcohol for 24 hours prior to the dose.

Hydration: Drug was administered with 150 ml of water, followed by 150 ml of water ("Perrier") at 1, 2, 3, and 4 hours after drug administration. Patients were instructed to consume 150 ml of water upon rising the morning of the study which began at 9:00 a.m.

Subjects: Six, healthy, elderly subjects(2 male, 4 female) between the ages of 67 and 74 years participated in the study. Subjects were reported to be neither grossly overweight nor underweight for their height and build. Basis for determination of normality, inclusion and exclusion criteria were provided. Subjects with a creatinine clearance of greater than or equal to 70 ml/min/1.73 meter squared were included in the study.

Specimens:

Blood - 0(control), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 and 24 hours after the dose.

Urine(intervals) - 0-1, 1-2, 2-3, 3-4, 4-6, 6-8, 8-12, 12-24 hours.

Analytical Methods: Norfloxacin concentration in plasma and urine was assayed at BIOS, LTD. by using HPLC methodology. It is reported that the method is specific and sensitive for norfloxacin and that calibration standards and quality control specimens were processed along with each batch of samples.

Data Analysis: Pharmacokinetic computations were done by Drug Metabolism Department, MSDRL. AUC was estimated using the trapezoid method and extrapolated to infinity using renal clearance. Renal clearance was derived from corresponding increments of urinary recovery and AUC. The effective serum half life of norfloxacin was estimated according to the method of Kwau, et al(JPS).

Tables/Figures:

Table 19-1 : Individual Urin Recov and Renal Clearance

Table 19-2 : Individual AUC, Cmax, Tmax and Effective T1/2

Table 19-3 : Individual Demographic Data

Figure 19-1 : Mean Plasma Concentration vs Time Curve

Results:

Pharmacokinetic Parameter			
Urin Recov (0-infin)	Mean S.D.	90.5 mg 28.0	N=6
% Dose Recov in Urin		22.3 % 6.9	N=6
Renal Clearance		154 ml/min 15.7	N=6
AUC(0-infin)		9.8 mcg*hr/ml 2.8	N=6
AUC(0-8)		7.5 mcg*hr/ml 2.2	N=6
Cmax		2.0 mcg/ml 0.8	N=6
Tmax		1.3 hr 0.4	N=6
Effective Half-life for Accumulation (8-hour dosing interval)		3.9 hr 0.3	N=6

Firm's Conclusions:

1. Pharmacokinetic parameters indicate elimination of norfloxacin may be slightly reduced in the elderly. This results in small increases in plasma levels and may also result in small increases in drug half-life.
2. Changes in norfloxacin disposition appear attributable to the slightly reduced renal function associated with a normal, elderly population.
3. No alteration of dosing regimen appears necessary for elderly subjects whose renal function is normal for this age group (creatinine clearance greater than or equal to 70 ml/min/1.73 meters squared).
4. A single 400 mg dose of norfloxacin appears safe in healthy, elderly subjects.

Study: Reference #20; vol 2.148, pg VII-01293

Title: An Open Study to Determine Serum Concentrations and Urinary Excretion Profile of a Single Oral Dose of MK-366 in Patients With Varying Degrees of Renal Dysfunction and in Subjects With Normal Renal Function

Investigator/Site: A. William Asscher
Welsch National School of Medicine
Renal Unit-Royal Infirmary
Cardiff, Wales

Objective: 1) To obtain serum concentration and urinary excretion data for a single 400 mg dose of norfloxacin in patients with varying degrees of renal dysfunction and to compare this data with data from subjects with normal renal function. 2) to obtain data for assisting in designing norfloxacin dosage regimens for patients with renal dysfunction. 3) to obtain information on the tolerability and safety of norfloxacin in this patient population.

Design: Open, Single-dose, subjects grouped according to renal function.

Dosing: 400 mg norfloxacin, PO, tablet

Subject Groups: I Healthy subjects with normal renal function
C1Cr greater than 100 ml/min/1.73 meters squared
II Patients with C1Cr 31 to 80 ml/min/1.73 meters squared
III Patients with C1Cr 10 to 30 ml/min/1.73 meters squared
IV Patients with C1Cr less than 10 ml/min/1.73 meters squared
(patients not on hemodialysis)

Patients fasted for 8 hours prior to dosing. A light snack was allowed 2 hours after the dose followed by lunch 4 hours after the dose.

Hydration: Drug was administered with 250 ml of water, followed by 150 ml at 1, 2, 3, and 4 hours after the dose. Patients were also instructed to consume 250 ml of water upon rising the morning of the study which began at 0800.

Patients: 9 healthy volunteers and 18 patients with varying degrees of renal dysfunction participated in the study. Patients were required to be neither grossly overweight or underweight for height and body build. Criteria for inclusion and exclusion were provided. Subjects with concomitant mild hypertension and stable renal disease were accepted into groups II, III and IV. Subjects were excluded from participating in groups II, III and IV if any of the following conditions were present: 1. A disease, other than renal, which might influence the pharmacokinetics of the study drug, 2. treatment with antibiotics or other drugs which might affect the pharmacokinetics or assay procedure of the study drug.

Specimens:

Blood - 0 (pre-treatment), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, and 48 hours after the dose.

Urine (intervals) - 0 (pre-treatment), 0-1, 1-2, 2-3, 3-4, 4-5, 5-6, 6-8, 8-10, 10-24, 24-48 and 48-72 hours post dosing. It was noted that sampling times and collection intervals varied somewhat that specified in the protocol and above. Occasionally urine collections were made at intervals such as 0-2, 2-4, 4-6, 6-8, 8-10 (or 8-12), 10-24 (or 12-24), 24-48 and 48-72 hours.

Analytical Methods. Serum samples were analyzed for norfloxacin by a HPLC method utilizing fluorescence detection. Urine samples were analyzed for norfloxacin by a HPLC method utilizing an ultraviolet detector. It is reported that both methods are specific for norfloxacin and that standards and quality controls were analyzed with the unknown samples.

Data Analysis: AUC was calculated using the trapezoid or spline method and extrapolated to infinity using renal clearance. Renal clearance was estimated using corresponding increments of urinary recovery and AUC. The effective half-life of norfloxacin was estimated from methods of Kwan, et al (reference # 23).

Tables:

- Table 20-1: Individual Demographic Data
- Table 20-2: Individual and Mean Urin Recov, % Dose Exctd & Renal Cl
- Table 20-3: Individual and Mean AUC
- Table 20-4: Individual and Mean Cmax & Tmax
- Table 20-5: Individual and Mean Effective Half-life
- Figure 20-1: Mean Norfloxacin concentration-time profiles

Results:

Parameters*	ClCr (ml/min/1.73 meters squared)							
	Group I GT 100		Group II 31 - 80		Group III 10 - 30		Group IV LT 10	
	Mean	N	Mean	N	Mean	N	Mean	N
AUC(0-8h) mcg*hr/ml	5.38 1.93	8	7.62 2.00	5	9.18 2.41	4	7.79 5.31	4
AUC(0-infin)	6.94 2.73	8	9.53 2.47	5	24.01 13.49	4	16.46 14.52	4
Cmax (mcg/ml)	1.51 0.56	9	1.91 0.71	6	1.70 0.43	6	1.70 0.92	6
Tmax (hr)	1.4 0.4	9	1.3 0.4	6	1.8 1.1	6	1.8 1.2	6
Effective T1/2 (hr) (Harmonic Mean), 8 hour dosing interval	3.47	8	3.38	5	6.57	4	6.4	4
Urin Recov(% Dose)	28.2 12.8	8	35.3 9.2	5	6.7 4.1	5	2.4 1.1	4
Renal Cl (ml/min)	297.1 117.4	8	264.5 83.2	5	17.8 4.4	4	14.7 8.4	5

* data taken from Bioanalytical-Biopharmaceutics Report

Statistical Evaluation

Parameter	Overall	Significant Pairwise Comparisons
Urinary Recovery (Dose)	p < LT* 0.0001	1,2 vs 3 p = 0.0002 1,2 vs 4 p = 0.0001
Renal Clearance	p < LT 0.0001	1,2 vs 3 p = 0.0002 1,2 vs 4 p = 0.0001
C _{max}	NS (p > 0.2)	
T _{max}	NS (p > 0.2)	
AUC(0-8hr)	NS (p > 0.2)	
AUC(0-infinity)	p = 0.03	1 vs 3 p = 0.004 2 vs 3 p = 0.04 1 vs 4 p = 0.06
Effective t _{1/2}	NS (p = 0.10)	

* - LT = less than, GT = greater than

Firm's Conclusions:

1. Based on the renal elimination rate of MK-366, no change is needed in the MK-366 regimen in subjects whose GFR exceeds 30 ml/min/1.73 meters squared.
2. When GFR is less than or equal to 30 ml/min/1.73 meters squared, the regular dose of MK-366 should be given once a day rather than twice a day.
3. The administered dose of norfloxacin appears to be safe in renally impaired patients.

Source: Reference # 21; vol 2.148, pg VII-01421, study #59

Title: An Open, Two-Way Crossover Study to Compare the Bioavailability of Norfloxacin Following Oral Administration of a 400 mg Original Formulation Tablet of MK0366 with a 400 mg New Formulation Tablet of MK0366 in Healthy Volunteers

Investigator/Title: Miguel Zinny, M.D.
Medical and Technical Research Assoc., Inc.
Boston, Mass 02130

Objective: a) To compare the plasma concentration profile and urinary excretion of norfloxacin following oral administration of a 400 mg new formulation tablet (MSD direct compression process) of MK0366 and a 400 mg old formulation tablet (Kyorin) of MK0366 and b) to determine the antimicrobial activity found in the stool after oral administration of the 400 mg new formulation tablet.

Design: Open, single dose, randomized, two-way crossover

Dosing: Each volunteer will receive,

- A. 400 mg norfloxacin tablet; new formulation (MSD direct compr)
- B. 400 mg norfloxacin tablet; original formulation (Kyorin-B)

Hydration: The dose was given with 8 oz (240cc) of water, followed by another 8 ounces of water at 1, 2, 4, 6, and 8 hours after the dose.

Treatments were separated by a 7 day washout period. Volunteers fasted from 10:00 PM of the night prior to dosing until 4 hours after the dose. No medications were allowed (including alcohol) from one week prior to initiation of the study until its completion.

Subjects: Twenty normal healthy male volunteers between 18 and 40 years of age entered and completed the study. Subjects were to have satisfied inclusion and exclusion criteria.

Specimens:

Blood: 0 (control), 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after dosing.

Urine (intervals): minus 1 to 0 (control), 0-1, 1-2, 2-3, 3-4, 4-6, 6-8, 8-12, 12-24, 24-48 hours.

Stool (only in subjects who received Tx A.): pre-study (control), and all specimens up to 48 hours after drug ingestion.

Analytical Methods: Serum and urine samples were assayed for MK0366 by MSD Research Laboratories. Serum samples were analyzed by HPLC methodology specific for MK0366 utilizing fluorescence detection. Urine samples were analyzed by HPLC methodology specific for MK0366 utilizing ultraviolet spectrophotometric detection. Antimicrobial activity in stool specimens were determined by Dr. Sheldon Landesman at The Infectious Disease Laboratory of the SUNY-Downstate Medical School.

Data Analysis: AUC(0-8 hrs) was measured using the trapezoidal rule method and extrapolated to infinity using renal clearance. Renal clearance of norfloxacin was estimated using corresponding increments of urinary recovery and AUC. The relative bioavailability of norfloxacin (MSD vs Kyorin) was calculated using the method of Kwan and Liu (submission ref #24) as modified by Hwang and Kwan (submission ref #25). The effective serum half-life was estimated from AUC(0-8) and AUC(0-infinity) as described in submission reference #23.

Tables:

- Table 21-1 : Individual Plasma concns - Kyorin tablet
- Table 21-2 : Individual Plasma concns - MSD tablet
- Table 21-3 : Individual Cmax concns - Kyorin tablet & MSD tablet
- Table 21-4a : Individual Urine concns - Kyorin tablet
- Table 21-4b : Individual Urine concns - MSD tablet
- Table 21-5 : Individual Total Urin Recov - Kyorin tab & MSD tab
- Table 21-6 : Individual Relative Bioavailability
- Table 21-7 : Individual Cum Renal Cl and Total AUC - Kyorin & MSD Tabs
- Table 21-8 : Mean Pharmacokinetic Parameters - Kyorin & MSD Tabs
- Figure 21-1 : Mean Plasma Conc'n Profiles - Kyorin & MSD Tabs

Results:

Parameter	Kyorin Tab	MSD Tab	ANOVA	POWER
AUC(0-infinity) (mcg/ml*hr)				(20% diff, alpha 0.05)
Mean	7.82	6.94	NS	85.6
S.D.	2.53	1.69		
N	19	18		
Cmax (mcg/ml)				
Mean	1.56	1.54	NS	75.4
S.D.	0.48	0.42		
N	20	20		
Tmax (hrs)				
Mean	1.35	1.07	Sig(P LT 0.05)	
S.D.	0.43	0.37		
N	20	20		
Urin Recov - % of dose*				
Mean	27.9	27.0		
S.D.	8.9	8.5		
N	19	18		
Renal Clearance (ml/min)				
Mean	261.9	270.0		
S.D.	80.7	63.4		
N	20	18		

* Based on administered doses of 412 and 414 mg for the Kyorin and MSD formulations, respectively. Refer to Assay Content of norfloxacin in table "Dosage Form Characteristics", pg VII-01425, vol. 2, 148.

Ratio of AUC(0-8h) (New) MSD/Kyorin

Mean Ratio 0.967
S.D. 0.31
C.V. 32.4 %

Percentage of 175% -- $10/17 = 58.8 \% ; 3 \text{ III}, 4 \text{ IV}$

Relative Bioavailability*(New-MSD/Old-Kyorin) as calculated by methods described above.

Geometric Mean 0.94 Power 20% Diff 0.81
N 17 25% Diff 0.99
95% C.I. 0.80 - 1.09

* values for individual subjects were not provided.

Stool Samples

It is reported that peak norfloxacin activity in the stool occurred approximately 24 hours following ingestion and ranged from 348 to 1916 ug/gm stool.

Firm's Conclusions:

1. The 400 mg norfloxacin tablets formulated by the old Kyorin process and the new MSDRL direct compression process are similarly bioavailable (the new formulation is 94% as bioavailable as the old formulation).
2. Norfloxacin was absorbed faster following the ingestion of tablets manufactured by the new MSDRL process.

Comment: THE MSD PRODUCT UTILIZED IN THIS INVESTIGATION HAS A DIFFERENT COATING THAN THAT OF THE PROPOSED MARKETED TABLET. THE PROPOSED MARKETED TABLET WAS NOT INVESTIGATED IN ANY OF THE BA/PK STUDIES SUBMITTED BY THE FIRM.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs and Biologics

Attachment I

Date: April 2, 1985

To: Jerome H. Skoloff, Ph.D.
Acting Director, Division of Biopharmaceutics, HFN-270

From: E. Warren Reed, M.D.
Medical Officer, HFN-815

Through: Edward Taber, M.D. *E. Taber 4/3/85*
Director, Division of Anti-Infective Drug Products, HFN-815

Subject: Norfloxacin-induced crystalluria (NDA 19-384)

This request is a follow-up to our Biopharmaceutics Division consultation request regarding norfloxacin, NDA 19-384 from Merck, Sharp and Dohme Research Laboratories which is now under review in this Division. We sent copies of the four volumes which contain pharmacokinetic data, Volumes No. 2.145-2.148, to your Division on March 11, 1985.

In your response to our consultation request, please include your comments regarding the possibility that norfloxacin might precipitate into crystals in the human kidney and cause obstruction there or elsewhere in the urinary tract.

Norfloxacin is an orally absorbed member of the quinolone group of antibacterial agents. Crystalluria has been reported in clinical studies of other members of this class. The presence of drug crystals with one member of this class that was never approved for marketing was so troublesome that several products which would acidify urine in an attempt to increase the drug's solubility were given concomitantly during clinical investigations. Later, the pharmaceutical manufacturer suggested that crystallization occurred after voiding while the urine cooled instead of before voiding within the urinary tract.

In animal studies of norfloxacin, crystalluria, consisting of the dihydrate and the magnesium salts of norfloxacin, occurred in rats at 200 and 600 mg/kg/day doses. Crystalluria occurred in beagle dogs given norfloxacin at 50, 150, and 300 mg/kg/day for 26 weeks but not in the 25 mg/kg/day dose group. The incidence was dose related. Three dogs, one in the 150 mg/kg/day and two in the 300 mg/kg/day dose groups, were found dead or were sacrificed due to urinary obstruction from drug crystals. Since emesis occurred in all dose groups in dogs and occurred frequently after dosing, one cannot be sure what proportion of the dose was retained and absorbed. The crystalluria in dogs and rats was attributed to low solubility of the drug in alkaline urine. Crystalluria decreased when urine was acidified by the administration of ammonium chloride. Drug crystals shaped as sea urchins and/or fine needles were occasionally seen in urine from dogs in each of the drug-treated groups.

Norfloxacin is a new drug entity. We are two months into the 180-day new-NDA time period and the application has high priority.

Theresa Anne Reed

cc Orig NDA 19-384, HFN-815, HFN-815/Reed, HFN-815/Reed, HFN-815/Reed, HFN-815/CSO 3585b

2/24

Correspondence

Reduced Intestinal Absorption of
Ciprofloxacin in the Presence of
Antacids

Sir
Ciprofloxacin, a new quinolone carboxylic acid derivative, has high in vitro activity against a wide range of pathogens including members of the family *Enterobacteriaceae* and *Pseudomonas aeruginosa* (1). The pharmacokinetics after oral administration of the drug are characterized by rapid absorption, good diffusion into the extracellular space, and elimination by biliary excretion, hepatic metabolism, glomerular filtration and tubular secretion (2).

In a study in fasting volunteers the absolute bioavailability ranged from 0.63 to 0.77, and the cumulative urinary excretion of unmetabolized drug in 24-hour-urine accounted for approximately 35% of the initial oral dose (2). To assess the effect of antacids on intestinal absorption of orally administered ciprofloxacin, we performed a randomized study in ten healthy volunteers (5 females, 5 males, mean age 30 years, mean body weight 67.5 kg) who were given 500 mg ciprofloxacin orally either in a fasting state or 24 h after administration of the antacid 10 X 600 mg Mg-OH + 900 mg Al-OH (Maalox). Serum and urine concentrations were determined by a bioassay and high performance liquid chromatography. The pharmacokinetic parameters were calculated using an open two-compartment model. Administration of the antacid led to a pronounced decrease of the peak serum concentration from a mean of 1.7 mg/l (range 1.3-2.6 mg/l) after ciprofloxacin alone to a mean of 0.1 mg/l (range 0.06-0.2 mg/l) after ciprofloxacin plus antacid ($p < 0.001$). The time after which the serum concentration peaked was only slightly prolonged (73 ± 13 min versus 87 ± 21 min). The cumulative urinary excretion of unmetabolized ciprofloxacin in 24-hour-urine after ciprofloxacin administered alone accounted for 24% (range 19-34%) of the administered dose as against only 2.1% (range 0.9-4.7%) after prior administration of the antacid.

A possible explanation for the reduced absorption rate of ciprofloxacin administered after the antacid is that Mg⁺⁺ or Al⁺⁺⁺ chelates form. In fact, chelate complexes of the drug with Mg⁺⁺ have been reported to reduce bactericidal concentrations of ciprofloxacin tested in nutrient broth against *Escherichia coli* K12 (3). In addition, association constants for Mg⁺⁺ complexes of nalidixic and oxolinic acid, analogous substances, were reported to be 3.0 and

3.3 respectively. The diminished absorption of ciprofloxacin seen in our study could be explained by a reduced rate of absorption of the Mg⁺⁺ and Al⁺⁺⁺ ciprofloxacin chelate complexes. It would have been difficult to assess the significance of the decrease in absorption. Nevertheless, the pronounced effect of antacids on the bioavailability of ciprofloxacin should be considered if both these drugs are administered to a patient. Furthermore, all other new quinolone derivatives should be tested for such interaction with antacid drugs.

G. Höffken
K. Borner
P. D. Glatzel
P. Koeppe
H. Lode*

Section for Chemotherapy and Infectious Diseases, Medical Department, Klinikum Steglitz, Hindenburgdamm 30, 1000 Berlin 45, FRG

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2. Wise, R., Lockley, M., Webberly, M., Deum, J.: Pharmacokinetics of intravenously administered ciprofloxacin. *Antimicrobial Agents and Chemotherapy* 1984, 26, 208-210.
3. Ratcliffe, N. T., Smith, J. T.: Effects of magnesium on the activity of 4-quinolone antibacterial agents. *Journal of Pharmacy and Pharmacology* 1983, 35, 61.

In Vitro Activity of Ciprofloxacin
against Mycobacteria

Sir,
Ciprofloxacin is a new broad-spectrum quinolone derivative with activity against many gram-positive and gram-negative bacterial species. As little is known about its activity against mycobacteria we decided to investigate the antimycobacterial activity of ciprofloxacin in comparison with enoxacin, another quinolone derivative. One hundred mycobacteria strains were tested for sensitivity to ciprofloxacin and 50 of these strains were also used for the comparative study with enoxacin. The 100 strains consisted of 69 strains of *Mycobacterium tuberculosis*, 12 of *Mycobacterium*

Appendix B

Tables and Figures

1 Page(s)

Redacted

Table 1b

~~XXXXXXXXXX~~

XXXXXXXXXX

Study 59 - Dissolution Profile

Dissolution Profile - Kyorin Tablets (400 mg)

Kyorin 400 mg vs Merck 400 mg NDC 029-010

0.1 M Acetate Buffer, pH 5.0, 100 RPM

0.1 M Acetate Buffer, Paddles, 50 RPM

200 mg Lot 031-101

Kyorin Formula - Lot 029-001 (400 mg)

15 min 30 min 45 min 60 min

15 min 30 min 45 min 60 min

$\bar{X} = 68\%$ 98% 100% 100%

$\bar{X} = 59\%$ 75% 85% 91%

400 mg Lot 031-101

Merck Formula - Lot 029-007 (400 mg)

15 min 30 min 45 min 60 min

15 min 30 min 45 min 60 min

$\bar{X} = 41\%$ 96% 104% 105%

$\bar{X} = 98\%$ 99% 99% 99%

200 mg 400 mg

Kyorin MSD (blue)

Source: Kyorin Kyorin

Kyorin MSD-USA

MSD-USA MSD-USA

["developed for overseas markets"
International Blue]

- Same Composition
- Direct Compression
- "USA-pink"

MSD (pink)
029-010

MSD (pink)
029-012

$\bar{X} = 99\%$ 100% 100%

100%

Table 1b (cont)

<u>Batch No.</u>	<u>Dissolution (30 minutes) %</u>	<u>Average</u>
850261A		90
850261B		90
850449A		93
850449B		96
850450A		94
850450B		90
850514A		94
850514B		96
850638A		94
850638B		95

~~XXXXXXXXXX~~
 NOROXIN Tablets - First Market Image 400 mg

Lot 0366 PCT 029-C013

First Production Demonstration Lot

% Dissolved

15 Min. 30 Min. 45 Min.

Mean	100	100	100
Rel. Std. Dev.	2%	1%	2%

Source :

MSD Italy

- Direct Compression
- blue

MSD - USA

- Direct Compression
- USA pink

Table 2

Identity of All Oral Formulations Used in Clinical Studies of
Morfloxacin Pharmacokinetics and Bioavailability

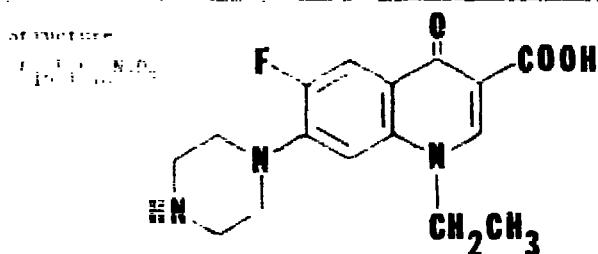
Study Description	Pivotal (P) or Comparative (C)	Type of Formulations Used	Formulation and Batch Number	Batch Size	Number of Subjects Studied
Single, Single Dose Study (ref. #10, Study #1)	P	Capsule (200 mg)	0366-DPC-001-B01		14
Multiple (BID) Dose Study (ref. #10, Study #45)	C	Kyorin Tablets (400 mg)	0366-PCT-005-C02		25
Multiple (TID) Dose Study (ref. #11, Study #68)	C	Kyorin Tablets (400 mg)	0366-PCT-006-C01		26
Tablet Bioavailability vs. Oral Solution (ref. #18, Study #11)	P	Kyorin Tablets (200 mg) Kyorin Tablets (400 mg)(A) Oral Solution	0366-PCT-002-B03 0366-PCT-001-C01 0366-OSO-001-A01		15
Tablet Bioavailability; Kyorin Tablet vs. Merck Direct Compression Tablet (ref. #21, Study #59)	P	Kyorin Tablets (400 mg)(B) Merck Direct Compression Tablet (400 mg)	0366-PCT-006-C01 0366-PCT-020-C017		20

Tablets from the particular batch of 200-mg Kyorin tablets identified in Table I were used in pivotal clinical studies in acute uncomplicated urinary tract infections (Study #3, #6, #7) and acute urinary tract infections (Study #8, #10, #12). Likewise, tablets from the largest batch of 400-mg Kyorin tablets were used in key clinical studies in acute urinary tract infection (Study #28) and to suppress aerobic bowel flora in patients with granulocytopenia (Study #15, #19). Similarly prepared batches of Kyorin tablets were used in other key studies to define efficacy in these areas (#2, #5, #11, #9, #14, #505, #543, #521, #16, #17, #37, #38, #27, #25, #36, #40, #35, #554, #545, #535, #539, #549, #528, #565, #542, #564, #530, #518, #551, #534, #533, #541, #528, #537, #532, #519, #555, #548, #53, #24, #507, #508, #512, #509, #512, #509, #510, #511, #568, #567, #693, #573, #694, #574, #692), as well as in pivotal studies in acute bacterial gastroenteritis (#14, #588, #591, #595, #609, #590, #589, #634, #31) and in uncomplicated gonorrhoea (#30, #48, #49).

Figure 1

Physical and Chemical Information for Norfloxacin

Physical and Chemical Information



Molecular Weight: 319.3

Description: White odorless powder

Melting Point: 220-224°C

Metabolites of Norfloxacin.

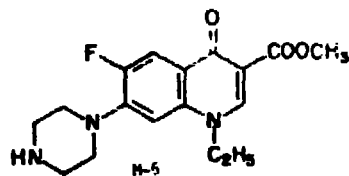
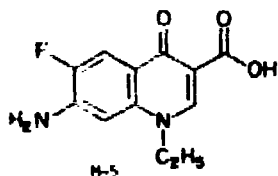
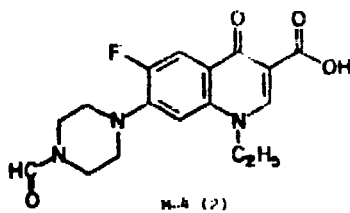
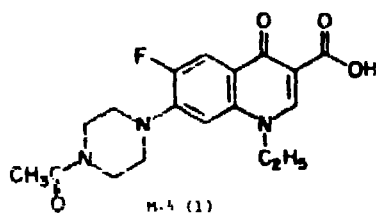
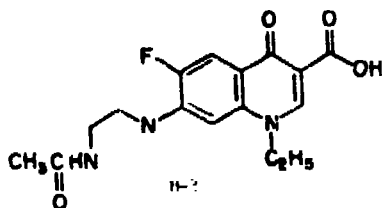
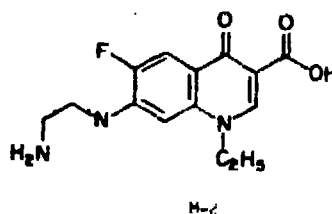
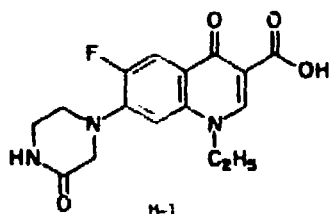


Table 3

TABLE 3. Urinary excretion of AM-715 after oral administration of 200 mg of AM-715 in humans

Treatment	Subject no.	Clearance (ml/min)	Creatinine clearance (ml/min)	AM-715 clearance (ml/min)	Clearance ratio	Urinary recovery (% dose) ^a
Without probenecid	1					
	2					
	3					
	4					
	5					
With probenecid	1					
	2					
	3					
	4					
	5					
Mean ± S.E.						
		3-5	111.6 ± 10.6	266.0 ± 32.6 (72A)	2.4 ± 0.3	
		5-7	135.3 ± 11.7	387.5 ± 65.3 (146)	3.4 ± 0.5	28.0 ± 6.9
		7-9	125.8 ± 7.4	351.1 ± 19.4 (34.8)	2.8 ± 0.3	(S.D. = 15.5)
				$\bar{x}$ 334.9 ± 62.4 (S.D.)		
Mean ± S.E.		3-5	150.1 ± 23.4	164.8 ± 22.9	1.2 ± 0.2	
		5-7	119.9 ± 8.1	144.3 ± 12.9	1.2 ± 0.1	13.9 ± 2.1
		7-9	118.9 ± 4.7	181.8 ± 19.7	1.5 ± 0.1	(S.D. = 4.7)
				$\bar{x}$ 163.6 ± 18.8 (S.D.)		

^a Recovery of AM-715 12 h after administration.
^b ND, No detectable serum concentration of AM-715.

Figure 3

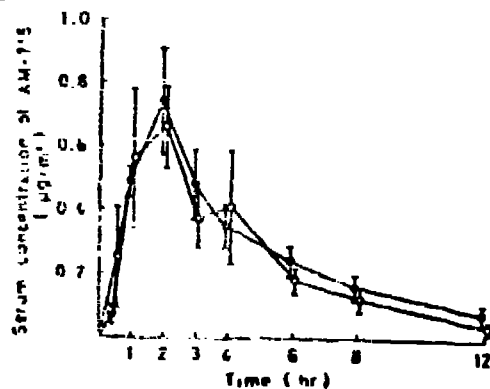


Figure 3. Mean ± standard error serum concentration of AM-715 after oral administration of 200 mg of AM-715 without (○) and with (●) probenecid in human volunteers.

1 Page(s)

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Table 9-1

Table 1 Serum concentration of AM-715 after oral administration of 1,600mg of AM-715 to healthy human subjects ($\mu\text{g/ml}$)

Name	Time after administration (hr.)							
	0.5	1	2	3	4	6	8	12
SU								
S-								
A								
IT								
Mean	2.5	6	10.8	8	7.3	5	4	2.5
SD	2.6	3	2.6	2.9	1.7	1.7	0.8	0.5

Table 9-2

Table 2 Urinary concentration of AM-715 and its metabolites after oral administration of 200mg of AM-715 to healthy human subjects ($\mu\text{g/ml}$)

Name	Time (hr.)	AM-715	M-1	M-2	M-3	M-4	M-5
OZ							
SU							
UC							

Table 9-3

Table 3 Urinary concentration of AM-715 and its metabolites after oral administration of 1,600mg of AM-715 to healthy human subjects ($\mu\text{g/ml}$)

Name	Time (hr.)	AM-715	M-1	M-2	M-3	M-4	M-5
SU							
SA							
AO							
IT							

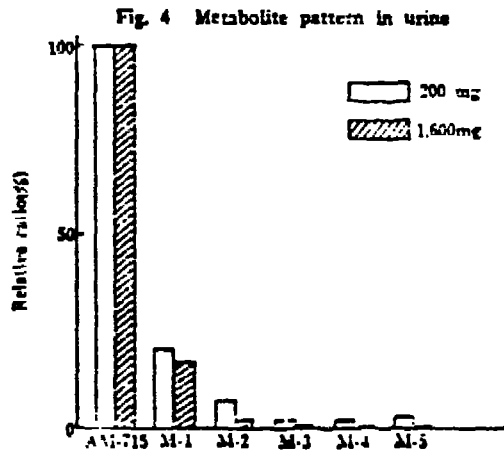
Table 9-4

Table 4 Primary excretion of AM-715 and its metabolites after oral administration of 200mg of AM-715 to healthy human subjects (mg)

Group	Time (hr)	AM-715	M-1	M-2	M-3	M-4	M-5	Total	% of dose
UC	0-2.5								
	2.5-5								
	5-9								
	9-24								
Total									
Reduced to AM-									
% of dose									
SU	0-2.5								
	2.5-5								
	5-9								
	9-24								
Total									
Reduced to AM-									
% of dose									
UC	0-2.5								
	2.5-5								
	5-9								
	9-24								
Total									
Reduced to AM-									
% of dose									

$\bar{X} = 26.6$ 5.1 1.5 0.33 ≤ 0.5 0.7 34.7
 S.D. 9.05 0.78 0.36 0.15 0.1 9.4
 range

Figure 9-3



This figure shows the mean ratio of urinary excretion of each metabolite during 24 hours when the ratio of excretion (% of dose) of unchanged form was taken as 100.

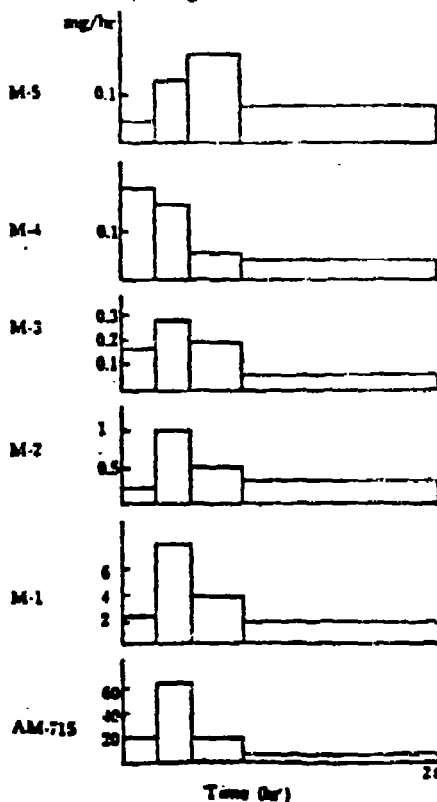
Table 9-5

Table 3 Urinary excretion of AM-715 and its metabolites after oral administration of 1,600mg of AM-715 to healthy human subjects (mg)

Phase	Time (hr)	AM-715	M-1	M-2	M-3	M-4	M-5	Total	% of dose
III	0-2.5								
	2.5-4								
	5-9								
	9-24								
	Total								
XI	0-2.5								
	2.5-5								
	5-9								
	9-24								
	Total								
AO	0-2.5								
	2.5-5								
	5-9								
	9-24								
	Total								
- II	0-2.5								
	2.5-5								
	5-9								
	9-24								
	Total								

$\bar{X}$ = 23.0 3.6 0.57 0.15 0.05 0.045 27.5
 S.D. 8.0 0.7 0.25 0.06 0.04 0.06 8.8

Fig. 5 Urinary excretion rate of AM-715 and its metabolites after oral administration of 1,600mg of AM-715



0.145
0.067

Figure 12-1

Figure: Urinary excretion of AM-715 in healthy male adults (200mg/person, p.o. single administration)

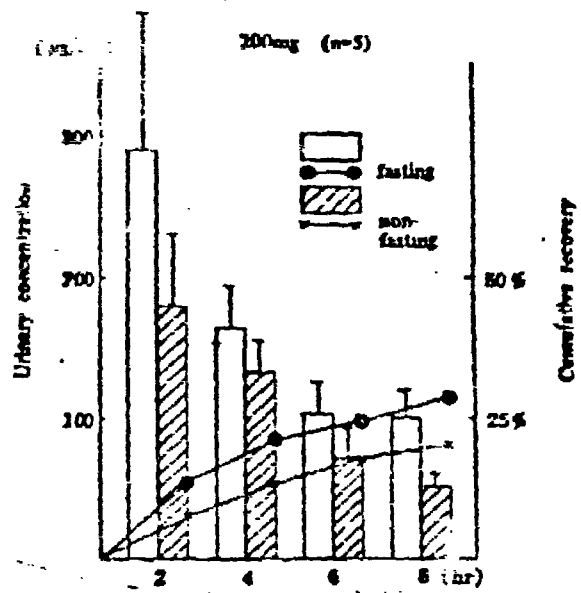


Table 12-1

Group	Volunteer	Urinary excretion				Recovery
		0-2h	2-4h	4-6h	6-8h	
fasting	O.U. 35y.M.	(µg/ml)				µg
		mg				µg
	T.O. 31y.M.	µg/ml				µg
		mg				µg
	Y.K. 28y.M.	µg/ml				µg
		mg				µg
non-fasting	H.N. 26y.M.	µg/ml				µg
		mg				µg
	H.K. 26y.M.	µg/ml				µg
		mg				µg
	O.U. 35y.M.	µg/ml				µg
		mg				µg
non-fasting	T.O. 31y.M.	µg/ml				µg
		mg				µg
	Y.A. 28y.M.	µg/ml				µg
		mg				µg
	H.N. 26y.M.	µg/ml				µg
		mg				µg
non-fasting	A.K. 26y.M.	µg/ml				µg
		mg				µg

$\bar{x}$ 181.6 134.8 72 53.2
 S.D. 109.5 53.8 44.2 24.1

$\bar{x}$ 28.3
 S.D. = 8.19
 CV = 28.9

$\bar{x}$ 19.9
 S.D. = 3.2
 CV = 16.1%

Table 10-2

Table 1 Plasma levels of AM-715 in healthy male adults
(fasting: person, p.o. single administration)

Group	Volume	Serum concentration (µg/ml)					
		1/2	1	2	4	6	8 (hr)
Fasting	G.U. 35y, M 57kg						
	T.O. 31y, M 69kg						
	Y.K. 28y, M 65kg						
	H.N. 26y, M 61kg						
	A.K. 26y, M 64kg						
Fom fasting	G.U. 35y, M 57kg						
	T.O. 31y, M 69kg						
	Y.K. 28y, M 65kg						
	H.N. 26y, M 61kg						
	A.K. 26y, M 64kg						

Table 15-1

Serum Concentration of MK-366 (mcg/ml)
After a Single 200 mg Oral Dose

Subject No.	Time After Dose (Hr.)									
	0	0.5	1	1.5	2	3	4	6	8	12
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
n =	13	14	14	12	14	13	14	14	13	13
mean	0.00	0.42	0.75	0.61	0.52	0.38	0.32	0.22	0.15	0.10

* Insufficient sample for analysis.

Table 15-2

Serum Concentration of MK-366 (mcg/ml)
After a Single 400 mg Oral Dose

Subject No.	Time After Dose (Hr.)									
	0	0.5	1	1.5	2	3	4	6	8	12
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
n =	14	14	14	14	14	13	13	14	14	14
mean	0.00	0.44	1.39	1.32	1.07	0.78	0.55	0.42	0.29	0.20

* Insufficient sample for analysis.

Table 15-3

Serum Concentration of MK-366 (mcg/ml)
After a Single 800 mg Oral Dose

Subject	Time After Dose (Hr.)									
	0	0.5	1	1.5	2	3	4	6	8	11
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
n =	14	14	14	13	13	14	14	14	14	14
mean	0.00	1.13	2.12	2.06	2.03	1.50	1.16	0.76	0.61	0.40

* Insufficient sample for analysis.

Table 15-4

Serum Concentration of MK-366 (mcg/ml)
After a Single 1200 mg Oral Dose

Subject No.	Time After Dose (Hr.)									
	0	0.5	1	1.5	2	3	4	6	8	11
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
n =	14	14	13	13	12	13	14	14	14	14
mean	0.00	1.33	2.76	2.70	3.05	2.36	1.90	1.28	1.00	0.52

* Insufficient sample for analysis.

Table 15-5

Mean Concentration of MK-366 (mcg/ml)
After a Single 1600 mg Oral Dose

Subject	Time After Dose (Hr.)									
1	2	3	4	6	8	12	14	16	18	20
1	2	3	4	6	8	12	14	16	18	20
n =	14	14	13	14	14	14	14	14	14	14
mean	0.90	1.44	2.68	3.22	3.65	2.87	2.13	1.55	1.19	0.76

* Insufficient sample for analysis.

Figure 15-1

Figure 1
MK-366 Study #1
Mean Serum Concentration

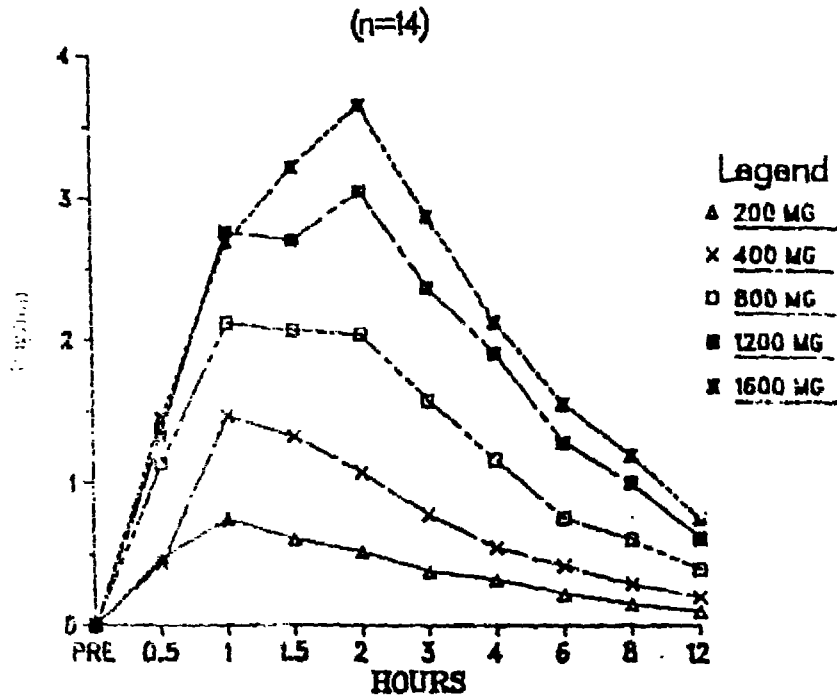


Table 15-6

Individual Peak Serum Levels of MK-366 and Time to Peak Following Single Oral Doses of Drug

Subject No.	Dose (mg) MK-366									
	200		400		800		1200		1600	
	C _{max} (ug/ml)	t _{max} (hr)	C _{max} (ug/ml)	t _{max} (hr)	C _{max} (ug/ml)	t _{max} (hr)	C _{max} (ug/ml)	t _{max} (hr)	C _{max} (ug/ml)	t _{max} (hr)
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11 ¹										
12										
13 ²										
14										
Mean	0.79	1.1	1.55	1.1	2.18	1.4	1.64	1.7	3.67	1.8

- 1 Inefficient sample for analysis at 1.3 hr.
- 2 Inefficient sample for analysis at 2 hr.
- 3 Inefficient sample at 1, 1.5, 2, and 3 hr.
- 4 Inefficient sample at 1 hr.
- 5 Excluded from mean.

400 mg

C_{max} $\bar{x}$ 1.57
(n=14) S.D. 0.45

T_{max} $\bar{x}$ 1.1
(n=14) S.D. 0.35

Table 15-7

Effective Serum Half-Life ($t_{1/2}$) of MK-366
Following Single Oral Doses of Drug
(For a dosing interval of 8 hours)

Subject No.	$t_{1/2}$ (hr) Following...Dose MK-366				
	200 mg	400 mg	800 mg	1200 mg	1600 mg
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
Mean	2.18	2.19	2.29	2.39	2.48

- 1 Incomplete urinary recovery.
- 2 Insufficient serum data.

Individual 8-Hour Area Under the Curve, $[AUC]_0^8$,
for MK-366 Following Single Oral Doses of the Drug

Table 15-8

Subject No.	$[AUC]_0^8$ (mcg·hr/ml) Following...Dose of MK-366				
	200 mg	400 mg	800 mg	1200 mg	1600 mg
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
Mean	2.77 (±0.59)	5.19 (±1.31)	9.57 (±1.91)	14.34 (±3.51)	16.71 (±5.17)

¹ Insufficient serum sample for analysis at 1, 1.5, 2, 3, 4, and/or 8 hr. Serum concentration estimated.

² Insufficient serum data.

Table 15-2

Individual Estimates of Total Area Under the Curve,
 $[AUC]_{\infty}$, for MK-366 Following Single Oral Doses of the Drug

Subject No.	$[AUC]_{\infty}$ (mcg·hr/ml) Following...Dose MK-366				
	200 mg	400 mg	800 mg	1200 mg	1600 mg
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
Mean	3.36 (±0.78)	6.20 (±1.78)	12.19 (±2.63)	19.09 (±5.42)	24.06 (±8.03)

¹ Incomplete urinary recovery.

² Insufficient serum data.

Table 15-10

Urinary Excretion of MK-366 (mg)
After a Single 200 mg Dose, p.o.

Subject	Collection Intervals (hr)										
	0-1	1-2	2-3	3-4	4-6	6-8	8-12	Total 0-12	12-24	24-48	Total 0-48
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
13											
14											
Mean	8.56	14.8	7.83	6.80	7.62	5.38	3.97	53.6	5.93	1.90	61.9
S.D.	4.30	3.05	3.43	2.64	2.18	3.60	1.87	10.3	2.21	0.96	12.6

† - probable incomplete collection
* - repeatable assay value

Table 15-11

Urinary Excretion of MK-366 (mg)
After a Single 400 mg Dose, p.o.

Subject	Collection Intervals (hr)								Total 0-12	12-24	24-48	Total 0-48
	0-1	1-2	2-3	3-4	4-6	6-8	8-12					
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
13												
14												
Mean	11.9	31.6	14.5	13.0	14.6	11.6	8.21	104.5	10.4	4.94	119	
S.D.	6.86	7.18	7.07	7.46	5.03	3.79	3.39	21.7	2.44	3.16	27.2	

* - probable incomplete collection
 * - repeatable assay value

Table 15-12

Urinary Excretion of MK-366 (mg)
After a Single 800 mg Dose, p.o.

Subject	Collection Intervals (hr)										
	0-1	1-2	2-3	3-4	4-6	6-8	8-12	Total 0-12	12-24	24-48	Total 0-48
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
13											
14											
Mean	16.9	46.8	28.0	29.1	30.1	18.4	16.8	186	43.5	10.1	219
S.D.	10.5	9.28	13.1	14.6	12.2	5.55	5.96	40.6	9.25	5.0	50.4

† - probable incomplete collection
* - repeatable assay value

Table 15-13

Urinary Excretion of MK-366 (mg)
After a Single 1200 mg Dose, p.o.

Subject #	Collection Intervals (hr)							Total 0-12	12-24	24-48	Total 0-48
	0-1	1-2	2-3	3-4	4-6	6-8	8-12				
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
13											
14											
Mean	22.3	60.6	45.0	37.6	44.8	34.5	30.5	273	41.9	14.6	337
S.D.	13.7	14.5	17.4	15.0	24.2	14.2	9.44	64.8	17.5	7.24	77.3

* - incomplete collection
 * - repeatable assay value

tbl 15-14

Primary Excretion of MK-466 (mg)
After a Single 1600 mg Dose, p.o.

Subject	Collection Intervals (hr)										
	0-1	1-2	2-3	3-4	4-6	6-8	8-12	Total 0-12	12-24	24-48	Total 0-48
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
13											
14											
Mean	24.9	65.6	70.1	49.9	61.8	40.2	46.6	353	56.5	18.9	448
S.D.	16.2	25.4	25.3	25.0	35.8	14.9	20.6	115	22.0	11.8	139

† - probable incomplete collection
 * - sample lost
 † - reportable assay value

Table 15-15

Concentration of MK-366 (µg/ml) in Urine
After a Single 200 mg Dose, p.o.

Subject	Pre-dose	Collection Intervals (hr)								
		0-1	1-2	2-3	3-4	4-6	6-8	8-12	12-24	24-48
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
Mean		133	124	88.5	75.9	48.1	44.0	19.7	10.3	2.35
S.D.		139	67.0	92.9	68.5	24.5	27.2	12.0	3.70	1.7P

† - probable incomplete collection
* - reproducible assay value

Table 15-16

Concentration of MK-366 (µg/ml) in Urine
After a Single 400 mg Dose, p.o.

Subject	Pre-dose	Collection Interval (hr)								
		0-1	1-2	2-4	4-6	6-8	8-12	12-24	24-48	
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
Mean		168	417	299	211	141	100	46.9	22.5	5.93
S.D.		129	589	369	168	98.3	81.0	37.4	12.5	3.07

1 - probable incomplete collection

2 - probable assay mix up with placebo for subject #13, 1-2 hr. Actual assay value was zero

3 - repeatable assay value

Table 15-17

Concentration of MK-366 ($\mu\text{g/ml}$) in Urine
After a Single 800 mg Dose, p.o.

Subject	Pre-dose	Collection Intervals (hr)								
		0-1	1-2	2-3	3-4	4-6	6-8	8-12	12-24	24-48
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
Mean		280	582	365	358	243	184	84.4	45.9	22.3
S.D.		257	470	260	206	138	97.7	53.1	21.0	16.3

* - probable incomplete collection
* - repeatable assay value

Table 15-18

Concentration of MK 366 ($\mu\text{g}/\text{ml}$) in Urine
After a Single 1200 mg Dose, p.o.

Subject	Collection Intervals (h)									
	Pre-Dose	0-1	1-2	2-3	3-4	4-6	6-8	8-12	12-24	24-48
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
Mean	0.53	359	897	657	550	424	272	143	73.5	25.7
S.D.	1.47	444	750	411	350	299	162	98.9	54.5	6.93

† - incomplete collection
* - repeatable assay value

Table 15-19

Concentration of MK-366 (µg/ml) in Urine
After a Single 1600 mg Dose, p.o.

Subject	Pre-Dose	Collection Intervals (hr)								
		0-1	1-2	2-3	3-4	4-6	6-8	8-12	12-24	24-48
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
Mean	0.37	750	881	625	421	518	405	188	101	19.1
S.D.	1.33	217	720	150	335	491	404	128	60.0	8.75

- - no sample
 * - probably incomplete collection
 • - repeatable assay value

Table 15-20

Individual Urinary Primary Recovery of MK-366 Following Single Oral Doses of Drug

Subject No.	200 mg	300 mg	400 mg	500 mg	600 mg	Mean
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
Mean	31.2 (±6.4)	31.5 (±7.2)	28.7 (±6.4)	29.0 (±7.3)	29.2 (±9.1)	

- 1 Low urine volume 12-24 hr or 24-48 hr. Included in mean.
 - 2 No void 4-6 hrs. Renal clearance indicates incomplete recovery. Excluded from mean.
 - 3 Questionable urinary collection 12-24 hr. Excluded from mean.
 - 4 No void 2-4 hrs. Renal clearance indicates incomplete urinary recovery. Excluded from mean.
 - 5 Urine sample lost 12-24 hr. Excluded from mean.
- * See Table 17 for average capsule dose of MK-366.

Table 15-21

Individual Cumulative Renal Clearance Following Single Oral Doses of MK-366

Subject No.	200 mg	300 mg	400 mg	500 mg	600 mg	Mean
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
Mean	50.0 (±55.0)	59.6 (±50.0)	305.8 (±92.3)	291.5 (±50.0)	508.5 (±111.1)	

* Insufficient serum data for analysis.

PK-356 TREATMENTS

PARAMETER (UNIT)	RESULT	A 200 MG			B 400 MG			C 600 MG			D 1200 MG			E 3000 MG		
		N	MEAN	STD	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD
48-HOUR URINARY RECOVERY (%)	MS	14	32.4	6.2	14	31.3	6.7	14	28.7	6.4	14	29.0	7.3	14	18.0	9.7
CUMULATIVE RENAL CLEARANCE (ml/min)	MS	14	113.4	19.7	14	119.6	50.0	14	305.6	92.3	13	290.8	50.1	14	308.5	39.2
0-8 HR AREA UNDER CURVE (dose adjusted)	MS	14	2.0	0.3	14	0.2	1.3	14	9.4	1.0	13	14.3	3.5	14	6.7	4.2
TOTAL AUC (dose adjusted)	MS/PP	13	3.4	0.8	12	6.2	1.8	14	12.2	2.6	13	19.1	5.4	13	24.1	9.0
MEAN RESIDUE (hr)	MS	14	0.6	0.2	14	1.6	0.5	14	2.4	0.5	14	3.3	1.0	14	3.0	1.2
TIME TO PEAK (hr)	M	14	1.1	0.4	14	1.1	0.3	14	1.4	0.4	14	2.0	1.0	14	1.9	0.5
SERUM HALF-LIFE (hr)	M	13	2.2	0.2	12	2.2	0.2	14	2.3	0.2	13	2.4	0.2	13	2.9	0.2

MS NO SIGNIFICANT LINEAR TREND AND NO SIGNIFICANT DIFFERENCE BETWEEN TREATMENTS.
 * RESPONSE WAS HIGHER FOR THE HIGHER 2 DOSES THAN FOR THE LOWER 3 DOSES (P<0.01).
 † A LINEAR TREND WAS PRESENT BETWEEN RESPONSE AND DOSE LEVEL (P<0.01).
 PP A PROPORTIONAL DOSE-RESPONSE RELATIONSHIP WAS OBSERVED.

Mean and SD of Experimental Data Parameters

Table 15-22

	POSTERIOR PROBABILITY P(TRUE DIFFERENCE <20%)	POWER OF DETECTING 20% DIFFERENCE AT α=0.05
48-HOUR URINARY RECOVERY	0.937	0.967
CUMULATIVE RENAL CLEARANCE	0.999	> 0.999
0-8 HR AREA UNDER CURVE (dose adjusted)	0.852	0.956
TOTAL AREA UNDER CURVE (dose adjusted)	0.961	0.935

Figure 15-2

MK-366 Study #1
Mean Cumulative Urine Excretion

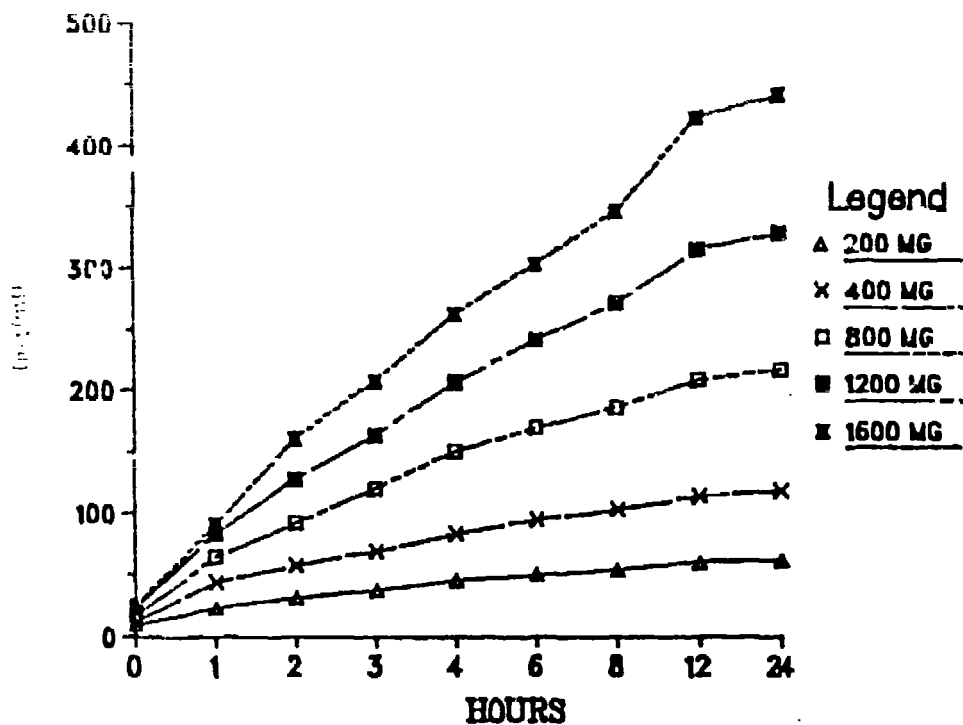


Figure 16-1

Mean Norfloxacin Plasma Concentration Profiles

[REDACTED]
 listing presenting the demographic data of the 27
 at entry into this study.

VOLUNTEER DEMOGRAPHIC DATA

SEX	Age (yrs.)	Height (in.)	Weight (lbs.)	RACE
M	41	71	157	Caucasian
M	29	69	160	Caucasian
M	27	71	155	Caucasian
M	21	71	202	Caucasian
M	39	70	170	Caucasian
M	24	72	179	Caucasian
M	31	65	148	Caucasian
M	23	70	150	Caucasian
M	21	69	166	Caucasian
M	44	70	155	Caucasian
M	20	76	180	Caucasian
M	21	71	155	Caucasian
M	45	77	159	Black
M	36	72	163	Caucasian
M	20	76	190	Caucasian
M	34	68	146	Caucasian
M	24	74	170	Caucasian
M	19	71	157	Caucasian
M	31	72	204	Caucasian
M	24	71	162	Caucasian
F	57	61	124	Caucasian
M	24	70	171	Caucasian
F	34	68	164	Caucasian
F	50	67	164	Black
M	27	68	143	Caucasian
M	19	66	148	Caucasian
M	31	69	155	Caucasian

Age - 19 - 50 years
 Height - 6' - 76 inches
 Weight - 124 - 204 pounds

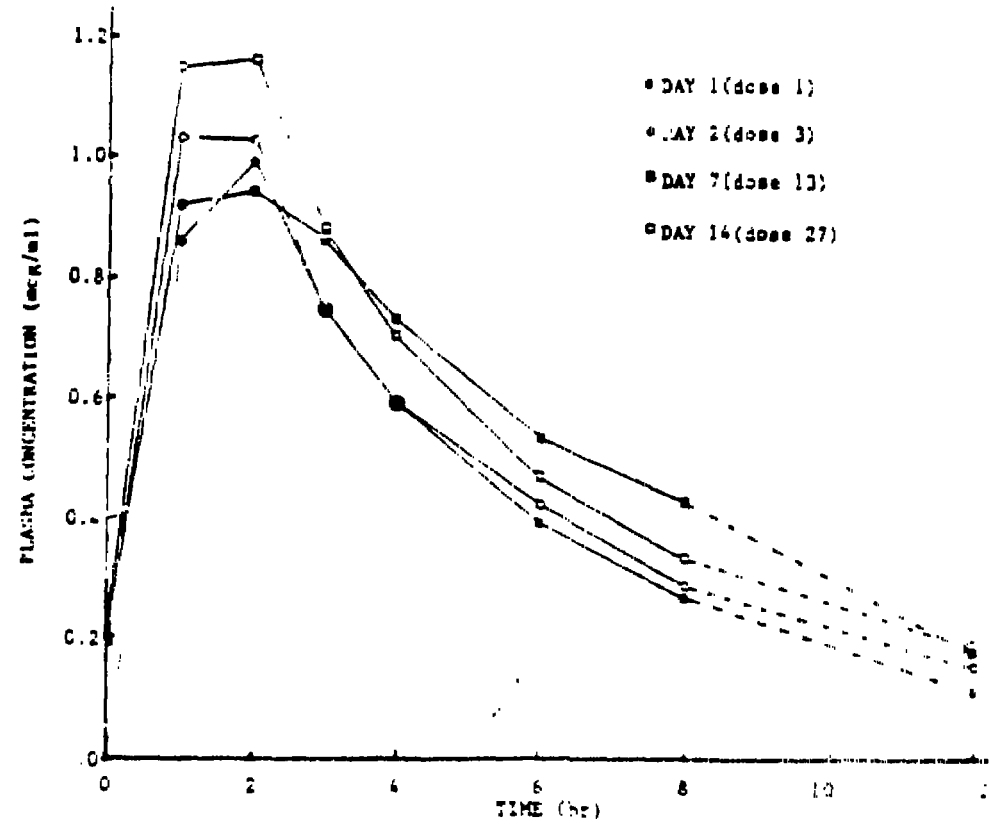


Table 16 - 1

Below is a table representing the demographics of winners at every race this year.

WINNERS AT EVERY RACE THIS YEAR

Year	Age	Sex	Weight	Height
1	41	M	157	157
2	24	M	150	150
3	21	M	155	155
4	31	M	202	202
5	39	M	170	170
6	24	M	179	179
7	31	M	148	148
8	23	M	150	150
9	21	M	166	166
10	44	M	155	155
11	20	M	180	180
12	21	M	155	155
13	45	M	159	159
14	36	M	163	163
15	30	M	190	190
16	34	M	146	146
17	24	M	170	170
18	19	M	150	150
19	31	M	204	204
20	24	M	182	182
21	31	F	124	124
22	24	M	171	171
23	34	F	164	164
24	50	F	164	164
25	21	M	143	143
26	19	M	149	149
27	31	M	155	155

Ranges: Age - 19 - 50 years
 Height - 61-76 inches
 Weight - 124-204 pounds

Table 16-2

Individual 12-Hour Urinary Excretion (U₀₋₁₂) of Norfloxacin Following Twice Daily Administration

$$\% \text{ of Dose} = \frac{X}{400} = (\quad)$$

U₀₋₁₂ (mg) Following 1st Dose on Day . . .

Subject No.	1 (Day 1)	2	3	4
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				

Table 16-3

Individual Cumulative 12-Hour Urinary Excretion (U₀₋₁₂) of Norfloxacin Following Twice Daily Administration

Subject No.	1	2	3	4
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				

	Day 1	Day 2	Day 14
Estimated from cumulative urinary excretion profile:			(n=25)
using all data	$\bar{X} = 16.5$	$\bar{X} = 17.75$	$\bar{X} = 18.9$
(n=26)	S.D. = 6.7	S.D. = 6.5	S.D. = 8.2
	C.V. = 40.6%	C.V. = 34.9%	C.V. = 43.4%
* Range:	1.0 - 27.75	6.2 - 21.0	7.1 - 40.9

2 Pages

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Table 16-5

Individual Peak Plasma Concentrations (Peak) of Norfloxacin Following Twice Daily Administration

Peak (mcg/ml) Following 1st Dose on Day . . .

Subject No.	1	2
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
17		
18		
19		
20		
21		
22		
23		
24		
25		
26		
27		
Mean (S.D.)	2.13 (0.41)	1.27 (0.35)
		1.35 (0.39)

- 1 No blood samples taken as per protocol.
- 2 Unusually low plasma concentrations.
- 3 Dose not administered.

Table 16-6

Individual Times (Days) that Peak Plasma Concentrations of Norfloxacin Occurred Following Twice Daily Administration

Days (hr) Following 1st Dose on Day . . .

Subject No.	1	2
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
17		
18		
19		
20		
21		
22		
23		
24		
25		
26		
27		
Mean (S.D.)	2.5 (0.6)	2.2 (2.1)

- 1 Blood samples not taken.
- 2 Unusually low plasma concentrations.
- 3 Dose not administered.

Table 16-7

continued

Included - various plasma concentrations (µg/ml) of Acetylsalicylic Acid in the Administration

Subject: Male (44 M), following dose no. 1

Subject	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25

Time (hr)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24

Plasma concentration (µg/ml)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24

1. No blood sample taken as per protocol.
 2. Dose not administered.
 3. Relatively low plasma concentrations.

1. (AC) - Administration during the study.
 2. Drug not administered as per protocol.
 3. Relatively low plasma concentrations.
 4. Dose not administered.

Table 6-21

NUMBER OF VOLUNTEERS WHO WITHDREW PARTICIPATION
OTHER THAN STUDY DRUG

Study No.	Assigned Group	Period No.	Medication	Reason for Withdrawal
1	Non-steroid	1	Analgesic	Headache
	Placebo	2	Haloperidol	Headache
2	Placebo	2	Ducolax	Constipation
	Placebo	2	Ibuprofen	Headache
3	Placebo	2	Polysporin Ointment	Swelling on left leg and toes
	Non-fluoxacin	1	Nylanta	Headache
4	Placebo	1	Penicillin VK	Strep throat
19	Fluoxacin & Non-fluoxacin	1 & 2	Cortisporin	Roll in external right ear
	Placebo	1	Ibuprofen	Headache
20	Non-Study	*	Tetracycline	Reaction lymph nodes
24	Placebo	2	Ibuprofen	Sore throat & chills

* Seven days after terminating Period 1 and being dropped from study.

2 Pages

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Table 17-1

Individual Plasma Concentrations (C_p) of Norfloxacin Following Administration of 400 mg Every 8 Hours for 5 Days

Subj. No. (Period)	Day	C_p (mcg/ml) at . . . hr							
		0	1	2	3	4	5	6	8
101 (1)	1								
	2								
	5								
102 (2)	11								
	14								
	17								
103 (1)	1								
	2								
	5								
126 (1)	1								
	2								
	5								
Mean		1	0	1.74	1.37	0.994	.746	.535	.364
		2	.627	1.28	1.46	1.29	1.02	.707	.518
		5	.771	1.32	1.41	1.01	.874	.626	.436

Table 17-2

Individual Maximum Plasma Concentrations (C_{max}) and Times Those Peaks Occurred (t_{max}) for Norfloxacin Following Administration of 400 mg Every 8 Hours for 5 Days

Subject No.	Day 1 (Dose 1)		Day 2 (Dose 4)		Day 5 (Dose 13)	
	C_{max} (mcg/ml)	t_{max} (hr)	C_{max} (mcg/ml)	t_{max} (hr)	C_{max} (mcg/ml)	t_{max} (hr)
101						
102						
103						
126						
Mean (S.D.)	1.50 (0.40)	1.3 (0.5)	1.73 (0.33)	1.8 (1.0)	1.49 (0.38)	1.5 (0.6)

Table 17-3

Individual 8-Hour Area Under the Plasma Concentration-Time Curve, $[AUC]_0^8$, for Norfloxacin Following Administration of 400 mg Every 8 Hours for 5 Days

Subject No.	$[AUC]_0^8$ (mcg·hr/ml) Following First Dose on Day . . .		
	1	2	5
101			
102			
103			
126			
Mean (S.D.)	6.34 (0.88)	7.79 (2.36)	7.04 (1.97)

Mean Plasma Concentrations of Norfloxacin

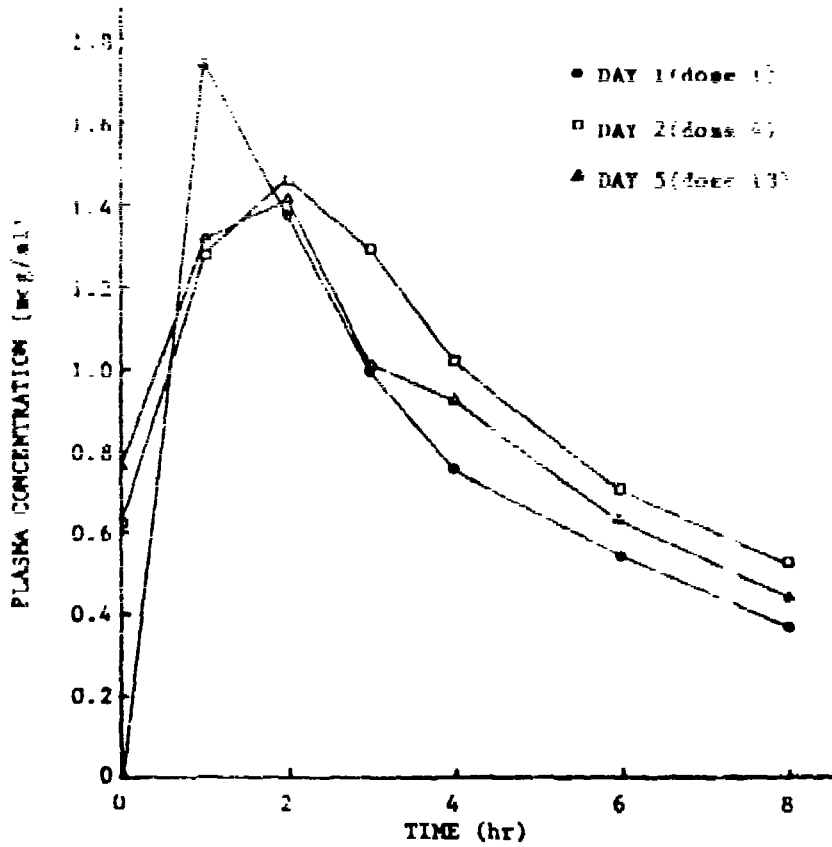


Table 17-4

Individual Minimum Plasma Concentrations (C_{min}) of Norfloxacin Following Administration of 400 mg Every 8 Hours for 5 Days

Subject No.	C_{min} (mcg/ml) Following Dose No. . . .					
	0	1	3	4	12	13
101						
107						
103						
125						
Mean (S.E.)	0	.36 (.06)	.62 (.21)	.52 (.29)	.77 (.78)	.44 (.15)

1

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Table 18-1

Individual Estimates of Total Area Under the Curve, [AUC]₀[∞], for MK-366 Following Single Oral Doses of Drug

Subject No.	[AUC] ₀ [∞] , ug-hr/ml		
	200-mg Tab	400-mg Tab	400-mg Soln
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
Mean (SD)	2.66 (±1.17)	5.02 (±2.45)	6.04 (±1.90)

Table 18-2

Individual Estimates of Total Area Under the Curve, [AUC]₀[∞], for MK-366 Following Single Oral Doses of the Drug

Subject No.	[AUC] ₀ [∞] , ug-hr/ml			400 mg Soln (dosed as if 200 mg)
	200-mg Tab Sub 200	400-mg Tab Sub 400	400-mg Soln	
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
Mean (SD)	5.52 (±1.54)	6.56 (±1.28)	7.58 (±2.08)	7.05 (S.D. = 1.77)
	7/12 within 15 12.5%	3/12 = 25%	5/13 = 38.5%	

Tab 400 mg (dosed as if 200 mg)
Tab 200

1 Incomplete urinary recovery. ✓

With $\bar{x} = .998$ (S.D. = 0.42) [CV = 42.1%]
 With $\bar{x} = .987$ (S.D. = 0.49) [CV = 49.6%]

$x = 1$
 S.D. = 0.33
 7/12 58.3%

Table 18-3

Effective Serum Half-Life ($t_{1/2}$) of Norfloxacin Following Single Oral Doses of Drug

Subject No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Mean ($\pm$ SD)	0.76 (0.32)	1.36 (0.58)	1.87 (0.66)	$\bar{x} = 1.74$			SD = 0.61								
CV	42.1%	38.7%	35.3%	35%											
% in 75-125%	9/15	5/15	6/15												

Table 18-4

Effective Serum Half-Life ($t_{1/2}$) of Norfloxacin Following Single Oral Doses of Drug (For 8 hr dosing interval)

Subject No.	$t_{1/2}$, n (hr)		
	Treatment A	Treatment B	Treatment C
1	1	..	..
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
Arithmetic Mean	3.3	3.2	3.0

1 No estimate of $[AUC]_0$ because of incomplete urinary recovery of drug

Tab 400 (a) 1. 2. 3. 4. 5. 6. 7. 8. 9. 10. 11. 12. 13. 14. 15. 16. 17. 18. 19. 20. 21. 22. 23. 24. 25. 26. 27. 28. 29. 30. 31. 32. 33. 34. 35. 36. 37. 38. 39. 40. 41. 42. 43. 44. 45. 46. 47. 48. 49. 50. 51. 52. 53. 54. 55. 56. 57. 58. 59. 60. 61. 62. 63. 64. 65. 66. 67. 68. 69. 70. 71. 72. 73. 74. 75. 76. 77. 78. 79. 80. 81. 82. 83. 84. 85. 86. 87. 88. 89. 90. 91. 92. 93. 94. 95. 96. 97. 98. 99. 100.

Table 18-5

Estimated 24-Hour Urinary Recovery (U_{0-24}) of NR-366 Following Single Oral Doses of Drug

Subject	200-mg Tab.		400-mg Tab.		400-mg Soln	
	U_{0-24} (mg)	% Dose ⁴	U_{0-24} (mg)	% Dose ⁴	U_{0-24} (mg)	% Dose ⁴
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
Mean (SD)		25.5 (±9.1)		26.5 (±9.1)		25.4 (±6.7)

- 1 Renal clearance estimates indicate incomplete urinary recovery of drug 1-2 hr and -6 hr. Excluded from: n.
- 2 Renal clearance estimates indicate incomplete urinary recovery of drug 2-1 hr. Excluded from mean.
- 3 Renal clearance estimates indicate incomplete urinary recovery of drug 1-2 hr. Excluded from mean.
- 4 For dose estimates see Table 13.

Table 18-6

MEANS OF BIOAVAILABILITY PARAMETERS NORFLIXACIN STUDY 015-- DR. ZIMM

RELATIVE BIOAVAILABILITY	200 MG TAB/STANDARD	400 MG TAB/STANDARD	200 MG TAB/400 MG TAB
N	12	13	12
MEAN (SD)	0.89 (0.89)	0.90 (0.90)	1.00 (1.00)
95% C.I.	0.70-1.16	0.72-1.23	0.79-1.26
POWER (95% DIFFERENCE)	0.77	0.70 (0.78)	0.80 (0.80)
POSTERIOR PROB. (10%)	0.43	0.47	0.45
(15%)	0.65	0.70	0.64
(20%)	0.82	0.84	0.94
(75%)	0.93	0.95	0.98
(90%)	0.97	0.98	0.99

(S) - GEOMETRIC MEANS TABULATED.

None of the above ratios is significantly different from unity.

APPL # : 919384

GENERIC
TRADE
NAME

FIRM
NAME

NOROX
NORFLOXACIN TABLETS

2 OF 2

Table 18-7

Individual Estimates of Norfloxacin Relative Bioavailability from 200-mg and 400-mg Market Image Tablets as Compared to Solution Administration of the Drug

Based on the method of Kwan and Till (as modified by Hwang and Kinson)

Subject No.	Tab 200 / Soln 400 F_A/F_C	Tab 400 / Soln 400 F_B/F_C	Tab 200 / Tab 400 F_A/F_B
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
Geometric Mean	0.89	0.90	1.00

Subscripts A, B and C refer respectively to the 200-mg tablet, the 400-mg tablet, and the 400-mg solution treatments.

- 1 Incomplete urinary recovery Treatment A.
- 2 Incomplete urinary recovery Treatment C.
- 3 Based on the ratio of 1-dose urinary recovery.
- 4 Incomplete urinary recovery Treatment B.

Table 18-8

Individual Cumulative Renal Clearance ($\bar{v}_{Cl,R}$) of MK-366 Following Single Oral Doses of the Drug

Subject No.	$\bar{v}_{Cl,R}$ (ml/min)		
	200-mg Tab	400-mg Tab	400-mg Soln
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
Mean (SD)	263.4 (±76.1)	299.3 (±93.0)	276.4 (±71.3)

Table 18-9

MEANS OF BIOAVAILABILITY PARAMETERS
 NEWFLOXACIN STUDY 813-- DR. XINQY

	UNITS	430 MG SOL ⁿ (STANDARD)	200 MG TABLET	400 MG TABLET
40-MIN URINARY EXCRETION				
TOTAL				
	N	14	13	14
	MEAN	121.91	82.15 ^{0.05, 0.01}	108.74
	S.D.	28.96	18.63	24.22
X-DOSE				
	N	14	13	14
	MEAN	28.20	25.45	26.45
	S.D.	6.76	9.00	9.11
0-HR AUC				
MCB-MG/ML (A)				
	N	15	15	15
	MEAN	6.84	5.57	5.44
	S.D.	1.90	2.36	2.65
ESTIMATED TOTAL AUC				
MCB-MG/ML (A)				
	N	14	13	14
	MEAN	7.50	6.06	7.70
	S.D.	2.00	3.23	3.56

(A) -- DOSE ADJUSTED UP TO 430 MG.

0.05 SIGNIFICANTLY LOWER THAN STANDARD 430 MG SOL., P<0.05, 0.01 RESPECTIVELY.
 0.01 SIGNIFICANTLY LOWER THAN 400 MG TABLET, P<0.05, 0.01 RESPECTIVELY.

	UNITS	430 MG SOL ⁿ (STANDARD)	200 MG TABLET	400 MG TABLET
CLIN. RENAL CLEARANCE				
	N	15	15	15
	MEAN	276.27	263.79	279.86
	S.D.	71.31	76.13	94.06
PEAK SERUM CONC--C_{MAX}				
MCB/ML (A)				
	N	15	15	15
	MEAN	1.87	1.60	1.62
	S.D.	0.66	0.64	0.62
TIME TO PEAK SERUM CONC--T_{MAX} HR				
	N	15	15	15
	MEAN	0.70	1.03 ⁰	1.03 ⁰
	S.D.	0.37	0.35	0.35
HALF-LIFE				
	N	14	13	14
	MEAN (M)	2.99	3.26	3.22
	95% C.I.	2.63-3.47	2.82-3.81	2.92-3.99

(A) - DOSE ADJUSTED UP TO 430 MG.

(M) - HARBROOK MEAN TABULATED.

0.05 - SIGNIFICANTLY DIFFERENT FROM STANDARD 430 MG SOL., P<0.05, 0.01, RESPECTIVELY.
 NO SIGNIFICANT DIFFERENCES WERE FOUND BETWEEN THE TWO TABLETS.

Table 19-1

INDIVIDUAL 24-HOUR URINARY RECOVERY (U_{0-24})
 TOTAL URINARY RECOVERY (U_{∞}), AND RENAL CLEARANCE
 ($\dot{V}Cl_{1,R}$) OF NORFLOXACIN IN HEALTHY ELDERLY VOLUNTEERS

SUBJECT NUMBER	URINARY RECOVERY			$\dot{V}Cl_{1,R}$ (ML/MIN)
	U_{0-24} (MG)	U_{∞} (MG)	% OF DOSE ¹	
1				
2				
3				
4				
5				
6				
Mean			22.3	154.0
(S.D.)			(6.9)	(15.7)

- 1 Assay content was 405 mg of norfloxacin per tablet
 2 Questionable urinary recovery three to twelve hours; U_{0-24} estimated from renal clearance (zero to three hours) and AUC_{0-12} plus U_{12-24}

Table 19-2

INDIVIDUAL PHARMACOKINETIC PARAMETERS FOR NORFLOXACIN
 IN PLASMA OF HEALTHY, ELDERLY VOLUNTEERS*

(98° dosing interval)

SUBJECT NUMBER	$[AUC]_0^8$ (MCG.HR/ML)	$[AUC]_{\infty}$ (MCG.HR/ML)	C_{max} (MCG/ML)	T_{max} (HR)	$t_{1/2,e}$ (HR)
1					
2					
3					
4					
5					
6					
Mean	7.48	9.80	2.02	1.3	3.9 (harmonic mean)
(S.D.)	(2.24)	(2.93)	(0.77)	(0.4)	(0.3)

* Plasma parameters.

$[AUC]$ = Area under the plasma concentration-time curve

C_{max} = Maximum plasma concentration

T_{max} = Time to peak, (t_{max})

$t_{1/2,e}$ = Effective plasma half-life

Figure

19-1

MEAN NORFLOXACIN PLASMA CONCENTRATION IN HEALTHY ELDERLY SUBJECTS GIVEN A SINGLE 400 MG TABLET

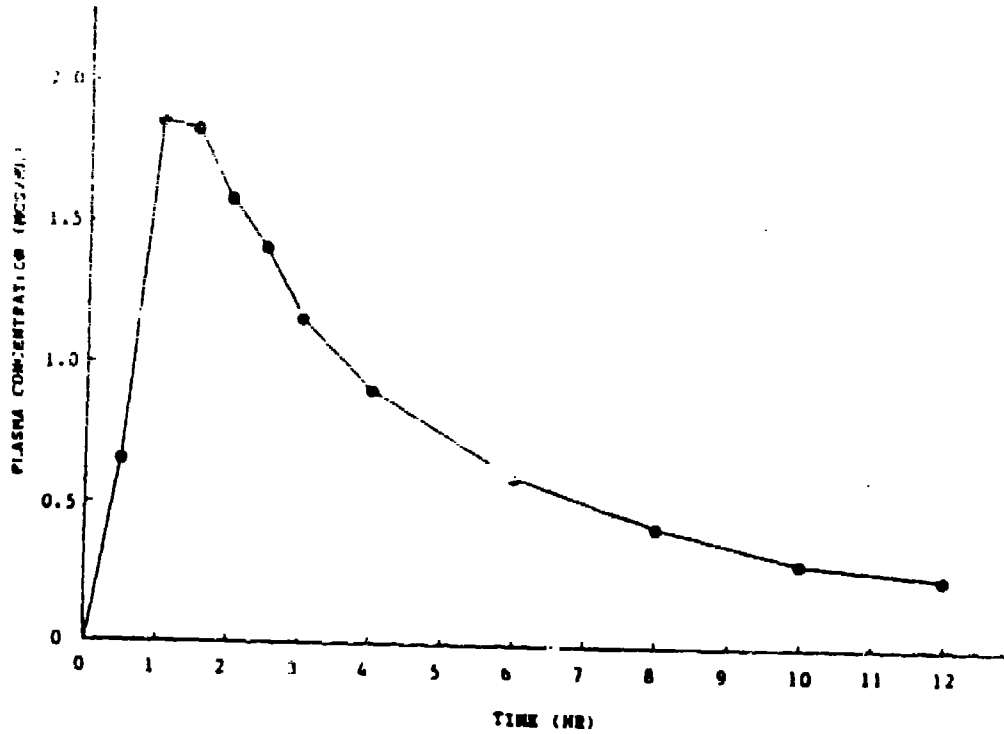


Table 19-3

DEMOGRAPHIC DATA FOR SUBJECT POPULATION

SUBJECT NUMBER	SEX	AGE, YR	WEIGHT, KG	HEIGHT, IN.	CREATININE CLEARANCE ML/MIN/1.73 m ²
<u>Individual Data</u>					
1	F	69	56.8	64	86
2	F	68	69.1	68	11
3	M	69	60.9	65	95
4	M	74	69.5	66	72
5	F	67	60.0	62	88
6	F	68	56.2	63	90
<u>Averages By Sex</u>					
1,2,5,6	F	68.0	61.0	64.3	94.8
3,4	M	71.5	65.2	65.5	83.5
<u>Overall Average (S.D.)</u>					
1 to 6	4F, 2M	69.2 (2.5)	62.4 (5.5)	64.7 (2.2)	91 (14.1)

Table 20-1

Individual Demographic Data

Subject No.	Sex	Age (Yr)	Wt (Kg)	GFR (ml/min/1.73m ²)	Other Medication
Group I					
1	M	51	72	96 ¹	None
2	M	35	4	117 ³	None
7	M	23	103	131 ⁴	None
9	M	27	53	115	None
10	M	16	53	125 ²	None
14	M	27	70	110 ²	None
20	M	31	73	111	None
8	M	49	39	148 ³	Warfarin, Fimozide
21	M	21	65	94	Hydroxychloroquine, Prednisolone
Group II					
5	M	60	62	60 ⁴	Furosemide, Slow K
6	M	51	88	31	Mixard, Furosemide, Spironolactone
12	M	56	64	46	Atenolol
25	F	55	75	56	Atenolol, Moduretic
26	F	45	43	60 ⁵	Captopril, Nifedipine, Diazide, Nitrazepam
27	M	53	73	74 ⁵	None
Group III					
3	M	69	62	12 ⁶	Aminophylline, Salbutamol, Furosemide, Aldrox
11	M	52	78	28	Chlorpropamide, Prednisolone, Furosemide
13	F	52	64	13	Flurbiprofen, Slow K, Insulin, Vit. B
15	M	65	57	17	Captopril, Hydralazine, Furosemide, Ampicillin, Erythromycin
17	M	72	55	11	Allopurinol, Lactulose, Alucaps, Temazepam
18	M	51	80	15	Alfacalcidol, Aluminum hydroxide

Individual Demographic Data (Continued)

Subject No.	Sex	Age (Yr)	Wt (Kg)	GFR (ml/min/1.73m ²)	Other Medication
Group IV					
19	F	23	54	9.1	Atenolol, Bendroflumazide
23	F	69	68	7.5	Nifedipine, Hydralazine
16	M	54	53	6.6	Prednisolone, Ascorbic acid, dinitrate, Allopurinol, Furosemide, Slow K
4	F	54	49	8.0 ³	Ferrous sulphate, Frazonin, Furosemide, Alucaps
22	M	43	77	7.6	Furosemide, Aldrox, Slow sodium
24	F	62	61	9.1	Aluminum hydroxide, Thyroxine

GFR = Glomerular Filtration Rate as determined on study days by Cr⁵¹-EDTA clearance unless otherwise noted.

1 I^{131}/I^{125} Hippuran clearance (assuming a filtration factor of 0.1)

2 Creatinine Clearance

3 Determined 2 months after the study

4 Determined 1 month after the study

5 Determined 1 month before the study

6 ⁵¹Cr-EDTA clearance determined 2 months after the study. Creatinine clearance was 4 ml/min 3 days before the study.

Table 20-2

Individual Total Urinary Recovery (%) and Cumulative Renal Clearance ($\bar{V}_{CL,R}$) of Norfloxacin in Renal Insufficiency Study

Subject No.	$\bar{V}_{CL,R}$ (ml/min)	Dose	$\bar{V}_{CL,R}$ (ml/min)
Group I			
1			
2			
7			
8 ⁴			
9			
10			
14			
20			
21 ⁵			
Mean		28.2	297.1
(± S.D.)		(12.8)	(117.4)
		<i>from mean</i>	
Group II			
5 ⁴			
6 ⁵			
12			
25			
26			
27			
Mean		35.3	264.5
(± S.D.)		(9.2)	(83.2)
Group III			
3			
11 ¹			
13			
15 ²			
17 ³			
18			
Mean		6.7	37.8
(± S.D.)		(4.1)	(4.6)

Individual Total Urinary Recovery (%) and Cumulative Renal Clearance ($\bar{V}_{CL,R}$) of Norfloxacin in Renal Insufficiency Study (Continued)

Subject No.	$\bar{V}_{CL,R}$ (ml/min)	Dose	$\bar{V}_{CL,R}$ (ml/min)
Group IV			
4			
16			
19 ⁴			
22 ³			
23			
24			
Mean		11.1	14.7
(± S. D.)		(3.1)	(8.4)
1 Questionable urinary recovery 0-2 hr. No estimate of $\bar{V}_{CL,R}$ possible. Excluded from mean. 2 Questionable urinary recovery 4-8 hr. Urinary recovery 4-6 estimated from $\bar{V}_{CL,R}$ and AUC. 3 No drug detectable in urine. 4 Questionable urinary recovery 0-2 hr. Urinary recovery estimated from $\bar{V}_{CL,R}$ and AUC. 5 Questionable urinary recovery. Excluded from mean. 6 Questionable urinary recovery. No drug detectable in urine after 12 hr but serum levels detectable through 24 hr. Excluded from mean.			

Table 20-3

Individual Area Under the Serum Concentration-Time Curve (AUC) for Norfloxacin in the Renal Insufficiency Study

Subject No.	[AUC] ₀₋₈ (mcg·hr/ml)	[AUC] ₀₋₂₄ (mcg·hr/ml)
<u>Group I</u>		
1		
2		
7		
8		
9		
10		
14		
20		
21		
Mean	<u>5.38</u>	<u>6.94</u>
(±S.D.)	(1.93)	(2.73)
<u>Group II</u>		
5		
6		
12		
25		
26		
27		
Mean	<u>7.62</u>	<u>9.53</u>
(±S.D.)	(2.00)	(2.47)
<u>Group III</u>		
3		
11		
13		
15		
17		
18		
Mean	<u>9.18</u>	<u>24.01</u>
(±S.D.)	(2.41)	(13.49)
<u>Group IV</u>		
4		
16		
19		
22		
23		
24		
Mean	<u>7.79</u>	<u>16.46</u>
(±S.D.)	(5.31)	(14.52)

1 See Table 20-1 for details.

2 Excluded from mean.

Table 20-4

Individual Maximum Serum Concentration (C_{MAX}) of Nifedipine and the Time that Maximum Occurred (T_{MAX}) in the Equal Insufficiency Study

Subject No.	C_{MAX} (mcg/ml)	T_{MAX} (hr)
<u>Group I</u>		
1		
2		
7		
8		
9		
10		
14		
20		
21		
Mean	<u>1.51</u>	<u>1.4</u>
(±S.D.)	(0.56)	(0.4)
<u>Group II</u>		
5		
6		
12		
25		
26		
27		
Mean	<u>1.91</u>	<u>1.3</u>
(±S.D.)	(0.71)	(0.4)
<u>Group III</u>		
3		
11		
13		
15		
17		
18		
Mean	<u>1.70</u>	<u>1.8</u>
(±S.D.)	(0.43)	(1.1)
<u>Group IV</u>		
4		
16		
19		
22		
23		
24		
Mean	<u>1.70</u>	<u>1.8</u>
(±S.D.)	(0.92)	(1.2)

Table 20-5

Additional Effective Serum Half-life ($t_{1/2, n}$) of Norfloxacin in
the Renal Insufficiency Study

Subject No.	$t_{1/2, n}$ (hr)	Subject No.	$t_{1/2, n}$ (hr)
<u>Group I</u>		<u>Group III</u>	
1		3	
2		11	
7		13	
8		15	
9		17	
10		18	
14		Mean ¹	6.57
20		<u>Group IV</u>	
21		4	
Mean ¹	3.47	16	
<u>Group II</u>		19	
5		22	
6		23	
12		24	
25		Mean ¹	6.40
26			
27			
Mean ¹	3.38		

¹ Harmonic Mean

² See Table 9.

Figure 20-1

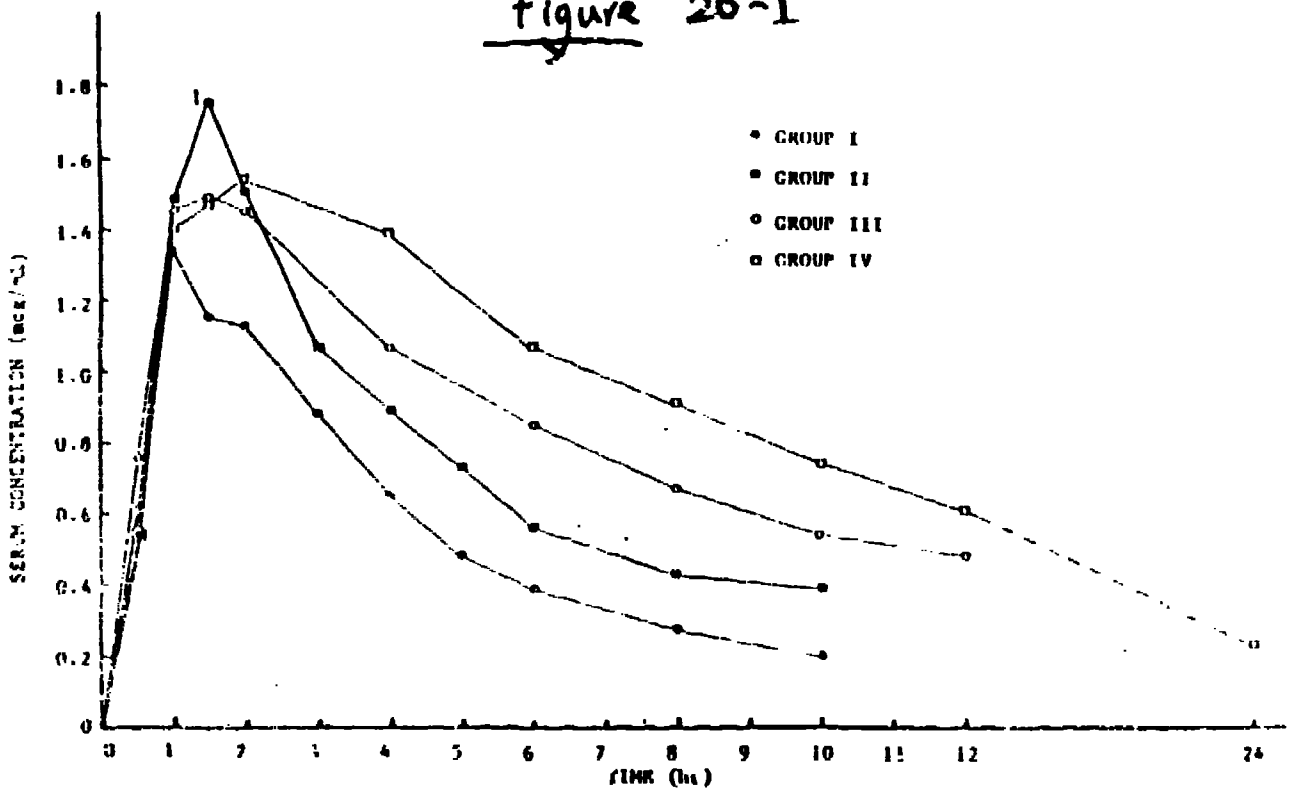


Figure 5. Mean norfloxacin serum concentration profiles.

Table 21-1

Individual Plasma Concentrations (C_p) of Norfloxacin Following Administration of One 400-mg Tablet (Old Formulation)

Subject No.	C_p ($\mu\text{g/ml}$) at ...hr.									
	0	0.5	1.0	1.5	2	3	4	6	8	12
51										
52										
53										
54										
55										
56										
57										
58										
59										
60										
61										
62										
63										
64										
65										
66										
67										
68										
69										
70										
Mean	-	0.48	1.17	1.35	1.29	0.96	0.78	0.55	0.40	0.23

Table: 21-2

Individual Plasma Concentrations (C_p) of Norfloxacin Following Administration of One 400-mg Tablet (New Formulation)

Subject No.	C_p ($\mu\text{g/ml}$) at ... hr									
	0	0.5	1.0	1.5	2	3	4	6	8	12
51										
52										
53										
54										
55										
56										
57										
58										
59										
60										
61										
62										
63										
64										
65										
66										
67										
68										
69										
70										
Mean	-	0.94	1.48	1.29	1.05	0.80	0.67	0.48	0.36	0.22

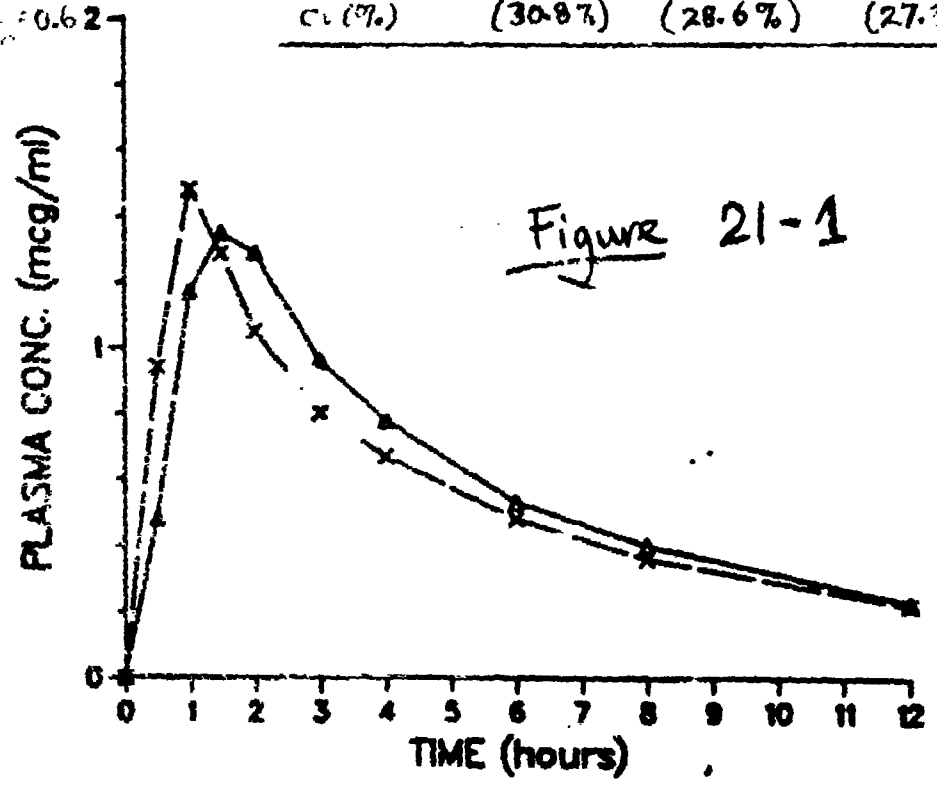
Table 21-3

Ratio (mg) (mg)

Individual Peak Plasma Concentration (C_{max}) of Norfloxacin and Time that Peak Occurred (T_{max}) After Tablet Administration

Subject No.	(Kyorin)		(MSD)		Ratio
	Old Formulation		New Formulation		
	C_{max} (ug/ml)	T_{max} (hr)	C_{max} (ug/ml)	T_{max} (hr)	
51					
52					
53					
54					
55					
56					
57					
58					
58					
60					
61					
62					
63					
64					
65					
66					
67					
68					
69					
70					
Mean	1.56	1.4	1.54	1.1	
(±S.D.)	(0.48)	(0.4)	(0.42)	(0.4)	
CV (%)	(30.8%)	(28.6%)	(27.3%)	(36.4%)	

12. = 0.62
 5 H
 36



1 Page(s)

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Table 21-5

Individual Total Urinary Recovery (U) of Norfloxacin Following Single Dose Administration of Old and New Tablet Formulations

Subject No.	Pyrimin 412 mg		FASD 412 mg	
	Old Formulation		New Formulation	
	U (ug)	I-Dose	U (ug)	I-Dose
51				
52				
53				
54				
55				
56				
57				
58				
59				
60				
61				
62				
63				
64				
65				
66				
67				
68				
69				
70				
Mean (±S.D.)		27.9 (8.9) (CV 31.9%)		27.0 (8.5) (CV 31.5%)

- 1 No sample or no void 1-2, and 6-8 hr. Excluded from mean.
- 2 No void 0-1 hr. Renal clearance indicates drug retrieved in 1-2 and 2-3 hr collection.
- 3 No sample or no void 4-6 hr.
- 4 No sample or no void 8-12 hr. Urinary excretion estimated from $V_{CL,R}$ and AUC.
- 5 No void 1-2 and 3-4 hr. Renal clearance indicates drug recovered in 2-3 hr collection.
- 6 No sample 12-24 hr. Excluded from mean.
- 7 No sample or no void 8-12 and 24-48 hr. Urinary excretion 8-12 estimated from $V_{CL,R}$ and AUC. Later sample assumed insignificant.
- 8 Five urine collections covered the interval 24-48 hr. One sample missing or no volume recorded.
- 9 Three and 7 urine collections covered the interval 12-24 and 24-48 hr., respectively. No volume given for 1 sample 12-24 and 2 samples 24-48 hr.
- 10 Four urine collections covered the interval 24-48 hr. No volume given for 1 sample or 1 sample missing.
- 11 No sample or no void 2-3 hr. Excluded from mean.

Table 21-6

Individual Estimates of Norfloxacin Relative Bioavailability
From 400-mg New Formulation Tablets (F_{NEW}) as Compared to
Old Formulation Tablets (F_{OLD})

Subject No.	F _{NEW} /F _{OLD}
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
Geometric Mean	0.94

¹ Incomplete urinary recovery

Cont 9

REL. BIOAVAILABILITY	NEW FORM/OLD FORM
N	17
GEOMETRIC MEAN	0.94 — 0.94
95% C.I.	0.80-1.09 — 0.80-1.09
POWER (15% DIFFERENCE)	.27 — 0.27
(15% DIFFERENCE)	.54 — 0.54
(20% DIFFERENCE)	.61 — 0.81
(25% DIFFERENCE)	.69 — 0.99
POSTERIOR PROB. (15%)	.60
(15%)	.67
(20%)	.77
(25%)	.89

NOTE: PATIENTS 8, 14, 60 AND 66 WERE EXCLUDED FROM BIOAVAILABILITY CALCULATIONS.
ALL INCLUSIONS/EXCLUSIONS WERE CARRIED OUT IN ACCORDANCE WITH THE BIOPHARMACEUTICS REPORT.

Table 21-7

~~TABLE~~

Individual Cumulative Renal Clearance ($\dot{V}_{CL,R}$) and Total Area Under the Plasma Concentration-Time Curve, $[AUC]_0$, for Norfloxacin

Subject No.	Kyarin		MSD		Ratios MSD/Kyarin
	Old Formulation		New Formulation		
	$\dot{V}_{CL,R}$ (ml/min)	$[AUC]_0$ (mcg.hr/ml)	$\dot{V}_{CL,R}$ (ml/min)	$[AUC]_0$ (mcg.hr/ml)	
51					
52					
53					
54					
55					
56					
57					
58					
59					
60					
61					
62					
63					
64					
65					
66					
67					
68					
69					
70					
Mean	261.9	7.82	270.0	6.94	
(±S.D.)	(80.7)	(2.53)	(63.4)	(1.69)	
CV(%)	30.5	32.3	23.3	24.3	

¹ Incomplete urine collection

$$\frac{415}{414} = 0.995 \rightarrow 1$$

$$\frac{414}{412} = 1.005 \rightarrow 1$$

$$\% \text{ within } 75-125 = \frac{10}{17} = 58.8$$

$$\bar{x} = 0.967$$

$$S.D. = 0.313$$

$$CV \% = 32.4 \%$$

BASED ON SUBJECTS WITH COMPLETE URINARY RECOVERY ON B O T H F O R M U L A T I O N S

PARAMETER	N	OLD FORMULATION		NEW FORMULATION		CHANGE (NEW-OLD)		
		MEAN	S.D.	MEAN	S.D.	MEAN	S.D.	
PEAK SERUM CONC.--MCG/ML	20	1.96	0.48	1.94	0.42	-0.02	0.58	NS
TIME TO PEAK CONC.--HR	20	1.35	0.43	1.07	0.37	-0.27	0.57	*
AUC--MCG/ML X HR	17	7.71	2.58	6.98	1.73	-0.82	2.14	NS
RENAL CLEARANCE--ML/MIN	18	266.18	83.98	269.98	63.44	3.80	61.25	NS
URINARY RECOVERY--MG (UNADJ)	20	117.43	37.78	106.55	36.94	-10.88	36.74	N/A
URINARY RECOVERY--X DOSE (A)	17	27.74	8.98	26.72	8.62	-1.02	7.68	NS

NOTE: BASED ON 412 AND 414 MG FOR THE OLD AND NEW FORMULATIONS RESPECTIVELY.

NOTE: SUBJECT 860 WAS EXCLUDED FROM MEAN OF UR-X DOSE BECAUSE OF INCOMPLETE URINARY RECOVERY FOLLOWING TREATMENT A (OLD FORMULATION)
 SUBJECTS 854 AND 868 WERE EXCLUDED FROM MEAN OF UR-X DOSE BECAUSE OF INCOMPLETE URINARY RECOVERY FOLLOWING TREATMENT B (NEW FORMULATION).
 RENAL CLEARANCE CALCULATIONS WERE AVAILABLE FOR SUBJECT 860 BUT NOT FOR SUBJECTS 854 & 868.
 ALL THREE SUBJECTS WERE EXCLUDED FROM AND ANALYSES ON AUC AND RELATIVE BIOAVAILABILITY.

ALL EXCLUSIONS WERE CARRIED OUT IN ACCORDANCE WITH THE BIOPHARMACEUTICS REPORT.

NS-- NOT STATISTICALLY SIGNIFICANT.

N/A--NOT ANALYSED.

*-- DIFFERENCE IS STATISTICALLY SIGNIFICANT, P<0.05

ANALYSES ADJUSTED FOR PERIOD.

Means of Pharmacokinetic Parameters

Table 21-8

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs and Biologics
Office of Drug Standards

DATE : **MAY 6 1986**

TO : Edward Labor, M.D., Director
Division of Anti-Infective Drug Products, HFN-815

FROM : Jerome Skelly, Ph.D., Director
Division of Biopharmaceutics, HFN-220

SUBJECT : Biopharmaceutics Recommendation of Approval
NDA-19,384 ; Norfloxacin - 400 mg tablet
Merck, Sharp & Dohme Research Labs

Background:

Norfloxacin is a quinoline carboxylic acid antibacterial agent structurally related to compounds such as nalidixic, oxolinic, and pipemidic acids. The proposed indications are for the treatment of infections caused by susceptible strains of micro-organisms, in complicated and uncomplicated cystitis, gonococcal urethritis, acute gastroenteritis and prophylactically in profound neutropenia. The proposed dosing follows.

Uncomplicated UTI - 400 mg BID X 7-10 days
Complicated UTI - 400 mg BID X 10-60 days
Uncomplicated GC urethritis - 600 mg followed by 600 mg 4 hours later
Acute gastroenteritis - 400 mg BID X 5 days
Prophylaxis in neutropenia - 400 mg TID for duration of neutropenia
(no recommendations available beyond 8 weeks)

There is no record of any previous submissions to the Division of Biopharmaceutics concerning norfloxacin, the subject of NDA 19-384. Norfloxacin is licensed by Merck from Kyorin Pharmaceutical Co., Ltd. (Japan).

Results:

Dose proportionality was determined by administration of 200, 400, 800, 1200 and 1600 mg single doses to 14 subjects. Based on AUC, dose proportionality across the single dose range 200-1600 mg exists for norfloxacin. However, the peak concentration (C_{max}) of norfloxacin does not increase proportionately with the increase in a single dose beyond 800 mg. After a 400 mg single dose (capsule), mean C_{max} was approximately 1.6 ug/ml (T_{max} about 1 hour), whereas following a single 1600 mg dose, C_{max} was approximately 3.8 ug/ml (T_{max} about 2 hours). The mean C_{max} observed after a single 400 mg dose (MSD direct compression tablet) was 1.5 ug/ml with a corresponding mean T_{max} of about 1 hour.

Because clinical studies utilized products manufactured by different processes and with different formulations (Kyorin vs MSD), Zinny conducted a bioequivalency study with the MSD direct compression tablet and the Kyorin product. Based on this study, the MSD and clinically studied Kyorin tablet products have equivalent extents of absorption. Based on mean T_{max} , the rate of absorption of the MSD formulation is faster than the Kyorin formulation (1.07 vs 1.35 hrs). The MSD-400 mg tablet proposed for marketing is very slightly different from that studied in the bioavailability and bioequivalency studies. Dissolution data on both dosage forms indicate the equivalence of both dosage forms. The relative bioavailability of the 400 mg tablet compared to a solution showed a mean dose adjusted AUC(0-infinity) ratio of 0.99 (C.V. 49 %). While the power is inadequate to establish statistical equivalence to the administered solution, it is adequate to define the pharmacokinetics. About 30-35 % of the administered dose of norfloxacin is recovered in the urine over 24-48 hours as parent (25-30 %) and metabolites (4-8 %). Fecal recovery accounts for approximately 30 % of the administered dose but may be much greater. Although fecal recovery is difficult to quantitate because of analytical assay difficulties, it may be accounted for by incomplete GI absorption, biliary excretion and/or other factors. Thus while the fraction of the administered dose orally absorbed cannot be determined on the basis of the data submitted, one may conclude that it is at least 30-35 percent. The elimination half-life of the parent drug norfloxacin is about 5 hours. Protein binding of norfloxacin measured by ultrafiltration is about 14 %. The "effective half-life for accumulation" for an 8 hour dosing interval is about 3 hours. The renal clearance of norfloxacin measured in adults with normal renal function is about 300 ml/min.

Because of the effect of pH on the solubility of norfloxacin, as well as data from an inconclusive study by Kumasaka where the administration of norfloxacin with food appeared to alter the absorption characteristics of the drug, the effect of food on the proposed marketed product needs investigation. If food effects are not resolved with a controlled study, then this issue should be addressed in the labeling. In addition, since reduced enteral absorption of ciprofloxacin (a quinoline carboxylic acid derivative) has been demonstrated, coadministration of norfloxacin and antacids should be discouraged in the labeling because of the possibility of complexation resulting in a decrease in absorption.

The dose of norfloxacin needs to be adjusted in the elderly and patients with renal dysfunction. We recommend that dosing guidelines provided by the firm be clarified because of drug accumulation/decreased clearance.

Our concern about crystalluria which were discussed in a meeting with BPH-814 on March 13, 1988 are outlined in Section IX of the attached biopharmaceutics review. It appears that with the recommended doses of levofloxacin, crystallization should not be a problem with the parent compound in most patients. However, concern is expressed about the potential for formation of crystals under conditions commonly seen (e.g. low urine flow, alterations in urine pH), when receiving doses greater than those recommended, and in vegetarians who characteristically have a high urine pH. Crystallization has been reported in subjects given 1200 and 1600 mg as a single dose. Although drug crystals were not reported in the bioavailability studies submitted, the fluid loaded condition of the subjects prevents interpretation of the clinical results of these studies for resolving safety issues by the Division of Biopharmaceutics. Labeling should include specific instructions concerning maintenance of a good fluid intake in all patients so as to prevent crystallization of drug in the urinary tract.

The proposed dissolution method and specification are the following,

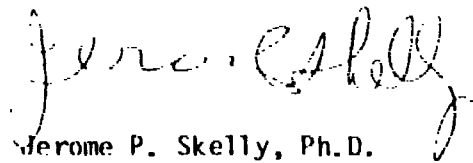
ISP Apparatus II, 50 rpm, 37 degrees centigrade,
750 ml of 0.05 M sodium acetate buffer (pH 4.0)
Q specification of [REDACTED]
Assay via HPLC methodology

The dissolution method and specification are acceptable from a biopharmaceutics perspective.

Overall Conclusion:

The data provided in NDA 19,384 for the 400 mg tablet is acceptable from a Division of Biopharmaceutics point of view. This submission fulfills the bioavailability and bioequivalence requirements set forth in the regulation of 21 CFR, part 320. However, suggested phase IV commitment (i.e. food/antacids effect study) as outlined in the review should be conveyed to the firm.

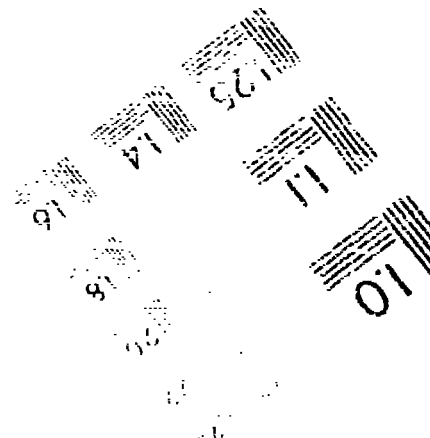
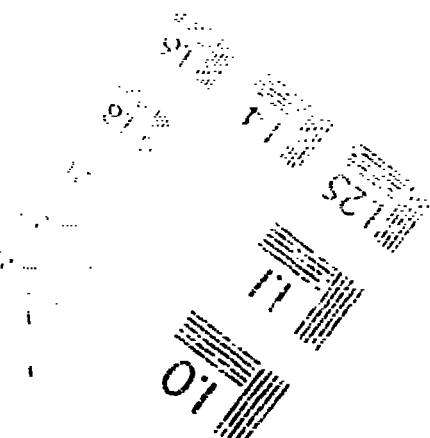
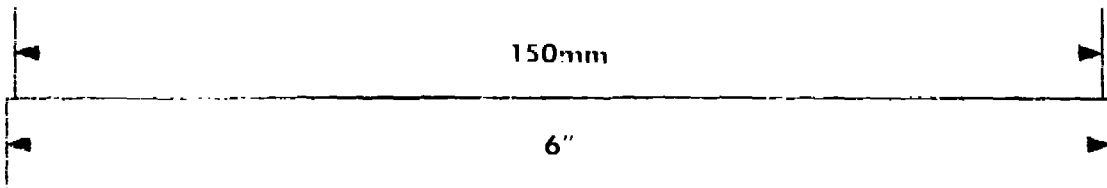
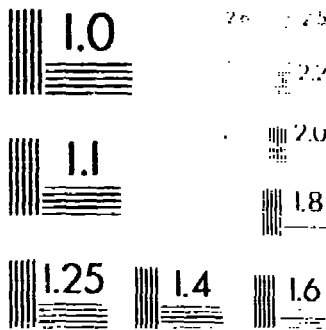
Comments in the review pertaining to labeling should be considered by HEM-215 when evaluating the package insert. These issues include food effects, co-administration of norfloxacin with antacids and ensuring adequate hydration in patients.



Jerome P. Skelly, Ph.D.

Prepared by Gene D. Mason, Pharm.D.
RD Initialed by John Hunt
FT Initialed by C.T. Viswanathan, Ph.D.

IMAGE EVALUATION TEST TARGET (MT-3)



 **APPLIED IMAGE**
1653 E. MAIN STREET
ROCHESTER, NY 14609
TEL (716) 482-0500
FAX (716) 288-5089

END

N19-384 1 of 2

MDDA 19284

Norfloxacin
Noroxin[®] Tablet
400 mg tablet
NDA 19-384
Reviewer: Gene D. Mason, Pharm.D.

Merck Sharp & Dohme
Research Laboratories
West Point, PA 19486
Submissions Dated:
March 14, & July 18, 1985
Feb 14, 24 & March 28, 1985

Review of an NDA

MAY 6 1986

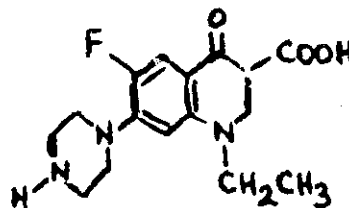
I BACKGROUND

Norfloxacin is a quinoline carboxylic acid antibacterial agent structurally related to compounds such as nalidixic, oxolinic, and pipemidic acids. The proposed indications are for the treatment of infections caused by susceptible strains of micro-organisms, in complicated and uncomplicated cystitis, gonococcal urethritis, acute gastroenteritis and prophylactically in profound neutropenia.

There is no record of any previous submissions to the Division of Biopharmaceutics concerning norfloxacin, the subject of NDA 19-384. Norfloxacin is licensed by Merck from Kyorin Pharmaceutical Co., Ltd. (Japan).

Attachment I of this review is a memo from HFN-815(Dr. Reed) requesting comments on the possibility of crystallization of norfloxacin in the urinary tract based on pharmacokinetic data.

II CHEMISTRY



Structure:

Chemical Name: 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazonyl)-3-quinoline carboxylic acid

Molecular Formula: C₁₆H₁₈FN₃O₃ Mol. Wt.: 319.3 Daltons

pKa: 6.3 and 8.8

Solubility: pH solubility profiles in water and urine are given in figures 2a, b, & c of this submission, respectively.

Practically insoluble in water and methyl ether; freely soluble in glacial acetic acid; slightly soluble in methanol, ethanol, ethyl acetate and benzene.

Generic Name: Norfloxacin

Merck Sharp & Dohme Code Names: MK-366, MK0366, AM-715

It is stated by the sponsor that there are no known polymorphs of norfloxacin.

III FORMULATION

Because norfloxacin is licensed by Merck from Kyorin Pharmaceutical Co., Ltd(Japan) several different formulations have been used in clinical studies prior to the development of the final market image tablet. In addition, different manufacturing processes were utilized by Kyorin Pharmaceutical Co. and Merck Sharp and Dohme. After changing the manufacturing process, MSD subsequently altered the coating formulation. The proposed market image tablet formulation made by direct compression is below. Table 1a of this review compares the proposed formulation to the other formulations used in pivotal bioavailability/pharmacokinetic studies. Table 2 identifies preparations used in pivotal clinical studies. THE FINAL MARKET IMAGE TABLET FORMULATION WAS NOT UTILIZED IN ANY OF THE BIOAVAILABILITY STUDIES OR IN PIVOTAL CLINICAL EFFICACY AND SAFETY STUDIES. THIS ISSUE IS DISCUSSED FURTHER IN SECTION VI-DISSOLUTION.

<u>Ingredient</u>	<u>Merck, 400 mg Market Image Tablet*</u> <u>Amount (mg) per tablet</u>
<u>Core</u>	
Anhydrous Norfloxacin	400.00

* The 200 mg strength tablet is an exact half-size multiple. AT THIS TIME THE SPONSOR DOES NOT SEEK APPROVAL OF THE 200 MG TABLET STRENGTH.

IV PROPOSED DOSING

(taken from proposed circular insert, vol 2.145, pg VII-00186)

Uncomplicated UTI - 400 mg BID X 7-10 days
Complicated UTI - 400 mg BID X 10-60 days
Uncomplicated GC urethritis - 600 mg followed by 600 mg 4 hours later
Acute gastroenteritis - 400 mg BID X 5 days
Prophylaxis in neutropenia - 400 mg TID for duration of neutropenia
(no recommendations available beyond 8 weeks)

One multiple dose study submitted(reference #16, Zinny) utilized the regimen 400 mg BID and submitted relevant pharmacokinetic data in 23 subjects. The regimen of 400 mg TID was used in clinical study #66(Zinny ref #17), however, pharmacokinetic data was obtained in only 4 subjects in this study. A single dose of 1600 mg was administered in study #15(Ferguson).

V STUDIES REVIEWED

Study Reference #	Title/Location	Objective
1 / Bland, et al, (literature reference)	Vol 2.145, pg VII-00061	Assay
2 / Paulukonis, et al, (literature reference)	Vol 2.145, pg VII-00065	Assay
8 / Nagatsu, et al, (literature reference)	Vol 2.145, pg VII-00211	Metabolism-Animal
9 / Ozaki, et al, (literature reference)	Vol 2.145, pg VII-234	Metabolism-Human
11 / Nagatsu, et al, (literature reference)	Vol 2.145, pg VII-00272	Metabolism-Animal
12 / Kumasaka, et al, Vol 2.145, pg VII-00309	?? tab/cap 200 mg PO (literature reference,	Food Effects (SD)
15 / Ferguson(#1) Vol 2.146, pg VII-00450	caps 200 mg 400 mg 800 mg 1200 mg 1600 mg	Dose-propor. (SD)
16 / Zinny(#45) Vol 2.147, pg VII-00627	tabs 400 mg BID	Multi-dose (N=23)
17 / Zinny(#66) Vol 2.147, pg VII-00856	tabs 400 mg TID	Multi-dose (data, N=4)
18 / Zinny(#13) Vol 2.147, pg VII-00993	tabs 200 mg 400 mg soln 400 mg	BA/BE (SD)
19 / Martin(#661) Vol 2.148, pg VII-01142	tabs 400 mg	Elderly (SD)
20 / Asscher(#576) Vol 2.148, pg VII-01293	tabs 400 mg	Renal Failure
21 / Zinny(#59) Vol 2.148, pg VII-01421	tabs 400 mg (old vs new formulation)	BE
26 / Anon, Vol 2.148, pg VII-01590		Assay

SECTION VII OF THIS REVIEW CONTAINS THE SUMMARY AND CONCLUSIONS FROM THE ABOVE STUDIES. APPENDIX A CONTAINS A DETAILED DESCRIPTION OF EACH OF THE STUDIES AND THEIR INDIVIDUAL RESULTS. ALL CORRESPONDING TABLES AND GRAPHS ARE ATTACHED IN APPENDIX B.

VI DISSOLUTION

The following dissolution methods and specifications were proposed by the firm. Table 1b of this review contains dissolution information.

USP Apparatus II, 50 rpm
750 ml of 0.05 M sodium acetate buffer(pH 4.0), 37 degrees centigrade,

Q specification of [REDACTED]
Assay via HPLC methodology

The firm provided the following,

1. individual dissolution characteristics of 12 tablets in the final market image,
2. justification/data to support the above dissolution method and specification, and
3. individual in-vitro dissolution profiles for various lots used in the bioavailability studies utilizing the proposed methodology for the purpose of comparing the dissolution characteristics of the different formulations.

Inspection of table 1a shows that the MSD-direct compression tablet utilized in study reference #21(Zinny study #59) and the MSD-final market image tablet are identical in core components and differ slightly in amounts of coating constituents(excluding coloring). The amounts of [REDACTED] in the coating on the MSD-final market image product were each decreased by [REDACTED]. The MSD-final market image tablet was not utilized in any bioavailability study submitted. Because of the magnitude and direction of the changes made, it was decided that the MSD-final market image tablet could be evaluated with in-vitro dissolution methods. Several discussions with the firm about the appropriate dissolution conditions(i.e. pH, sampling times, lots to study) and the purpose of the investigation occurred on 3/14, 3/24 & 3/27/86. After evaluation of dissolution data submitted by the sponsor with justification for the chosen methodology(submission dated 3/28/86) the Division of Biopharmaceutics agreed that the proposed methodology appears to be discriminating between Kyorin and MSD manufactured products and produces data consistent with the results of in-vivo investigations. Thus, the Division of Biopharmaceutics concluded that it was appropriate to employ in-vitro dissolution methods to evaluate the various formulations and support/justify approving the 400 mg MSD-final market image tablet.

VII SUMMARY OF RESULTS AND CONCLUSION

Bioavailability

Reference # 18 - Zinny(single dose; 200,400mg-Kyorin A vs 430mg Soln)
 Reference # 12 - Kumasaka(food effects)

Below are the results of the relative bioavailability study conducted by Zinny(#18).

Parameter	ANOVA	Power*	% Ratios w/in 75/75-125		
			T200/S200	T400/S400	T400(b)/T200

For all treatments			T200/S200	T400/S400	T400(b)/T200
AUC(a)	NS	50%	3/12=25%	5/13=38.5	7/12=58.3
Cmax(b)	NS	42%	5/15=33.3%	6/15=40.0	5/15=33.3
Tmax	Sig (P LT 0.05)				

2 One-Sided Hypothesis

AUC	Tab 200 vs Soln 400(b)	-	Accept Ho: Not BE
	Tab 400 vs Soln 400	-	Accept Ho: Not BE
	Tab 200 vs Tab 400(b)	-	Accept H1: Bioequivalent
Cmax	Tab 200 vs Soln 400(b)	-	Accept Ho: Not BE
	Tab 400 vs Soln 400	-	Accept Ho: Not BE
	Tab 200 vs Tab 400(b)	-	Accept Ho: Not BE

 * 20% diff, alpha = 0.05; T = Tablet, S = Solution;
 a - natural log, dose adj'd to 200 mg; b - dose adj'd to 200 mg

The mean time to peak concentration for the 200 mg and 400 mg tablet was significantly longer(P LT 0.05) than that for the reference solution(1.03, 1.03 vs 0.70 hrs). No significant difference was found for the parameter Tmax between the two tablets. The mean(+/- S.D.) relative bioavailability for dose adjusted Cmax, 400 mg tab/200 mg tab, was 1.1(0.52).

Based on the above observations it is concluded that the 200 mg tab and the 400 mg tab have similar rates and extent of absorption. It cannot be concluded that the solution is bioequivalent to the tablets.

The relative bioavailability(using the methods of Kwan & Till) for the comparisons 200 mg tab/soln, 400 mg tab/soln and 200 mg tab/400 mg tab, are 0.89, 0.90 and 1.0, respectively. The power(as determined by firm) to detect a 25% difference for the comparisons 200 mg tab/soln, 400 mg tab/soln and 200 mg tab/400 mg tab, are 0.77, 0.78 and 0.80, respectively. The relative bioavailabilities(mean +/- S.D.) based on dose adjusted AUC(0-infin) for the ratios tab 200/soln 400, tab 400/soln 400, tab 400/tab 200 are 1.0 +/- 0.42(42% C.V.), 0.99 +/- 0.49(50% C.V.), 1.0 +/- 0.33(33% C.V.), respectively. At this time, the Division of Biopharmaceutics conventionally uses AUC to compare product bioavailability(extent of absorption) and not the methods of Kwan and Till.

The effect of food was investigated by Kumasaka(#12) in 5 volunteers. The results are inconclusive because the AUC was measured only for 8 hours after the dose, and thus incomplete, and the product utilized was not the proposed marketed tablet. In addition, meal composition and timing relative to dose was not specified. Tmax for both treatments was 1-2 hours. Mean(S.D.) Cmax in plasma for fasting subjects was 0.46(0.13) vs 0.32(0.16) ug/ml for non-fasting subjects. The Cmax in urine was higher in the fasting group(334 vs 206 ug/ml). In one nonfasting subject, norfloxacin could only be detected(ug/ml) 2 hours after the 200 mg single dose. It appears that administration of the product utilized in this study with food can alter the absorption characteristics of the drug. Because the formulation, dosage form(tablet vs capsule) and source(probably manufactured by Kyorin) of the product administered in this study was not provided, extrapolation of the results of this study to the proposed marketed product is not possible. Because of the effect of pH on the solubility of norfloxacin, the effect of food on the proposed marketed product needs investigation.

A correspondence published in the European Journal of Clinical Microbiology, Vol 4, 1985, p 345(see Attachment II), reported reduced enteral absorption of ciprofloxacin(a quinoline carboxylic acid derivative) when coadministered with antacids. Ten healthy fasting volunteers randomly received 500 mg of ciprofloxacin orally either in a fasting state or "24 hours after administration of 10 X 600 mg Mg-OH + 900 mg Al-OH (Maalox)". A pronounced decrease of the peak serum concentration from a mean of 1.7 mg/L(range 1.3-2.6) after ciprofloxacin alone to a mean of 0.1 mg/L(range mg/L) after ciprofloxacin plus antacid(P LT 0.001) was reported. Tmax was only slightly prolonged(73 +/- 13 min versus 87 +/- min). The cumulative urinary excretion of parent drug over 24 hours after ciprofloxacin administered alone was 24%(range 19-34%) of the administered dose as compared to 2.1%(range 0.9-4.7%) after prior administration with antacids. It was postulated that the drug forms chelates of Mg++ or Al++ resulting in reduced absorption. The potential for a similar interaction may also exist for norfloaxacin, although the reviewer is not aware of any related investigations. Coadministration of norfloxacin and antacids containing magnesium and aluminum(even possibly calcium) should be discouraged until definitive data is available. It should be noted that in the above study the exact time of administration of antacids relative to ciprofloxacin dosing is unclear.

Another concern related to the above is absorption of norfloxacin in the elderly, who characteristically have a higher gastric pH and often are achlorhydric. Based on the pH solubility profile of norfloxacin, it is predicted that dissolution will be retarded in the pH range 6-9. The mean (S.D.) percent of a single dose recovered in the urine over 24 hours in an elderly population(age 67-74 yrs) was 22.3 %(S.D. 6.9) and ranged from 10.5 to 29.4%(ref #19, Martin). This contrasts with mean percents of 27-32 observed in younger subjects reported by other investigators based on urinary recovery to time infinity(#15,18,21). Even if absorption in the elderly differs from that of younger patients the clinical significance of this observation is not known at this time.

Bioequivalence

Reference #21 - Zinny(single dose x-over, 400 mg Kyorin vs 400 mg MSD)

Because Kyorin and MSD used different manufacturing methods to produce norfloxacin tablets, a bioequivalency study using products produced by both processes was conducted. IT SHOULD BE NOTED THAT THE MSD PRODUCT USED IN THIS STUDY IS DIFFERENT FROM THE PROPOSED MARKET IMAGE TABLET.

The following results were obtained,

	ANOVA	Power*	% w/in 75/75-125	Other
AUC	NS	85.6	----	
Cmax	NS	75.4	12/20 = 60 %	2 1-Sided Hyp Accept H1: Bio Equivalent
Tmax	Sig (P LT 0.05)			2 1-Sided Hyp Accept Ho: Not BE

* 20 % diff, alpha = 0.05

Based on the above results, it is concluded that the MSD and Kyorin tablets have equivalent extents of absorption. The Cmax for the two products were not statistically significantly different(1.56 +/- 0.48-Kyorin, 1.54 +/- 0.42ug/ml-MSD), however, the power for this evaluation was 75.4% and 75/75-125 Ratio Evaluation was 60 % within 75-125% of the reference product(Kyorin). A statistically significant difference(P LT 0.05) in mean Tmax was observed(1.35 +/- 0.43 hrs-Kyorin vs 1.07 +/- 0.37 hrs-MSD). It is concluded that the rate of absorption is similar(but not statistically equivalent) for the MSD and Kyorin products.

AN ACROSS STUDY COMPARISON OF CMAX, TMAX, AUC AND URINARY EXCRETION FROM A 400 MG DOSE FOLLOWS. THIS IS PROVIDED BECAUSE OF THE DIFFERENT FORMULATIONS UTILIZED IN INDIVIDUAL STUDIES.

	mean (S.D.) Cmax (ug/ml)	Tmax (hrs)	AUC*(ug/ml*hr)	% Dose Urinary Recov
Zinny(#16) tab(Kyorin-B), n=25	1.15 (0.41)	1.5 (0.6)	5.7 (2.8) (day 14)	18.9 (8.2) (day 14, 0-12hr)
Ferguson(#15) cap, n=14	1.6 (0.45)	1.1 (0.35)	6.2 (1.8)	31.3 (6.7) (0-48hr)
Zinny(#18) tab(Kyorin-A), n=15	1.5 (0.58)	1.03 (0.35)	7.1 (3.6)	26.5 (9.1) (0-48hr)
Zinny(#21) tab(MSD), n=18	1.54 (0.42)	1.07 (0.37)	6.9 (1.7)	27.0 (8.5) (0-48)

* AUC(0-12) at steady-state for the Multiple Dose study(#16) and AUC(0-infin) for the single dose studies(#15,18,21);

Note that the C_{max} , T_{max} and Urinary Excretion of norfloxacin in study # 16 differs from that in the other studies. The reason for the discrepancy is not apparent. Study #16 lacked a 1.5 hour plasma sampling time that was used in the other 3 studies. This explanation, as well as a decreased rate of absorption, could explain the difference in C_{max} and T_{max} . It could be suggested that the bioavailability (extent of absorption) of Kyorin-B product is less than that of the other products based on urinary excretion data, however, evaluation of AUC values does not support this conclusion. The data in study #16 should be interpreted with caution.

Dose Proportionality

Reference #15 - Ferguson (single rising dose, 200-1600mg, capsule)

Ferguson(#15) administered doses of 200, 400, 800, 1200 and 1600 mg of norfloxacin to 14 subjects in single rising doses. ANOVA evaluation of the dose adjusted AUC(0-infinity) resulted in no significant difference across dose amounts ($p > 0.05$, estimated Power 76%). The firm reported a linear trend between dose and AUC ($p < 0.05$) and stated that a proportional dose-response relationship was observed. A less than proportional increase in C_{max} occurred with the increase in dose. A comparison of the dose adjusted C_{max} values of norfloxacin showed that the 800, 1200 and 1600 mg doses were significantly different ($p < 0.05$) from the 200 mg dose. The time for the peak concentration to occur increased as the dose increased from 200 to 1600 mg. T_{max} at the 1200 and 1600 mg dose was significantly greater ($p < 0.01$) than that after the lower three doses.

It is concluded that dose proportionality across the recommended daily dose range (200 - 1600 mg) exists for AUC. However, C_{max} increases less than proportionally with the increase in dose above 400 mg and may be due to a slower rate of absorption as evidenced by the greater T_{max} at the higher doses.

Pharmacokinetic Parameters/ Linearity

This drug was not administered intravenously, thus information on pharmacokinetic linearity was gleaned by several methods using the data from the Ferguson study(#15). The similarity in the terminal elimination half-life (about 5 hours) after a single 200 mg and 1600 mg oral dose is consistent with linear elimination of drug at the concentrations observed. Some information is obtained by comparing AUC and dose. Assuming "F" is constant across the single dose range 200 to 1600 mg, the linearity between dose and AUC is consistent with a linear elimination process. Additionally, the percent of the dose administered that is excreted in the urine as parent drug is constant across the single dose range 200-1600 mg. In conclusion, the data is consistent with linear pharmacokinetic disposition up to the observed clinical concentration of approximately 3.5 ug/ml.

Pharmacokinetic Parameters

Adults(#18,21) - See "BIOEQUIVALENCE" Section Above For Cmax, Tmax, AUC & Urinary Excretion Comparison.

Adults (#15), capsule, n=14

Parameter	200 mg	400 mg	800 mg	1200 mg	1600 mg
Cmax - Serum (ug/ml)	0.8 0.2	1.6 0.5	2.4 0.5	3.3 1.0	3.8 1.2
Tpk - Serum (hr)	1.1 0.4	1.1 0.3	1.4 0.4	2.0 1.0	1.9 0.5
<u>EFFECTIVE T1/2*</u> (hr)	2.2 0.2	2.2 0.2	2.3 0.2	2.4 0.2	2.5 0.2
Renal Cl (ml/min)	mean 313.4 S.D. 55.0	319.6 50.0	305.8 92.3	290.8 50.2	308.5 39.8

* This values represents the "effective half-life for accumulation" as determined by the sponsor for a dosing interval of 6 hours.

Elderly (#19), n=6

	Mean	S.D.	Range
Cl Renal(ml/min)	= 154	15.7	127 - 174
Plasma* T 1/2 alpha(hr)	= 1.2	0.32	0.7 - 1.5
T 1/2 beta(hr)	= 5.6	2.1	3.2 - 8.7
Effective T 1/2 (hr) For Accumulation** (harmonic mean)	= 3.9	--	3.5 - 4.4

* based on 2-COM with 1st order absorption and elimination, ESTRIP program. Values for Cl & Vol were not reported.

** for a dosing interval of 8 hours

Protein Binding

It is reported that protein binding measured by ultrafiltration using pooled human serum at a concentration of 2.5 ug/ml was 13.8%(Vol 2.41, pg III-00327). Negligible binding to serum protein was reported at a drug concentration above 20 ug/ml.

Probenecid Effects

The excretion of norfloxacin with and without coadministration of 1 Gm of probenecid was investigated in 5 healthy volunteers in a crossover designed study(Shimada, et al, Antimicrob. Agents Chemother., 23(1):1-7, 1983). In the presence of probenecid the renal clearance of norfloxacin decreased from a mean(+/- S.D.) of 334.9(62.4) to 163.6(18.8) ml/min. The urinary recovery of unchanged norfloxacin decreased from a mean(S.D.) 28.0(+/- 15.5) % of the dose administered to 13.9(+/- 4.7) % when norfloxacin was given with probenecid as compared to control(Table 3 of this review). The renal clearance of norfloxacin was 2.4-3.4 times greater than the creatinine clearance

when norfloxacin was administered alone, compared to 1.2-1.5 times greater during coadministration of probenecid and norfloxacin. Probenecid had little effect on the mean plasma concentrations of norfloxacin (Figure 3 of this review). Because the data was quite variable and results for individual subjects were not provided any possible trends in plasma concentrations were not observed. It cannot be concluded that coadministration of probenecid does not effect norfloxacin concentrations.

Metabolism/Elimination

Reference # 9 - Ozaki (single dose, 200 or 1600 mg tablet)

Reference # 15 - Ferguson (single rising-dose, 200-1600 mg capsule)

24 hour urinary excretion - Study #9

<u>Dose</u>	Parent	M-1	M-2	M-3	M-4	M-5	Total**
	(% of administered AM-715 units)						
200 mg PO, SD (N=3)	26.6 (9.0)	5.1 (0.8)	1.5 (0.4)	0.33 (0.15)	0.5 ---	0.7 (0.1)	34.7 (9.4)
% of total recovered in urine	76.7	14.7	4.3	0.9	1.4	2.0	
1600 mg PO, SD (N=4)	23.0 (8.0)	3.6 (0.7)	0.57 (0.25)	0.15 (0.06)	0.05 (0.04)	0.14 (0.06)	27.5 (8.8)
% of total recovered in urine	83.6	13.1	2.1	0.5	0.2	0.5	

M-4 consists of M-4(1) & M-4(2) which could not be separated under study conditions.

48 Hr Urine Recovery - Study #15

Unchanged Parent

Urine Recovery* 29.9 %
(1.9)

*(mean of 200, 400, 800, 1200, 1600mg doses; N = 14 at each dose)

It is reported that no conjugates of norfloxacin or its metabolites were detected in urine (Vol 2.145, pg VII-00013, summary)

Fecal Recovery - Study #18(Zinny) & #21(Zinny)

	% Dose
24-48 hrs Specimen collection	30.0*

* Based on antimicrobial activity, thus includes parent and metabolite activity

Norfloxacin is recovered in urine and feces after oral administration to humans. Of drug recovered in the urine (parent and metabolites), approximately 80% represents unchanged parent compound. Approximately 30-35% of the dose administered is recovered in the urine over 24-48 hours as parent (25-30%) and metabolites (4-8%). Fecal recovery over 24-48 hours accounts for approximately 30% of the administered dose. Limited evidence suggests that biliary excretion of parent and metabolites also occurs. In a meeting with representatives of the firm on January 10, 1986, it was suggested by the firm that the remaining 35-40% of the drug not accounted for in urinary and fecal recovery is believed to be bound to feces. The firm later indicated that fecal inactivation of norfloxacin is possible and submitted supportive literature references (submission dated 02/14/86). This would cause underestimation of drug recovery from fecal specimens assessed with microbiological assay techniques.

Renal Insufficiency

Reference # 20 - Asscher (single dose, 400 mg MSD tablet)

The disposition of a single, oral, 400 mg dose of norfloxacin was studied in 18 patients with varying degrees of renal dysfunction. A statistically significant difference in AUC(0-infinity) and % Urinary Recovery was observed overall. No significant difference in Cmax and Tmax was observed (P Greater than 0.2). Significant pairwise comparisons of AUC(0-inf) and % Urinary Recovery are below.

Parameter	Overall	Significant Pairwise Comparisons
Uri Recov(% Dose)	p LT* 0.0001	I,II vs III p = 0.0002 I,II vs IV p = 0.0001
AUC(0-infinity)	p = 0.03	I vs III p = 0.004 II vs III p = 0.04 I vs IV p = 0.06

* - LT = less than, GT = greater than
 Group I - CrClr GT 100 ml/min/1.73 meters squared
 Group II - CrClr 31-80 ml/min/1.73 meters squared
 Group III - CrClr 10-30 ml/min/1.73 meters squared
 Group IV - CrClr LT 10 ml/min/1.73 meters squared

Generally, the greatest differences in AUC and Urinary Recovery are observed in subjects with ClCr less than 30 ml/min/1.73 meters squared (Groups III & IV). It is recommended by the firm that the regular dose be administered QD rather than BID in patients with ClCr less than 30 ml/min/1.73 meters squared. It should be noted that the lowest ClCr in Group II was 46 ml/min and no subjects between 28 and 46 ml/min/1.73 msqd were enrolled in this study. It is unclear whether the above recommended cutoff for a dose change should include patients in this range. A conservative recommendation is to use approximately 45 ml/min/1.73 meters squared as a cutoff value. In all cases, monitoring of norfloxacin levels is indicated in renal failure patients receiving long term therapy to insure adequate antimicrobial activity without excessive dosing.

Special Population - Elderly

Reference # 19 - Martin

The disposition of a single 400 mg dose of norfloxacin was studied in six, healthy, elderly subjects with a ClCr greater than 70 ml/min/meters squared. The percent of the dose recovered in the urine as parent compound was 22.3 %, a value lower but comparable to that observed in younger subjects (approx. 30 %). The renal clearance of norfloxacin in this group of subjects was 154 ml/min., compared to approximately 300 ml/min in younger subjects (#15). Despite this difference it appears that dose adjustment is not necessary in elderly subjects with ClCr greater than 70 ml/min/1.73 meters squared.

VII ANALYTICAL METHODOLOGY

Assay methodology employed and comments follow each study listed below.

Ref 9(Ozaki) - HPLC with detection via fluorophotometric analyzer for urine and plasma samples. This assay lacks adequate sensitivity with plasma samples for use in clinical studies. Limits: 1-2 ug/ml for AM-715 (parent drug) and metabolite M-1, 0.5-1 ug/ml for other metabolites

Ref 12(Kumasaka) - antimicrobial activity measured via paper disc method employing E. Coli. Validation of assay methodology was not provided. The results of the study were not utilized for reasons other than lack of assay documentation.

The following studies employed similar methodology--HPLC with uv detection (urine) and fluorescence detection (plasma). Documentation of assay specificity, sensitivity and reproducibility was provided.

Ref 15(Ferguson) - MSD (plasma) & T Jefferson (urine)

Refs 16 & 17 (Zinny) - MSD

Ref 18(Zinny) - MSD; antimicrobial activity in stool specimens & rectal swabs was quantitated by Dr. S Landsman of SUNY-Downstate Med School.

Ref 19(Martin) - MSD, assay cited in JPS 73(1);99-102, 1984, "Quantitation of Norfloxacin, a New Antibacterial Agent in Human Plasma and Urine by Ion-Pair Reverse-Phase Chromatography", Pauliukonis, et al(Ref # 2, vol 2.145, pg VII-00065).
Ref 21(Zinny) - MSD; antimicrobial activity in stool specimens & rectal swabs was quantitated by Dr. S Landsman of SUNY-Downstate Med School.

The following is a summary of results of a bioassay procedure for norfloxacin. The procedure is published in Eur J Clin Microbiol, 2(3):249-252, June 1983.

Ref 1(Huber) - MSD(plasma, urine, tissue); A disk-diffusion bioassay procedure employing *Klebsiella pneumoniae* ATCC 10031 was developed. The assay sensitivity(when incubated at 28 degrees C) was reported to be 0.2 ug/ml. Urine and serum standard curves were similar. Bioassay values in urine were comparable to those obtained by HPLC.

VIII COMMENTS(For Labeling and For Reviewed BA/PK Studies)

1. The following comments pertain to labeling and the proposed package insert in vol. 2.145, pg VII-00186.

a. pg 3 - "The effective half-life...is 3-4 hours". The mean(harmonic) values reported by Ferguson(ref # 15) range from 2.2-2.5, and those by Zinny(ref #18) 3.0-3.3. Individual values exist outside these ranges. Reporting 2-4 hours is probably more representative of the data, however, 2.5-3.5 is probably more exact. Whenever effective half-life for accumulation is reported the corresponding dosing interval used to calculate the effective half-life should also be reported. Since the value of effective half-life for accumulation is different for QD, BID and TID dosing, and each patient will not necessarily receive the same regimen, several values for effective half-life for accumulation should be provided in the package insert. The reviewer is concerned that the concept "effective half-life for accumulation" is unfamiliar to practitioners and needs an explanation when used. The conventional "elimination half-life"(about 5 hours) needs to be included in the package insert.

b. pg 4 - "In healthy elderly...renal function". Criteria for entry into the Martin study(Ref #19) was CrCl greater than or = to 70 ml/min/1.73 meters squared. This should be the basis of the recommendation in the labeling rather than normal renal function based on age.

c. pg 5 - "Disposition of the drug...creatinine clearance greater than 30 ml/min/1.73 meters squared". Although the limits for GFR used by Asscher(Ref #20) in Group II were 31 to 80 ml/min, no data was obtained in subjects with a measured GFR between 31 and 46 ml/min. The mean(+/- S.D.) GFR value in group II was 54.5(14.6). The drastic difference in AUC and Urinary Recovery observed between Group II and III may be due to failure to enroll subjects

representative of the entire GFR range in Group II. Thus, extrapolation of the results of this study to the GFR range 31-46 should be done with caution. It is recommended that approximately 45 ml/min be used in the package insert as the critical value for dose adjustment in patients with renal impairment.

d. pg 5 - "Norfloxacin is eliminated...and renal excretion". It is useful to specify the major route of elimination of norfloxacin. The data suggest that renal elimination of parent drug is the major route of elimination and metabolism of norfloxacin is minor. The extent of biliary excretion is unclear, however, a biliary concentration of 5 ug/ml was measured 1-2 hours after a 200 mg single dose. This information should be included in labeling.

e. pg 5 - "Within 24 hours of drug...of lesser antimicrobial potency." Insert 'in the urine' between the words 'recovered' and 'as', to clarify the statement.

f. pg 5 - "Two to three hours...200 mcg/ml or more...in the urine". Inspection of table 15-16 of this review(Ferguson, Ref #15) shows that 8 of 13 subjects(61 %) had urinary concentrations below 200 mcg/ml during the 2-3 hour urinary collection period. However, a concentration of 200 mcg/ml or greater was observed during either the 0-1, 1-2 or 2-3 hour urine collection period after the dose in 9 of 14 subjects(64 %). The data is variable and the information provided should reflect this. If excretion of drug is independent of urine flow, then the concentration of drug in the urine will vary with urine flow. Thus, the urine concentrations observed in fluid loaded subjects will be comparable to urine concentrations in fluid loaded patients.

g. pg. 13 - "Coadministration of probenecid does not...drug diminishes".

Based on the study provided, it cannot be concluded that coadministration of probenecid does not effect norfloxacin concentrations. The data was quite variable and the results for individual subjects were not provided.

h. pg 15 - "When a 200 mg dose...nursing mothers...in human milk". Additional information obtained in this investigation follows. At various times after administration of a 200 mg single oral dose, norfloxacin was detected in umbilical cord serum(0.1-0.5 ug/ml) at the time of delivery and amniotic fluid samples(0.18-0.92 ug/ml). However, drug concentration in the blood of neonates after delivery was below the limits of detection(approximately 0.1 ug/ml). It should be noted that human milk samples were only obtained from 1 to 6 hours after the dose.

i. pg 20 - "In patents with apparently normal renal function...greater than 30 ml/min/1.73 meters squared". Concern is expressed over the 30 ml/min/1.73 meters squared value used as the critical point for dose adjustment. See comment c. above in this section.

j. Labeling should include a caution against coadministration of norfloxacin with antacids until evidence demonstrating lack of an interaction resulting in decreased absorption is available.

k. Because of the effect of pH on the solubility of norfloxacin, the effect of food on the proposed marketed product needs investigation. For labeling purposes, administration of norfloxacin with food should be discouraged as a precaution until definitive data is available.

l. Labeling should include specific instructions to maintain a good fluid intake in all patients to prevent crystallization of drug in the urinary tract. Even greater emphasis on the potential for developing crystalluria with resulting complications should be stated in the package insert section "Overdosage". Maintaining adequate hydration should be directed toward this potential problem.

2. Each of the following comments pertain to the specific study referenced with the comment.

Reference #9

1. Biliary excretion data was obtained in only 1 patient. Raw data was not provided. The concentration of AM-715 reported in bile was 5 ug/ml. It is unclear how concentrations of metabolites M-3 thru M-5 in bile were determined. Based on the lower limits of quantitative determination reported by the firm, the concentrations implied by the report are lower than the limits given if ● ug/ml is the highest concentration observed for AM-715. Little can be concluded from the data presented.

2. The less than 100% recovery observed is consistent with incomplete urinary collection, elimination via other routes, incomplete GI absorption of drug and/or incomplete recovery of drug using the stated analytical methods.

3. The formulation and/or lot number of the tablet dosage form utilized in this study was not provided.

4. Age and weight of the patient with gallstone disease was not provided. Exclusion/inclusion criteria for volunteers was not provided.

Reference #12

1. The usefulness of the data in this pilot study is questioned. Urine and blood samples were collected for a period of 8 hours after dosing. It is possible that sample collection was incomplete, as the elimination half-life of norfloxacin is approximately 5 hours. A trend is observed in the data, however, the ability to extrapolate the results to the general population is limited, at best. The formulation and source (Kyorin vs MSD) of the product used in this study was not provided.

2. Validation of assay methodology was not provided.

3. For mean C_{max} in urine, the firm reported a value of 320.0 ug/ml. It appears that 320.0 is the result of using a 0-2hr urine concentration of ● ug/ml rather than the 6-8hr urine concentration of ● ug/ml in patient Y.K. If this subject is atypical then none of his values should be used. unacceptable. Total AUC(0-infinity) was used by the reviewer in the comparison of AUC across the dose

strenghts. However, it should be pointed out that Total AUC was estimated(not measured directly) using the measured renal clearance. It was concluded by the reviewer that Total AUC was calculated by dividing $X_u(\infty)$ by Renal Clearance.

2. C_{max} of MK0366 in serum dose not increase proportionately with increasing dose across the single-dose range 200 to 1600 mg(see table 15-6 of this review).

3. Subjects were fluid loaded in this study. Subjects received 250 ml of water 1 hour prior to dosing, 250 ml with dose administration, and 250 ml at 1, 2, 4, 6, and 8 hours post-dosing(total of 1750 ml over 9 hours). Fluids were subsequently permitted ad libitum.

4. The firm should have stated the lower limits of the assay for plasma samples and provided data on the specificity in plasma.

Reference #15

1. The usefulness of AUC(0-8) hours is limited because the remaining portion of the total AUC increases from approximately 18% to 31% as the dose increases from 200 mg to 1600 mg. Excluding 30% of the total AUC from the 0 to 8 hour AUC values used in the comparison is unacceptable. Total AUC(0-infinity) was used by the reviewer in the comparison of AUC across the dose strenghts. However, it should be pointed out that Total AUC was estimated(not measured directly) using the measured renal clearance.

2. C_{max} of MK0366 in serum does not increase proportionately with increasing dose across the single-dose range 200 to 1600 mg(see table 15-6 of this review).

3. It appears that an increasing trend in the value of "effective half-life for accumulation" occurs with an increase in dose. The firm concluded that the effective half-life is independent of dose.

4. The firm should have stated the lower limits of the assay for plasma samples and provided data on the specificity in plasma.

Reference # 16

1. In general, the data in this study should be used with caution because of the extrapolations and estimations made by the sponsor in the calculation of AUC(0-12), C_{min} values and obtaining urinary excretion data. These issues are discussed below in parts A, B, and C.

A. It is reported that the area under the plasma concentration-time curve(AUC) from 0 to 8 hours was measured directly by the sponsor using the trapezoid method. The remaining area through 12 hours was estimated using renal clearance or the norfloxacin half-life or measured directly using a log-linear trapezoidal approximation. Renal clearance was estimated from corresponding increments of urinary recovery and (AUC) for norfloxacin. It is unclear why the area under the curve from 8 to 12 hours was estimated rather than measured directly when plasma samples were obtained at 12 hours in all subjects and measurable values were reported in almost all of the subjects(see table 16-4 of this review). There is no need to estimate the area from 8 to 12 hours when it can be measured directly. The reviewer calculated AUC(0-12), when used, by the trapezoidal method. AUC values reported by the sponsor should be used with caution.

B. It is reported that blood samples for determination of Cmin after the second drug dose on days 1, 6 & 13, were actually drawn 30 minutes ahead of schedule. Plasma concentrations for these determinations were extrapolated to the end of the dosing interval using individual estimates of norfloxacin half-life.

C. The urinary excretion data in this study is inconsistent with that observed in other studies reviewed. The percent of the norfloxacin dose administered that was excreted over 12 hours on days 7 & 14 (under steady state conditions) was 17.7 and 18.9 %, respectively, in this study by Zinny (Ref #16). In addition, the mean Cmax appears to be lower, and Tmax longer than that in other studies. The urinary excretion data in this study contrasts with 25-30% of a single 400 mg dose excreted in the urine over 48 hours reported in other studies. This discrepancy could suggest reduced bioavailability of the Kyorin-B product utilized by Zinny compared to the other formulations studied. However, this suggestion is not supported by the plasma AUC data for the various studies. An across-study comparison of mean Cmax and Tmax (after the first dose of the multiple dose study), AUC and urinary recovery follows. Because of the inconsistencies in the data from this study (#16), the results should be interpreted with caution.

Mean*(S.D.)	Cmax (ug/ml)	Tmax (hrs)	AUC**(ug/ml*hr)	% Dose Urin Recov
Zinny(#16) tab(Kyorin-B), n=25	1.15 (0.41)	1.5 (0.6)	6.7 (2.8) (day 14)	18.9 (8.2) (day 14, 0-12hr)
Ferguson(#15) cap, n=14	1.6 (0.45)	1.1 (0.35)	6.2 (1.8)	31.3 (6.7) (0-48hr)
Zinny(#18) tab(Kyorin-A), n=15	1.5 (0.58)	1.03 (0.35)	7.1 (3.6)	26.5 (9.1) (0-48hr)
Zinny(#21) tab(MSD), n=18	1.54 (0.42)	1.07 (0.37)	6.9 (1.7)	27.0 (8.5) (0-48)

* 400 mg dose compared;

** AUC(0-12) at steady-state for the Multiple Dose study(#16) and AUC(0-infin) for the single dose studies(#15,18,21);

2. It is unclear whether or not the timing of meals relative to dosing is consistent for each dose. The protocol on page VII-00739, vol 2.147, says the following; "Volunteers will be fasting since midnight of the day prior to initial dosing (which should take place at approximately 0800 hours) and may resume a normal diet at lunchtime (approximately 3 to 4 hours after dosing...The subsequent dose of medication will be taken at 2000 hours, and no food shall be consumed from 1 hour before dosing until 1 hour after dosing". Ideally, food should be avoided 2 hrs before and 4 hours after the dose is given to satisfy fasting conditions. It is unclear whether or not patients fasted before each 0800 hour dose or only before the first dose of the 14 day treatment period. If subjects fasted only before the first dose, then fasting or nonfasting conditions for subsequent 0800 doses is not specified. It appears that subjects

received the first 0800 hour dose under fasting conditions, subsequent 0800 hour doses under unspecified conditions, and the 2000 hour dose regularly under less than ideal conditions. The significance of this depends on whether or not the presence of food effects the absorption characteristics of norfloxacin.

3. Subjects were fluid loaded in this study. Subjects received 250 ml of water 1 hour prior to dosing, followed by 250 ml of water with dose administration. Subjects were instructed to maintain a good fluid intake and to consume 250 ml of water every 2 hours after the dose up to 4 hours after the first dose each day.

Reference #17

1. The data in this study should be interpreted with caution because of the small number of subjects(4).

2. It is unclear whether or not the timing of meals relative to dosing is consistent for each dose. Subjects fasted overnight before starting the study and were instructed to avoid food 1 hour before to 1 hour after subsequent doses. The reviewer recognizes the restraints that TID dosing puts on attempts to ensure fasting conditions. The significance of inconsistent dosing conditions depends on whether or not the presence of food effects the absorption characteristics of norfloxacin.

2. Patients were instructed to drink 250 ml of water 1 hour prior to dosing, 250 ml with administration of the dose, and 250 ml every 2 hours postdosing up to 4 hours after the first dose of the day. Subjects were encouraged to maintain a good fluid intake.

Reference #18

1. It should be noted that patients were fluid loaded during each treatment of the study(1440 ml of water over an 8 hour period).

2. The dosing interval that corresponds to the effective half-life should be stated whenever values for effective half-life are reported.

Reference #19

1. Subjects were fluid loaded in this study. Subjects received 750 ml of water(including 150 ml with the dose) over a 4 hour period after administration of the drug. Subjects also received 150 ml of water several hours prior to dosing.

2. On pg VII-01272(Vol 2,148) of the biopharmaceutics Report, it is predicted that norfloxacin plasma levels should accumulate by approximately 32% on an 8-hour dosing regimen and by 13% on an 12-hour dosing regimen. The reviewer agrees with the value 32% but not with the 13% reported. The accumulation half-life for 12-hour dosing will differ from that calculated with 8-hour dosing. The accumulation fraction of 1.13 for 12 hour dosing was calculated using the effective half-life calculated for 8 hour dosing. The actual accumulation fraction for 12 hour dosing is probably less than 1.13.

Reference #20

1. Subjects were fluid loaded in this study. Subjects received 850 ml of water over a 4 hour period after dose administration(including 250 ml with the dose). Subjects were also instructed to take 250 ml of water upon rising the morning of the study, which begun at 0800.

2. Most patients in this study were also taking other medications during the study. The effect of these drugs on the disposition of norfloxacin is not known. Thus, the results of this study must be interpreted with caution.

3. Although the stated range of GFR in Group II is 31 to 80 ml/min, 5 of 6 subjects had a GFR greater than 46. The mean (+/- S.D.) GFR for subjects in Group II is 54.5 (14.6). Subject #6 had a GFR of 31 ml/min but was excluded in the evaluation of Renal Clearance, Urinary Recovery and AUC because of "questionable urinary recovery". Thus, no data was obtained in subjects with a measured GFR greater than 28 ml/min and less than 46 ml/min in this study. Extrapolation of the results of this study to this GFR range should be done with caution.

Reference #21

1. It should be noted that patients were fluid loaded (received 1440 ml of water over an 8 hour period) during each treatment of the study.

VII Comments (con't)

3. The following comment pertains to the Biopharmaceutics Summary, section D.(1) Metabolism in volume 2.145.

References 8 and 11 contain supportive metabolism data in animals. The values presented in the summary section are inconsistent with the data in the corresponding reference. It appears as if the individual study results were combined although the two studies measured different parameters. The discrepancy is not large, yet it is recommended that information on drug metabolism in animals be obtained from the individual studies submitted rather than from the Biopharmaceutics Summary section.

4. The following are general comments.

a. The sponsor investigated 400 mg BID in a multiple dose study (ref #16, Zinny). The regimen of 400 mg TID was utilized in clinical study #66 (Zinny ref #17), however, pharmacokinetic data was obtained in only 4 subjects. The extent of accumulation with TID dosing can be predicted using a linear system and basic pharmacokinetic principles (1-COM). Based on an elimination half-life of 5 hours and an 8 hour dosing interval, C_{min} at steady state should be approximately 1.5 times the C_{min} observed after a single dose (Gibaldi M, Biopharmaceutics and Clinical Pharmacokinetics, 3rd Ed, 1984).

IX CRYSTALLURIA ANALYSIS (see attachment I of this review)

The Division of Biopharmaceutics was asked to comment on the possibility that norfloxacin might precipitate into crystals in the human kidney and cause obstruction there or elsewhere in the urinary tract.

A Solubility

As shown in Figures 1 and 2, the solubility of norfloxacin in urine varies greatly with pH, being lowest between 6 and 10. Because urinary pH normally ranges from pH 6-8, the solubility of norfloxacin over this range is the focus of this discussion. Figure 2 shows the relative solubility of norfloxacin in urine at 25 and 37 degrees centigrade.

In animal studies of norfloxacin, crystalluria consisted of the dihydrate and magnesium salts of norfloxacin. It is unclear at this time whether the parent compound and/or the above salts should be the focus of discussion of the possibility of crystallization in humans. Swanson, et al (ref below), observed "drug crystals" in freshly voided urine specimens collected after administering single oral 1200 and 1600 mg doses to human volunteers. Crystals were not found at lower doses (200-800 mg). Urine pH of specimens with crystals was between 7 and 7.8. Drug was administered with only 250 ml of water under fasting conditions.

B Pharmacokinetic Predictions

Using data in the Ferguson (ref #15) and Zinny (ref #16) studies, it is possible to do calculations to determine if, on a theoretical basis, drug crystals of the parent compound norfloxacin are likely to be formed.

Assumptions/Conditions;

1. a worst case scenario is most useful
2. high single doses and/or the recommended multiple dose regimen
3. maintenance of a constant plasma concentration
4. solubility of norfloxacin in urine at 25 and 37 degrees C.

- I. Using the urinary excretion rate, compare the concentration of drug in the kidney with the solubility of the drug.

The ratio, $(A) \frac{\text{drug excretion rate}}{\text{rate of urine formation}}$, estimates the concentration of drug in the kidney tubules.

The solubility of norfloxacin was obtained from the pH solubility profile in urine.

Swanson B, et al. 1983. Norfloxacin Disposition After Sequentially Increasing Oral Doses. Antimicrob. Agents Chemother. 23(2):284-288.

A. Single dose evaluation

1610 mg PO

$$Cl_{renal} \times C_{max} = \frac{\text{maximum excretion rate}}{\text{(introduction of drug to kidney)}}$$

$$300 \text{ ml/min} \times 4.0 \text{ ug/ml} = 1200 \text{ ug/min (1.2 mg/min)}$$

(Consistent with actual values reported by the firm in table 15-14 of the BA review)

In normal individuals, the rate of urine formation(B) is approximately 1 ml/min(Guyton, Textbook of Medical Physiology, 6th Ed., 1981).

$$\frac{A}{B} = \frac{1200 \text{ ug/min}}{1 \text{ ml/min}} = 1200 \text{ ug/ml (1.2 mg/ml)}$$

1200 mg PO - $C_{max} = 3.0 \text{ ug/ml}$,
Excretion rate = 900 ug/min(0.9 mg/min)

Ratio A/B = 0.9 mg/ml

B. Multiple dose regimen,

	<u>Cmax</u>	<u>Est'd Drug Exct'n Rate</u>	<u>Ratio A/B</u>
400 mg BID	2.0 ug/ml	600 ug/min(0.6 mg/min)	0.6 mg/ml
400 mg TID	3.0 ug/ml*	900 ug/min(0.9 mg/min)	0.9 mg/ml

* predicted value(actual value in 4 subjects was approx. 2.0 ug/ml)

COMPARISONS WITH SOLUBILITY OF NORFLOXACIN IN URINE

Regimen	Ratio A/B	Solubility(mg/ml)				
		25	C	37	C	
1600 mg SD	1.2 mg/ml	pH 6 :	3.2	OK	10.0	OK
		pH 7 :	0.75	Exceeded	1.5	OK
		pH 8 :	0.6	Exceeded	1.9	OK
1200 mg SD	0.9 mg/ml	pH 6 :	3.2	OK	10.0	OK
		pH 7 :	0.75	Exceeded	1.5	OK
		pH 8 :	0.6	Exceeded	1.9	OK
400 mg BID	0.6 mg/ml	pH 6 :	3.2	OK	10.0	OK
		pH 7 :	0.75	OK	1.5	OK
		pH 8 :	0.6	Borderline OK	1.9	OK
400 mg TID	0.9 mg/ml	pH 6 :	3.2	OK	10.0	OK
		pH 7 :	0.75	Exceeded	1.5	OK
		pH 8 :	0.6	Exceeded	1.9	OK

II. It is well documented that the crystalluria can be avoided by assuring an adequate rate of urine flow (Gibaldi, Biopharmaceutics and Clinical Pharmacokinetics, 3rd Ed., 1984). Thus, the minimum rate of urine flow may be calculated by dividing the excretion rate of drug by its solubility at a given pH.

$$\text{Minimum Rate of Urine Flow} = \frac{\text{(A) Excretion Rate of Drug}}{\text{(B) Solubility in urine at a given pH}}$$

At TEMP 25 C

	pH 6	pH 7	pH 8
B(solubility)	= 3.2 mg/ml	= 0.75 mg/ml	= 0.6 mg/ml
Ratio	A/B	A/B	A/B
S.D. - 1600 mg Cmax = 4 ug/ml A* = 1.2 mg/min	0.375 ml/min	1.6 ml/min	2 ml/min
S.D. - 1200 mg Cmax = 3 ug/ml A = 0.9 mg/min	0.28	1.2	1.5
M.D. - 400 BID Cmax = 2 ug/ml A = 0.6 mg/min	0.19	0.8	1.0
M.D. - 400 TID Cmax = 3 ug/ml A = 0.9 mg/min	0.28	1.2	1.5

AT TEMP 37 C

	pH 6	pH 7	pH 8
B(solubility)	= 10 mg/ml	= 1.5 mg/ml	= 1.9 mg/ml
Ratio	A/B	A/B	A/B
S.D. - 1600 mg Cmax = 4 ug/ml A* = 1.2 mg/min	0.12 ml/min	0.8 ml/min	0.63 ml/min
S.D. - 1200 mg Cmax = 3 ug/ml A = 0.9 mg/min	0.09	0.6	0.47
M.D. - 400 BID Cmax = 2 ug/ml A = 0.6 mg/min	0.06	0.4	0.31
M.D. - 400 TID Cmax = 3 ug/ml A = 0.9 mg/min	0.09	0.6	0.47

* Drug Excretion Rate

C STUDY DOSING CONDITIONS

The possibility of crystalluria decreases if a water diuresis is created. A water diuresis of up to 8 ml/min urine output can occur within 1 hour of ingesting 1000 ml of water. EXAMINATION OF EACH BIOAVAILABILITY STUDY REVIEWED SHOWS THAT PATIENTS WERE FLUID LOADED TO VARIOUS DEGREES. Below is a summary of dosing conditions.

- Ref #15(Ferguson) - 1750 ml of water over a 9 hr period
- Ref #16(Zinny) - 1000 ml of water over a 5 hr period
- Ref #17(Zinny) - 1000 ml of water over a 5 hr period
- Ref #18(Zinny) - 1440 ml of water over an 8 hr period
- Ref #19(Martin) - 750 ml of water over a 4 hr period
- Ref #20(Asscher) - 1100 of water over a 5 hr period
- Ref #21(Zinny) - 1440 ml of water over a 9 hr period

It is standard practice that the drug under investigation be administered under conditions identical to those proposed for the general patient population. If conclusions about the safety of norfloxacin are drawn from these investigations then they should be limited to patients with a similar state of hydration. It is recommended that dosing conditions(hydration status) used in clinical studies be evaluated for additional information and consider the need to include in the package insert instructions to patients to ensure a sufficient fluid intake.

D CONCLUSION

Based on the above pharmacokinetic predictions, it appears that crystallization should not be a problem with the parent compound norfloxacin when using a solubility curve produced at 37 degrees centigrade(body temperature). Mixed results are obtained from a solubility curve produced at 25 degrees centigrade(room temperature). It should be emphasized that the above manipulations are theoretical and their limitations are demonstrated by the observations of crystals after large single doses(i.e. 1200 & 1600 mg) as reported by Swanson(1) et al. These predictions should be used in conjunction with actual clinical data to make conclusions about the safety of this drug with regards to crystalluria. The fluid loaded conditions used in the BA studies complicate interpretation of the clinical results of these studies for resolving safety issues. The above manipulations and conclusions do not apply to the dihydrate, magnesium or other salts of norfloxacin.

Concern is expressed about the potential for formation of crystals under abnormal conditions commonly seen. Some of these conditions are periods of low urine formation(e.g. dehydration), alterations in urine pH which effect renal tubular secretion and the solubility of the drug, and pathological conditions that alter kidney physiology. The labeling should include specific instructions to maintain a good fluid intake in all patients to prevent crystallization of drug in the urinary tract.

In conclusion, at pH 6, it appears that crystallization should not be a problem with the parent compound norfloxacin. The results are less clear at pH 7 and 8. However, since a worst case scenario was used, crystallization of norfloxacin at pH 7 is possible but unlikely. It should be emphasized that the above manipulations are theoretical and are likely to favorably change (crystallization less likely) if a norfloxacin solubility curve created at 37 degrees C (body temperature) is used rather than a curve produced at 25 degrees C (room temperature). The fluid loaded conditions used in the BA studies complicate interpretation of the clinical results of these studies for resolving safety issues. The above manipulations and conclusions do not apply to the dihydrate, magnesium or other salts of norfloxacin.

X OVERALL APPLICATION CONCLUSION

The Division of Biopharmaceutics concludes that the data submitted by the sponsor satisfies the requirements set forth in 21 CFR, part 320 describing bioavailability and bioequivalence requirements.

The data is summarized below.

1. Based on AUC, dose proportionality across the single dose range 200-1600 mg exists for norfloxacin. However, the C_{max} of norfloxacin does not increase proportionately with the increase in a single dose beyond 800 mg. After a 400 mg single dose (capsule), mean C_{max} was approximately 1.6 ug/ml (T_{max} about 1 hour), whereas C_{max} was approximately 3.8 ug/ml (T_{max} occurs at about 2 hours) after a single 1600 mg dose. The mean C_{max} observed after a single 400 mg dose (MSD direct compression tablet) was 1.5 ug/ml with a corresponding mean T_{max} of about 1 hour.
2. The MSD and clinically tested Kyorin tablet products have equivalent extents of absorption. Based on mean T_{max}, the rate of absorption of the MSD formulation is faster than the Kyorin formulation (1.07 vs 1.35 hrs).
3. Relative to a solution, the mean ratio of dose adjusted AUC(0-infinity) for a 400 mg tablet (Kyorin) to a solution administered as a single dose is 0.99 +/- 0.49. Statistical equivalence was not demonstrated.
4. Norfloxacin is recovered in urine and feces after oral administration to humans. About 30-35 % of the dose administered is recovered in the urine over 24-48 hours as parent (25-30 %) and metabolites (4-3 %). Fecal recovery accounts for approximately 30 % of the administered dose but is probably much greater. Fecal recovery is accounted for by incomplete GI absorption, biliary excretion and/or other factors. Thus the fraction of the administered dose absorbed orally is at least about 30-35 %.
5. The elimination half-life of the parent drug norfloxacin is about 5 hours. The "effective half-life for accumulation" for 8 hour dosing intervals is about 3 hours. The renal clearance of norfloxacin measured in adults with normal renal function is about 300 ml/min.
6. Because of the effect of pH on the solubility of norfloxacin, the effect of food on the proposed marketed product needs investigation.
7. Coadministration of norfloxacin and antacids should be discouraged in the labeling because of the possibility of complexation resulting in a decrease in absorption.

8. The dose of norfloxacin needs to be adjusted in the elderly and patients with renal dysfunction. Guidelines provided by the firm need clarification.
9. Protein binding of norfloxacin measured by ultrafiltration is about 14 %.

XII RECOMMENDATION

The Division of Biopharmaceutics recommends that the biopharmaceutic/pharmacokinetic data submitted to support NDA 19-384(the 400 mg tablet) be accepted.

HFN-815 should consider comment # 1(a-1) of section VIII above (pertaining to labeling) when evaluating the package insert. It is recommended that comment # 1 be forwarded to the sponsor.

The Division of Biopharmaceutics recommends that the proposed dissolution specification be accepted; Q= 80 % in 30 minutes using USP Method II at 50 rpm in 750 ml of 0.05 M sodium acetate buffer (pH 4.0), at 37 degrees C. The sponsor should use the USP Acceptance Table criteria for this specification.

When the sponsor conducts a food-effect study or seeks future approval of the 200 mg norfloxacin tablet, the Division of Biopharmaceutics recommends that the sponsor contact the Division of Biopharmaceutics to discuss the type of in-vivo study required for approval.

Gene D. Mason Pharm.D. 4/18/86

Gene D. Mason, Pharm.D.
Pharmacokinetic Evaluation Branch

RD Initialed by John Hunt 4/18/86

FT Initialed by C.T. Viswanathan, Ph.D. CTV 4/28/86

cc: Orig. NDA 19-384, HFN-815(2), HFN-815(Tabor), HFN-226(Mason), Chron, Drug and FOI files

GDM:gdm:6063x: 2/15/86

Appendix A

Individual Study Results

Study Reference: #9; Vol. 2.145, pg VII-234

Title: Study of the Metabolism of AM-715 in Humans by Means of High-Performance Liquid Chromatography

Investigator/Site: Ozaki T, Uchida H, Irikura T
normals - Department of Internal Medicine, Oyama City Hospital
patient - Department of Surgery, Kawasaki Municipal Hospital

Objective: To elucidate the distribution ratio of metabolites of AM-715 in the serum and urine of healthy volunteers and in the bile of one patient with choledocholithiasis following oral administration of AM-715 tablets.

Design:

- I. 7 normal adult(35-45 years old) males, 50 - 75 Kg in body wt.
 - 3 subjects received - 200 mg AM-715 Tablets, with a cup of water (three hours after a "light meal")
 - 4 subjects received - 1,600 mg AM-715 Tablets, with a cup of water (three hours after a "light meal")
- II. 1 patient with choledocholithiasis disease(?age & wt)
received - 200 mg AM-715 Tablets,

Hydration: Drug was administered with a cup of water

Specimens:

Normals -
200 and 1600 mg dose groups
Urine(intervals) - 0 to 2.5, 2.5-5, 5-9 and 9-24 hours after dosing
1600 mg group
Blood : 0.5, 1, 2, 3, 4, 6, 8 and 16 hours after dosing

Patient - Bile was collected for one to two hours(after the dose).

Analytical Methods:

Methods used to treat serum, urine and bile were provided. HPLC with fluorophotometric detection was used for separation and detection of parent and metabolites.

Limits of quantitative determination:

AM-715 & M-1 ug/ml
M-2 thru M-5 ug/ml

Tables:

- Table 9-1 -Serum concentrations of AM-715 after PO 1,600 mg
- Table 9-2 -Urine concentrations of AM-715 and metabolites post PO 200 mg
- Table 9-3 -Urine concentrations of AM-715 and metabolites post PO 1,600 mg
- Table 9-4 -Urinary excretion of AM-715 and metabolites post PO 200 mg
- Table 9-5 -Urinary excretion of AM-715 and metabolites post PO 1,600 mg
- Figure 9-3 -Metabolite pattern in urine
- Figure 9-1 -Chemical structure of parent and metabolites
- Figure 9-2a,b,c -Chromatograms and calibration curves

Results:

Serum

With the 1,600 mg dose, only unchanged parent drug could be detected in serum because the serum concentration of metabolites M-1, M-2, M-3, M-4 and M-5 was below the detection limits of the assay.

Urine (% of dose*)

Species	mean (S.D.)	200 mg (N=3)	1,600 mg (N=4)
AM-715 - parent		26.6 (9.0)	23.0 (8.0)
range		20.5 - 37.0	17.9 - 34.8
M-1 metabolite		5.1 (0.8)	3.6 (0.7)
range		4.6 - 6.0	3.1 - 4.6
M-2 metabolite		1.5 (0.4)	0.57 (0.25)
range		1.1 - 1.8	0.3 - 0.9
M-3 metabolite		0.33 (0.15)	0.15 (0.06)
M-4 metabolite		LT** or = 0.5	0.05 (0.04)
M-5 metabolite		0.7 (0.1)	0.14 (0.06)
Total - 24 hours		34.7 (9.4)	27.5 (8.8)
range		28.4 - 45.5	21.7 - 40.5

* % of administered AM-715 units

** LT = less than

It is stated that the results after treatment with beta-glucuronidase-arylsulfatase did not differ from those determined quantitatively in the urine which did not undergo enzyme treatment. It was concluded that the drug and its metabolites were all unconjugated when excreted in the urine.

Bile - The concentration of AM-715 found in the bile one to two hours after a 200 mg dose was reported as 5 ug/ml. It is reported that the concentrations of M-1, M-2, M-3, M-4 and M-5 observed relative to AM-715 are 13%, 10%, 1%, 2% and 2%, respectively. No raw data was provided.

Study Reference: # 12; vol 2.145, pg VII-00309

Title: Fundamental Study of AM-715

Investigator/Site: Kumasaka Y, Nakahata H, Imamura K, Takebe K
The Third Department of Internal Medicine
Hirosaki University, School of Medicine

Objective: 1) To investigate antibacterial activity and 2) to compare serum and urine levels after a single 200 mg dose.

Design: Single dose, cross-over

5 healthy male adults received (dosage form, formulation & source not identified)

- a. 200 mg non-fasting (meal composition not specified)
- b. 200 mg fasting

Hydration: Administration of drug with water was not stated.

Specimens:

Serum - 0.5, 1, 2, 4, 6 and 8 hours after dosing

Urine(intervals) - 0 to 2, 2-4, 4-6, and 6-8 hours after administration

Analytical Methods: Norfloxacin levels were determined with the paper disc method employing E. Coli NIHJ JC-2 as the test bacterium. Standard curves were prepared with human serum for serum level determination and pH 7.0 M/15 phosphate buffer was used for the urinary level determinations. Validation of assay methodology was not provided.

Tables:

Table 12-1 : Individual urinary excretion and recovery of AM-715

Table 12-2 : Individual concentrations of AM-715

Figure 12-1 : Urinary excretion displayed graphically

Results:

	Urinary Excretion (ug/ml)			% Recovery	
	0 - 2H	2-4H	4-6H	6-8H	(0-8 hrs)
Fasting mean	290	162	102	104	28.3
(N=5) S.D.	250.6	70.3	45.4	41.5	8.19
range					
Non-Fasting	182	135	72	53.2	19.9
(N=5)	109.5	54.8	44.2	24.1	3.2

	Plasma		Urine		mean
	Cmax	Tmax	Cmax*	Tmax	
	ug/ml	hours	ug/ml	hours	
Fasting mean (N=5) (S.D.)	0.46 (0.13)	1-2	334.4** (209.2)		0-2hrs(550 ug/ml): 2 subs 2-4hrs(208 ug/ml): 2 subs 6-8hrs(156 ug/ml): 1 sub
Non-Fasting (N=5)	0.32 (0.16)	1-2	206.0 (80.5)		0-2hrs(257 ug/ml): 3 subs 2-4hrs(129 ug/ml): 2 subs

* The value reported represents the mean value of the highest concentration observed for the 4 urine collection periods in each subject.

** The reviewer calculated this value. The firm reported a value of 320.0 ug/ml. It appears that 320.0 is the result of using a 0-2hr urine concentration of 84 ug/ml rather than the 6-8hr urine concentration of 156 ug/ml in patient Y.K. If this subject is atypical then none of his values should be used.

Firm's Conclusion:

1. The levels in serum and urine in the non-fasting state were slightly lower than those in the fasting state, but they are of a sufficient concentration to produce antibacterial activity and should have not influence on the clinical effectiveness.

Study Reference: # 15; vol 2.146, pg VII-00450, study #1

Title: A Double-Blind, Single Rising-Dose, Placebo-Controlled Study to Determine the Safety, Tolerability, Serum Profile, and of Doses of Placebo, and 200, 400, 800, 1200, and 1600 mg of MK-366 Administered Orally to Healthy Male Volunteers.

Investigator/Site: Roger Ferguson, M.D., Clinical Pharmacology Unit
Thomas Jefferson University Hospital
Philadelphia, PA 19107

Objective: 1) To determine the serum profile and urinary excretion of MK0366 when given in single rising doses from 200 to 1600 mg orally in man and 2) to assess the safety and tolerability of the drug when administered under double blind conditions.

Design: Single-dose, rising-dose regimen with two placebo treatments randomly interspersed in the scheme, double-blind, volunteers

Dosing: Each volunteer received one treatment per period and each treatment period was separated by a 6 day washout period. Below are the treatments administered in order of increasing dose. Each subject received all treatments. The two placebo treatments were randomly interspersed in the scheme.

Treatment A: 1 x 200 mg MK0366 capsules, 7 x 200 mg placebo
Treatment B: 2 x 200 mg MK0366 capsules, 6 x 200 mg placebo
Treatment C: 4 x 200 mg MK0366 capsules, 4 x 200 mg placebo
Treatment D: 6 x 200 mg MK0366 capsules, 2 x 200 mg placebo
Treatment E: 8 x 200 mg MK0366 capsules
Treatment F: placebo - 8 x 200 mg placebo
Treatment G: placebo - 8 x 200 mg placebo

Subjects will fast from midnight on the day prior to dosing and until 3 hours after dose administration.

Hydration: 250 ml of water 1 hour prior to therapy, 250 ml with dose administration, followed by 250 ml at 1, 2, 4, 6, and 8 hours post-treatment.

Subjects: 14 healthy male volunteers ranging in age from 21 to 31 years participated in the study. Volunteers were required to be within +/- 10 % of IBW for age and height based on Metro Life Ins Co Stat Bull No 40, 1959. Volunteers were judged normal on basis of medical history, physical examination, clinical laboratory data, and standard ECG. Exclusion Criteria: Hx of renal or hepatic disease, any major systemic disorder including cardiac and GI disorders, ingestion of drugs (including alcohol and salicylates) within 7 days of study, history of drug or food allergy, inclusion in a drug study within 3 months of the present study.

Concurrent Medications: None Allowed from 7 days prior to study until completion of the study.

Specimens:

Blood - 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after dosing.
Urine(intervals) - minus 1 to 0(control), 0-1, 1-2, 2-3, 3-4, 4-6, 6-8, 8-12, 12-24, and 24-48 hours after dosing.

Analytical Methods: Specimens were analyzed via HPLC methodology with fluorescence(plasma) or uv(urine) detection. Representative standard curves and chromatographs for urine and plasma were provided. Urine specimens with a concentration less than 10 ug/ml were reassayed using a 10 ml sample volume instead of a 5 ml volume. The lower limit of sensitivity for 10 ml urine samples was 10 ug/ml. Urine specimens with a concentration above 10 ug/ml were diluted 10 in water and reassayed as before. Specificity of the assay with respect to metabolites was established by comparing the retention time of MK-366 with that of several metabolite standards. Using the methods described to prepare urine samples, it is stated that none of the metabolites of MK-366 interfere with assay of the parent drug.

Results:

Parameter	200 mg	400 mg	800 mg	1200 mg	1600 mg	ANOVA	Power
48 Hr Ur Rec (%dose)	32.4 6.2	31.3 6.7	28.7 6.4	29.0 7.3	28.0 9.7	N.S.	0.97
Renal Cl mean (ml/min)	313.4	319.6	305.8	290.8	308.5	N.S.	1.0
S.D.	55.0	50.0	92.3	50.2	39.8		
AUC(0-inf) (ug/ml*hr)	3.4 0.8	6.2 1.8	12.2 2.6	19.1 5.4	24.1 8.0		
Cmax - Serum (ug/ml)	0.8 0.2	1.6 0.5	2.4 0.5	3.3 1.0	3.8 1.2		
Tpk - Serum (hr)	1.1 0.4	1.1 0.3	1.4 0.4	2.0 1.0	1.9 0.5		
EFFECTIVE T1/2* (hr)	2.2 0.2	2.2 0.2	2.3 0.2	2.4 0.2	2.5 0.2		

* This values represents the effective half-life for accumulation as determined by the firm for a dosing interval of 8 hours.

Tables:

- Table 15-1 : Serum concentrations of MK-366 after 200 mg
- Table 15-2 : Serum concentrations of MK-366 after 400 mg
- Table 15-3 : Serum concentrations of MK-366 after 800 mg
- Table 15-4 : Serum concentrations of MK-366 after 1200 mg
- Table 15-5 : Serum concentrations of MK-366 after 1600 mg
- Table 15-6 : Individual Cmax and Tmax values
- Table 15-7 : Individual Effective Half-life values
- Table 15-8 : Individual 8-hour AUC values
- Table 15-9 : Individual Total AUC(0-infin) values
- Table 15-10 : Urinary excretion of MK-366 after 200 mg
- Table 15-11 : Urinary excretion of MK-366 after 400 mg
- Table 15-12 : Urinary excretion of MK-366 after 800 mg
- Table 15-13 : Urinary excretion of MK-366 after 1200 mg
- Table 15-14 : Urinary excretion of MK-366 after 1600 mg

Table 15-15 : Concentration of MK-366 in urine after 200 mg
Table 15-16 : Concentration of MK-366 in urine after 400 mg
Table 15-17 : Concentration of MK-366 in urine after 800 mg
Table 15-18 : Concentration of MK-366 in urine after 1200 mg
Table 15-19 : Concentration of MK-366 in urine after 1600 mg
Table 15-20 : Individual 48-hr Urinary Recovery
Table 15-21 : Individual Cumulative Renal Clearance of MK-366
Table 15-22 : Mean MK-366 Biopharmaceutic Parameters
Figure 15-1 : Mean MK-366 concentrations displayed graphically
Figure 15-2 : Mean Cumulative Urine Excretion

Firm's Conclusions:

1. Increasing the MK-366 dose does not effect the total absorption of the drug although absorption is somewhat delayed at higher dose levels.
2. The effective serum half-life of MK-366 is independent of the dose.
3. The elimination of MK-366 from serum following single oral doses of 200, 400, 800, 1200 and 1600 mg doses is linear.
4. The AUC increases in proportion to the dose.
5. Average renal clearance is 300 ml/min with no apparent change over the range of doses administered.
6. Urinary recovery of unchanged MK-366 is 30% in 48 hours regardless of the dose.
7. MK-366 was well tolerated by the volunteers.

Study Reference: # 16 ; vol 2.147, pg VII-00627, study # 45

Title: A Double-Blind, Multiple Dose, Crossover Study to Investigate the Safety and Tolerance of Norfloxacin (MK0366) Versus Placebo

Investigator/Site: Miguel A Zinny, M.D.
Medical and Technical Research Associates
Clinical Unit
410 South Huntington Avenue
Jamaica Plain, MA 02194

Objective: 1) To investigate the safety and tolerability of these multiple doses of norfloxacin with respect to clinical, hematologic, neurologic and biochemical parameters and 2) to determine the plasma levels and urinary excretion following multiple oral doses of norfloxacin in healthy adult males and females.

Design: multiple dose, randomly assigned crossover with placebo, double-blind, healthy volunteers

Dosing: Oral administration using the following scheme,

1 x 400 mg norfloxacin tablet(Kyorin-B), q 12 hours x 14 days
1 matching norfloxacin image placebo tablet, q 12 hours x 14 days

Day 1 thru 14 - Treatment Period 1
Day 15 thru 21 - washout
Day 22 thru 35 - Treatment Period 2
Day 37 - Sampling Day

Volunteers fasted since midnight of the day prior to the 0800 hour dose until 3-4 hours after dosing and avoided food 1 hour before until 1 hour after the 2000 hour dose(see comment # 2). Time of dosing is referred to as zero (0) hour.

Hydration: Treatments were given with 250 ml of water, followed by 250 ml every 2 hours up to 4 hours post first dose of the day.

Concurrent Medications: None allowed from 7 days prior to study until its completion. See table 16-9 for a listing of volunteers who recieved medications other than the study drug and reasons for use.

Subjects: 27 (24 males, 3 females) healthy volunteers entered the study, however, 23 (20 males, 3 females) completed the study. Three volunteers were discontinued because of adverse clinical effects and 1 volunteer did not ingest one placebo dose. Subjects ranged in age from 19-50 years old, were to weigh within 15% of IBW for ages and height according to the Metro Life Ins Co Stat Bull #40, 1959, and judged normal on basis of medical history, physical examination and clinical laboratory screening.

Exclusion Criteria: hx of, or lab evidence of renal, hepatic, cardiac, pulmonary or hematologic disease, hx of epilepsy, neurologic disease, psychiatric disturbance, emotional instability or ophthalmologic conditions, ingestion of drugs of any kind(including alcohol) in the 7 days preceding initiation of the study, pregnant or lactating women, inability to complete the study.

Specimens:

Blood

Days 1 and 22

1 hour prior to dosing

Days 1, 2*, 7, 14, 22, 23*, 28 and 35

0 (prior to dosing), 1, 2, 3, 4, 6, 8, and 12 hours after dosing

Urine(intervals)

Days 1 and 22

collected for a one hour period prior to dosing

Days 1, 2*, 7, 14, 22, 23*, 28 and 35

0-1, 1-2, 2-4, 4-6, 6-8, and 8-12 hours after dosing

* urine and blood collections on Days 2 and 23 were only collected during period 2.

Analytical Methods: Plasma and urine samples were shipped to MSD for analysis by Drug Metabolism Department. Plasma samples were analyzed for norfloxacin by a HPLC method utilizing fluorescence detection. It is reported that this method is specific for norfloxacin and the daily standard curve is linear from a range of [redacted] ug/ml of control plasma. The results for the validation of this method for plasma samples, quality controls, and a representative curve is given in Table 16-10 and Figure 16-2. Urine samples were analyzed for norfloxacin by a HPLC chromatographic system utilizing a spectrophotometric ultraviolet detector. It is reported that this method is specific for norfloxacin and the daily standard curve is linear from a range of [redacted] ug/ml of control urine. The results for the validation of this method for urine samples, quality controls, and a representative standard curve is given in Tables 16-11 and Figure 16-3.

Tables:

Table 16-1 - Volunteer Demographic Data

Table 16-2 - Individual Urinary Excretion of norfloxacin

Table 16-3 - Individual renal Clearance

Table 16-4 - Individual Plasma concentrations of norfloxacin

Table 16-5 - Individual Peak Plasma concentrations of norfloxacin

Table 16-6 - Individual Tmax values

Table 16-7 - Individual Cmin concentrations

Table 16-8 - Individual AUC(0-12hrs) values

Table 16-9 - Other medications taken by volunteers

Table 16-10 - Assay validation in plasma

Table 16-11 - Assay validation in urine

Figure 16-1 - Mean norfloxacin plasma concentrations displayed graphically

Figure 16-2 - Plasma calibration curve

Figure 16-3 - Urine calibration curve

Results:

		(Post 1st dose on...)	Day 1	Day 2	Day 7	Day 14
Renal Clearance (ml/min)	mean		276.6	330.4	239.6	266.0
	S.D.		112.0	39.0	39.5	78.6
	(n)		(9)	(3)	(8)	(9)
Cmax (mcg/ml)	mean		1.15	1.18	1.27	1.35
	S.D.		0.41	0.55	0.50	0.39
	(n)		(25)	(13)	(26)	(25)
Tmax (hr)	mean		1.5	2.2	2.2	1.4
	S.D.		0.6	1.6	2.0	0.6
	(n)		(25)	(13)	(26)	(25)
AUC(0-12hr)*	mean		5.23	5.69	6.57	6.52
	S.D.		2.02	1.99	2.99	2.86
	(n)		(23)	(13)	(25)	(25)

Cmin** (mcg/ml) following dose number...

Dose #	1 (Day 1)***	2 (Day 2)	3 (Day 2)	2 (Day 7)	13 (Day 7)	26 (Day 14)	27 (Day 14)
mean	0.12	0.20	0.15	0.20	0.17	0.23	0.18
S.D.	0.09	0.11	0.05	0.14	0.11	0.21	0.13
(n)	(25)	(13)	(13)	(26)	(26)	(25)	(25)

* In the majority of the subjects on each day, a portion of the total AUC(0-12) was estimated (not measured directly) using norfloxacin half-life or renal clearance(see Comments section of this review).

** It is reported that blood samples for determination of Cmin after the second drug dose on days 1, 6 & 13, were actually drawn 30 minutes ahead of schedule. Plasma concentrations for these determinations were extrapolated to the end of the dosing interval using individual estimates of norfloxacin half-life.

*** Day of active treatment, not study day

Firm's Conclusions:

1. Results indicate that norfloxacin, when administered twice daily to volunteers with normal renal function, produces similar (0.15 - 0.18 g/ml) serum levels 12 hours after dosing on the 2nd, 7th, and 14th day of administration. Steady state is established between 2 and 7 days of drug administration (400 mg q 12 hours).
2. Analysis of the safety profile indicated that norfloxacin at a dose of 400 mg q 12 hours is safe and well tolerated.

Study Reference: # 17 ; vol 2.147, pg VII-00856

Title: A Double -Blind, Multiple Dose, Five-Day Crossover Study to Investigate the Safety and Tolerance of Norfloxacin(MK-366) Versus Placebo

Investigator/Site: Miguel A Zinny, M.D.
Medical and Technical Research Associates, Inc.
408 South Huntington Ave
Jamaica Plain, MA 02194

Objective: 1) To evaluate the safety and tolerability of norfloxacin at the highest daily dosage schedule(1200 mg) used in clinical trials. 2) to determine the serum levels and urinary excretion this dosage regimen would produce in those volunteers sampled(four subjects).

Design: multiple dose, double blind, random crossover

Dosing: oral administration of either A. or B., followed by the other Tx.

- A. 400 mg q 8 hours, norfloxacin X 5 days; Kyorin-B product
- B. placebo X 5 days

A seven day washout period separated treatments. Subjects fasted since midnight of the day prior to initial dosing(AM) and resumed a normal diet at approximately 3-4 hours after the morning dose. No food was consumed from 1 hour before to 1 hour after dosing for subsequent doses.

Hydration: 250 ml of water 1 hour prior to dosing, 250 with administration of the dose, and 250 ml every 2 hours postdosing up to 4 hours after the first dose of the day. Subjects were encouraged to maintain a good fluid intake.

Concurrent Medications: None allowed(including alcohol) from seven days prior to the initiation of the study until its completion.

Subjects: Although 26 healthy male(25) and female(1) volunteers between the ages of 19 and 40 years of age participated in the study, PLASMA SAMPLES FOR PHARMACOKINETIC ANALYSIS WERE OBTAINED IN ONLY FOUR SUBJECTS.

Selection criteria included weight within 15% of IBW for age and height(M.I.C.S.B, 1959) and in good health on basis of medical Hx, physical examination and clinical laboratory values. Exclusion criteria: hx of renal, hepatic, cardiac, pulmonary or hepatic disease, hx of epilepsy, neurologic disease, psychiatric disorders, and pregnant or lactating females.

Specimens:

Blood - Days 1, 2 and 5 of both periods

-1, 0(prior to dose), 1, 2, 3, 4, 6 and 8 hours after dosing.

Urine(intervals) - Days 1, 2 and 5 of both periods

-1 to 0(day 1 only), 0-1, 1-2, 2-4, 4-6 and 6-8 hours

Analytical Methods: Plasma and urine samples were analyzed by MSD for norfloxacin by a HPLC method utilizing fluorescence detection. Urine samples were analyzed by HPLC methodology specific for norfloxacin utilizing ultraviolet spectrophotometric detection. A representative standard curve and results of quality controls were provided.

Data Analysis: AUC was estimated using the trapezoid method through 8 hours. Renal clearance of norfloxacin was estimated from corresponding increments of urinary recovery and AUC.

Tables:

- Table 17-1: Individual Plasma Concentrations
- Table 17-2: Individual Cmax & Tmax values
- Table 17-3: Individual AUC Values
- Table 17-4: Individual Cmin Values
- Table 17-5: Urine Concentrations
- Table 17-6: Individual Urinary Recovery
- Table 17-7: Individual Renal Clearance
- Figure 17-1: Mean Plasma Concentrations

Results:

		Day 1(Dose 1)	Day 2(Dose 4)	Day 5(Dose 13)
Cmax (ug/ml)	mean	1.5	1.73	1.49
	S.D.	0.4	0.33	0.38
	range			
Tmax (hrs)	mean	1.3	1.8	1.5
	S.D.	0.5	1.0	0.6
	range			
AUC(0-8hrs) (ug*hr/ml)	mean	6.34	7.79	7.04
	S.D.	0.88	2.36	1.97
Renal Cl (ml/min)				
Sub # 102		216.9	---	171.3
Sub # 103		---	146.4	161.2

Firm's Pharmacokinetic Conclusions:

1. Too few volunteers (4) participated in the pharmacokinetic phase of this study to demonstrate to what degree norfloxacin accumulation might occur on a 400 mg q8h regimen. It appeared, however, that norfloxacin concentrations in plasma are lowest after the first dose and reach peak concentrations after the second day. Plasma concentrations did not increase thereafter.

Study Reference: #18; vol 2.147, pg VII-00993, study #13

Title: An Open, Triple Crossover Study to Compare the Bioavailability of Norfloxacin (MK0366) Following Oral Administration of 200 mg and 400 mg Market Image Tablets of MK0366 With a 400 mg Solution of MK0366 Given by Gavage in Healthy Volunteers.

Investigator/Site: Miguel Zinny, M.D.
Medical and Technical Research Assoc., Inc.
Needham, Massachusetts 02194

Objective: The Biopharmaceutic objective of this study was to compare the serum concentrations and urinary excretion profiles of norfloxacin following PO administration of 200 mg and 400 mg market image tablets of MK0366 and 430 mg solution of the drug given by nasogastric intubation. The clinical objectives included determining the effects of norfloxacin on stool Enterobacteriaceae and other gram-negative bacilli as well as determining antimicrobial activity in stool specimens.

Design: Open, single dose, randomized triple-crossover

Dosing: Each of the volunteers received each of the following treatments,

- Tx A: 200 mg market image norfloxacin tablet(Kyorin-A formulation)
- Tx B: 400 mg market image norfloxacin tablet(Kyorin-A formulation)
- Tx C: 430 mg norfloxacin solution, given via a nasogastric tube
(The protocol originally specified 400 mg, however, the average assayed solution dose was 430 mg.)

Dosing occurred after a 10 hour fast. Normal meals were resumed 4 hours after each treatment. No other medications(including alcohol) was allowed from 1 week before study start until study completion.

Hydration: 8 ounces(240 ml) of water was given with the dose, followed by 8 ounces at 1, 2, 4, 6 and 8 hours after each treatment.

Subjects: 15 healthy male volunteers 21 years of age or older and within +/- 10% of their IBW for height and age according in the Metropol. Life Insur. Co. Stat Bull No. 40, 1959, participated in the study. Subjects were judged normal on basis of medical history, physical examination and clinical laboratory data. Exclusion Criteria: Hx of renal or hepatic disease, major systemic disorders including cardiac, GI and neurologic disorders, drug taking(including alcohol and salicylates) in the preceding seven days, hx of drug or food allergy and involvement in a drug study during the preceding 3 months.

Specimens:

Blood - 0(before dosing), 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours after dosing.

Urine(intervals) - minus 1 to 0(control), 0 to 1, 1-2, 2-3, 3-4, 4-6, 6-8, 8-12, 12-24 and 24-48 hours.

Rectal Swabs(for bacterial culture and bioassay determination) - before, 12 and 24 hours after dosing.

Stool(in 400 mg tablet group) - prestudy and up to 48 hours after dosing.

Analytical: Serum and urine samples were assayed for MK0366 by MSD Research Laboratories. Serum samples were analyzed by HPLC methodology specific for MK0366 utilizing fluorescence detection. Urine samples were analyzed by HPLC methodology specific for MK0366 utilizing ultraviolet spectrophotometric detection. Antimicrobial activity in stool specimens and rectal swabs were determined by Dr. Sheldon Landsman at The Infectious Disease Laboratory of the SUNY-Downstate Medical School.

Data Analysis: AUC(0-8 hrs) was measured using the trapezoid or sline method and extrapolated to infinity using renal clearance. Renal clearance of norfloxacin was estimated using corresponding increments of urinary recovery and AUC. The relative bioavailability of norfloxacin (tablet vs solution) was calculated using the method of Kwan and Till (submission ref #24) as modified by Hwang and Kwan (submission ref #25). The effective serum half-life was estimated from AUC(0-8) and AUC(0-infinity) as described in submission reference #23.

Results:

Parameter		430 mg SOLN	200 mg TAB	400 mg TAB
<u>Urin Recov-48 hr-Unadjusted for dose (mg)</u>				
Total	Mean	121.91	52.15	105.14
	S.D.	28.96	18.63	36.22
	N	14	13	14
% Dose	Mean	28.38	25.45	26.48
	S.D.	6.74	9.08	9.12
	N	14	13	14
<u>AUC-Dose adjusted up to 430 mg (mcg/ml*hr)</u>				
(0-8 hr)	Mean	6.04	5.57	5.44
	S.D.	1.90	2.36	2.65
	N	15	15	15
<u>Total Estimated(0-infin)</u>				
	Mean	7.58	6.96	7.1
	S.D.	2.08	3.23	3.56
	N	14	13	14
<u>Cmax-Dose adjusted up to 430 mg (mcg/ml)</u>				
	Mean	1.87	1.60	1.62
	S.D.	0.66	0.66	0.62
	N	15	15	15
<u>Tmax (hrs)</u>				
	Mean	0.70	1.03	1.03
	S.D.	0.37	0.35	0.35
	N	15	15	15
<u>Effective Half-Life (hr) - 8 hour dosing interval</u>				
	Harmonic Mean	2.99	3.26	3.22
	95% C.I.	2.63-3.47	2.85-3.81	2.92-3.59
<u>Cum. Renal Clearance (ml/min)</u>				
	Mean	276.37	263.39	299.26
	S.D.	71.31	76.13	94.96
	N	15	15	15

Relative Bioavailability*			
	200 mg Tab/Soln	400 mg Tab/Soln	200 mg Tab/400mg Tab
Mean**	0.89	0.90	1.00
95% C.I.	0.70-1.14	0.72-1.13	0.79-1.26
Power (25% Difference)	0.77	0.78	0.80

* Based on the method of Kwan and Till as modified by Hwang & Kwan (submission references #24 & 25)

** Geometric mean

Relative Bioavailability Based on Ratio of Dose Adjusted AUC(0-infin)		
	200 Tab/200 Soln	400 Tab/400 Soln
Mean Ratio	0.998	0.987
S.D. +/-	0.42	0.49
C.V.	42.1 %	49.6 %
% w/in 75-125%	25% (3/12) 4 Hi, 5 Lo	38.5% (5/13) 3 Hi, 5 Lo

Tables:

- Table 18-1 : Individual 8 hour AUC
- Table 18-2 : Individual Estimates of Total AUC(0-infin)
- Table 18-3 : Individual Cmax concentrations
- Table 18-4 : Individual Effective Half-Life for Accumulation
- Table 18-5 : Individual 48-hour Urinary Recovery
- Table 18-6 : Bioavailability Parameters
- Table 18-7 : Individual Estimates of Relative Bioavailability
- Table 18-8 : Individual Cumulative Renal Clearance
- Table 18-9 : Summary of Bioavailability Parameters

Firm's Conclusions:

1. Norfloxacin is equally bioavailable from the two tablet strengths studied.
2. Bioavailability from tablet formulations was 90% relative to the solution given by NG tube.

Study: Reference #19; Vol 2.148, pg VII-01142

Title: An Open Study to Determine the Pharmacokinetics of a Single Dose of Norfloxacin in the Elderly.

Investigator/Site: Dr. K.B. Martin, R.L. Brown
Bios(Consultation & Contract Research) Ltd.
Bagshot, Surrey, England

Objective: To document the safety and to obtain a pharmacokinetic profile of norfloxacin in healthy elderly subjects after a single 400 mg oral dose.

Design: Single oral dose

Dosing: 400 mg MK-366, PO ; film-coated tablet, MK-366;
formulation # 81-54-62, MSD

Drug was administered after an over-night fast. No food was allowed for 2 hours after the dose, at which time a standard breakfast was served. No medicine was allowed for 72 hours prior to the dose and no alcohol for 24 hours prior to the dose.

Hydration: Drug was administered with 150 ml of water, followed by 150 ml of water("Perrier") at 1, 2, 3, and 4 hours after drug administration. Patients were instructed to consume 150 ml of water upon rising the morning of the study which began at 9:00 a.m.

Subjects: Six, healthy, elderly subjects(2 male, 4 female) between the ages of 67 and 74 years participated in the study. Subjects were reported to be neither grossly overweight nor underweight for their height and build. Basis for determination of normality, inclusion and exclusion criteria were provided. Subjects with a creatinine clearance of greater than or equal to 70 ml/min/1.73 meter squared were included in the study.

Specimens:

Blood - 0(control), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 and 24 hours after the dose.

Urine(intervals) - 0-1, 1-2, 2-3, 3-4, 4-6, 6-8, 8-12, 12-24 hours.

Analytical Methods: Norfloxacin concentration in plasma and urine was assayed at BIOS, LTD. by using HPLC methodology. It is reported that the method is specific and sensitive for norfloxacin and that calibration standards and quality control specimens were processed along with each batch of samples.

Data Analysis: Pharmacokinetic computations were done by Drug Metabolism Department, MSDRL. AUC was estimated using the trapezoid method and extrapolated to infinity using renal clearance. Renal clearance was derived from corresponding increments of urinary recovery and AUC. The effective serum half-life of norfloxacin was estimated according to the method of Kwan, et al(JPS).

Tables/Figures:

Table 19-1 : Individual Urin Recov and Renal Clearance

Table 19-2 : Individual AUC, Cmax, Tmax and Effective T1/2

Table 19-3 : Individual Demographic Data

Figure 19-1 : Mean Plasma Concentration vs Time Curve

Results:

<u>Pharmacokinetic Parameter</u>			
Urin Recov (0-infin)	Mean S.D.	90.5 mg 28.0	N=6
% Dose Recov in Urin		22.3 % 6.9	N=6
Renal Clearance		154 ml/min 15.7	N=6
AUC(0-infin)		9.8 mcg*hr/ml 2.8	N=6
AUC(0-8)		7.5 mcg*hr/ml 2.2	N=6
Cmax		2.0 mcg/ml 0.8	N=6
Tmax		1.3 hr 0.4	N=6
<u>Effective Half-life for Accumulation (8-hour dosing interval)</u>		3.9 hr 0.3	N=6

Firm's Conclusions:

1. Pharmacokinetic parameters indicate elimination of norfloxacin may be slightly reduced in the elderly. This results in small increases in plasma levels and may also result in small increases in drug half-life.
2. Changes in norfloxacin disposition appear attributable to the slightly reduced renal function associated with a normal, elderly population.
3. No alteration of dosing regimen appears necessary for elderly subjects whose renal function is normal for this age group (creatinine clearance greater than or equal to 70 ml/min/1.73 meters squared).
4. A single 400 mg dose of norfloxacin appears safe in healthy, elderly subjects.

Study: Reference #20; vol 2.148, pg VII-01293

Title: An Open Study to Determine Serum Concentrations and Urinary Excretion Profile of a Single Oral Dose of MK-366 in Patients With Varying Degrees of Renal Dysfunction and in Subjects With Normal Renal Function

Investigator/Site: A. William Asscher
Welsch National School of Medicine
Renal Unit-Royal Infirmary
Cardiff, Wales

Objective: 1) To obtain serum concentration and urinary excretion data for a single 400 mg dose of norfloxacin in patients with varying degrees of renal dysfunction and to compare this data with data from subjects with normal renal function. 2) to obtain data for assisting in designing norfloxacin dosage regimens for patients with renal dysfunction. 3) to obtain information on the tolerability and safety of norfloxacin in this patient population.

Design: Open, Single-dose, subjects grouped according to renal function.

Dosing: 400 mg norfloxacin, PO, tablet

Subject Groups: I Healthy subjects with normal renal function
CICr greater than 100 ml/min/1.73 meters squared
II Patients with CICr 31 to 80 ml/min/1.73 meters squared
III Patients with CICr 10 to 30 ml/min/1.73 meters squared
IV Patients with CICr less than 10 ml/min/1.73 meters squared
(patients not on hemodialysis)

Patients fasted for 8 hours prior to dosing. A light snack was allowed 2 hours after the dose followed by lunch 4 hours after the dose.

Hydration: Drug was administered with 250 ml of water, followed by 150 ml at 1, 2, 3, and 4 hours after the dose. Patients were also instructed to consume 250 ml of water upon rising the morning of the study which began at 0800.

Patients: 9 healthy volunteers and 18 patients with varying degrees of renal dysfunction participated in the study. Patients were required to be neither grossly overweight or underweight for height and body build. Criteria for inclusion and exclusion were provided. Subjects with concomitant mild hypertension and stable renal disease were accepted into groups II, III and IV. Subjects were excluded from participating in groups II, III and IV if any of the following conditions were present: 1. A disease, other than renal, which might influence the pharmacokinetics of the study drug, 2. treatment with antibiotics or other drugs which might affect the pharmacokinetics or assay procedure of the study drug.

Specimens:

Blood - 0(pre-treatment), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, and 48 hours after the dose.

Urine(intervals) - 0(pre-treatment), 0-1, 1-2, 2-3, 3-4, 4-5, 5-6, 6-8, 8-10, 10-24, 24-48 and 48-72 hours post dosing. It was noted that sampling times and collection intervals varied somewhat that specified in the protocol and above. Occasionally urine collections were made at intervals such as 0-2, 2-4, 4-6, 6-8, 8-10(or 8-12), 10-24(or 12-24), 24-48 and 48-72 hours.

Analytical Methods: Serum samples were analyzed for norfloxacin by a HPLC method utilizing fluorescence detection. Urine samples were analyzed for norfloxacin by a HPLC method utilizing an ultraviolet detector. It is reported that both methods are specific for norfloxacin and that standards and quality controls were analyzed with the unknown samples.

Data Analysis: AUC was calculated using the trapezoid or spline method and extrapolated to infinity using renal clearance. Renal clearance was estimated using corresponding increments of urinary recovery and AUC. The effective half-life of norfloxacin was estimated from methods of Kwan, et al(reference # 23).

Tables:

- Table 20-1: Individual Demographic Data
- Table 20-2: Individual and Mean Urin Recov, % Dose Exctd & Renal Cl
- Table 20-3: Individual and Mean AUC
- Table 20-4: Individual and Mean Cmax & Tmax
- Table 20-5: Individual and Mean Effective Half-life
- Figure 20-1: Mean Norfloxacin concentration-time profiles

Parameters*	ClCr (ml/min/1.73 meters squared)							
	Group I GT 100		Group II 31 - 80		Group III 10 - 30		Group IV LT 10	
	Mean	N	Mean	N	Mean	N	Mean	N
AUC(0-8h) mcg*hr/ml	5.38 1.93	8	7.62 2.00	5	9.18 2.41	4	7.79 5.31	4
AUC(0-infin)	6.94 2.73	8	9.53 2.47	5	24.01 13.49	4	16.46 14.52	4
Cmax (mcg/ml)	1.51 0.56	9	1.91 0.71	6	1.70 0.43	6	1.70 0.92	6
Tmax (hr)	1.4 0.4	9	1.3 0.4	6	1.8 1.1	6	1.8 1.2	6
Effective T1/2 (hr) (Harmonic Mean); 8 hour dosing interval	3.47	8	3.38	5	6.57	4	6.4	4
Urin Recov(% Dose)	28.2 12.8	8	35.3 9.2	5	6.7 4.1	5	2.4 1.1	4
Renal Cl (ml/min)	297.1 117.4	8	264.5 83.2	5	17.8 4.4	4	14.7 8.4	5

* data taken from Bioanalytical-Biopharmaceutics Report

Statistical Evaluation

Parameter	Overall	Significant Pairwise Comparisons
U:ri Recov(% Dose)	p LT* 0.0001	1,2 vs 3 p = 0.0002 1,2 vs 4 p = 0.0001
Renal Clearance	p LT 0.0001	1,2 vs 3 p = 0.0002 1,2 vs 4 p = 0.0001
Cmax	NS (p GT* 0.2)	
Tmax	NS (p GT 0.2)	
AUC(0-8hr)	NS (p GT 0.2)	
AUC(0-infin)	p = 0.03	1 vs 3 p = 0.004 2 vs 3 p = 0.04 1 vs 4 p = 0.06
Effective t1/2	NS (p = 0.10)	

* - LT = less than, GT = greater than

Firm's Conclusions:

1. Based on the renal elimination rate of MK-366, no change is needed in the MK-366 regimen in subjects whose GFR exceeds 30 ml/min/1.73 meters squared.
2. When GFR is less than or equal to 30 ml/min/1.73 meters squared, the regular dose of MK-366 should be given once a day rather than twice a day.
3. The administered dose of norfloxacin appears to be safe in renally impaired patients.

Study: Reference # 21; vol 2.148, pg VII-01421, study #59

Title: An Open, Two-Way Crossover Study to Compare the Bioavailability of Norfloxacin Following Oral Administration of a 400 mg Original Formulation Tablet of MK0366 with a 400 mg New Formulation Tablet of MK0366 in Healthy Volunteers.

Investigator/Site: Miguel Zinny, M.D.
Medical and Technical Research Assoc., Inc.
Boston, Mass 02130

Objective: a) To compare the plasma concentration profile and urinary excretion of norfloxacin following oral administration of a 400 mg new formulation tablet (MSD direct compression process) of MK0366 and a 400 mg old formulation tablet (Kyorin) of MK0366 and b) to determine the antimicrobial activity found in the stool after oral administration of the 400 mg new formulation tablet.

Design: Open, single dose, randomized, two way crossover

Dosing: Each volunteer will receive,

- A. 400 mg norfloxacin tablet; new formulation (MSD direct compr)
- B. 400 mg norfloxacin tablet; original formulation (Kyorin-B)

Hydration: The dose was given with 8 oz (240cc) of water, followed by another 8 ounces of water at 1, 2, 4, 6, and 8 hours after the dose.

Treatments were separated by a 7 day washout period. Volunteers fasted from 10:00 PM of the night prior to dosing until 4 hours after the dose. No medications were allowed (including alcohol) from one week prior to initiation of the study until its completion.

Subjects: Twenty normal healthy male volunteers between 18 and 40 years of age entered and completed the study. Subjects were to have satisfied inclusion and exclusion criteria.

Specimens:

Blood: 0 (control), 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after dosing.

Urine (intervals): minus 1 to 0 (control), 0-1, 1-2, 2-3, 3-4, 4-6, 6-8, 8-12, 12-24, 24-48 hours.

Stool (only in subjects who received Tx A.): prestudy (control), and all specimens up to 48 hours after drug ingestion.

Analytical Methods: Serum and urine samples were assayed for MK0366 by MSD Research Laboratories. Serum samples were analyzed by HPLC methodology specific for MK0366 utilizing fluorescence detection. Urine samples were analyzed by HPLC methodology specific for MK0366 utilizing ultraviolet spectrophotometric detection. Antimicrobial activity in stool specimens were determined by Dr. Sheldon Landesman at The Infectious Disease Laboratory of the SUNY-Downstate Medical School.

Data Analysis: AUC(0-8 hrs) was measured using the trapezoid or spline method and extrapolated to infinity using renal clearance. Renal clearance of norfloxacin was estimated using corresponding increments of urinary recovery and AUC. The relative bioavailability of norfloxacin (MSD vs Kyorin) was calculated using the method of Kwan and Till (submission ref #24) as modified by Hwang and Kwan (submission ref #25). The effective serum half-life was estimated from AUC(0-8) and AUC(0-infinity) as described in submission reference #23.

Tables:

- Table 21-1 : Individual Plasma concns - Kyorin tablet
- Table 21-2 : Individual Plasma concns - MSD tablet
- Table 21-3 : Individual Cmax concns - Kyorin tablet & MSD tablet
- Table 21-4a : Individual Urine concns - Kyorin tablet
- Table 21-4b : Individual Urine concns - MSD tablet
- Table 21-5 : Individual Total Urin Recov - Kyorin tab & MSD tab
- Table 21-6 : Individual Relative Bioavailability
- Table 21-7 : Individual Cum Renal Cl and Total AUC - Kyorin & MSD Tabs
- Table 21-8 : Mean Pharmacokinetic Parameters - Kyorin & MSD Tabs
- Figure 21-1 : Mean Plasma Conc'n Profiles - Kyorin & MSD Tabs

Results:

Parameter	Kyorin Tab	MSD Tab	ANOVA	POWER
AUC(0-infinity) (mcg/ml*hr)				(20% diff, alpha 0.05)
Mean	7.82	6.94	NS	85.6
S.D.	2.53	1.69		
N	19	18		
Cmax (mcg/ml)				
Mean	1.56	1.54	NS	75.4
S.D.	0.48	0.42		
N	20	20		
Tmax (hrs)				
Mean	1.35	1.07	Sig(P LT 0.05)	
S.D.	0.43	0.37		
N	20	20		
Urin Recov - % of dose*				
Mean	27.9	27.0		
S.D.	8.9	8.5		
N	19	18		
Renal Clearance (ml/min)				
Mean	261.9	270.0		
S.D.	80.7	63.4		
N	20	18		

* Based on administered doses of 412 and 414 mg for the Kyorin and MSD formulations, respectively. Refer to Assay Content of norfloxacin in table "Dosage Form Characteristics", pg VII-01425, vol. 2.148.

Ratio of AUC(0-infin) MSD/Kyorin

Mean Ratio = 0.967
S.D. +/- 0.31
C.V. 32.4 %

% Within 75-125% -- 10/17 = 58.8 % ; 3 HI, 4 Lo

Relative Bioavailability*(New-MSD/Old-Kyorin) as calculated by methods described above.

Geometric Mean	0.94	Power	20% Diff	0.81
N	17		25% Diff	0.99
95% C.I.	0.80 - 1.09			

* values for individual subjects were not provided.

Stool Samples

It is reported that peak norfloxacin activity in the stool occurred approximately 24 hours following ingestion and ranged from 348 to 1916 ug/gm stool.

Firm's Conclusions:

1. The 400 mg norfloxacin tablets formulated by the old Kyorin process and the new MSDRL direct compression process are similarly bioavailable (the new formulation is 94% as bioavailable as the old formulation).
2. Norfloxacin was absorbed faster following the ingestion of tablets manufactured by the new MSDRL process.

Comment: THE MSD PRODUCT UTILIZED IN THIS INVESTIGATION HAS A DIFFERENT COATING THAN THAT OF THE PROPOSED MARKETED TABLET. THE PROPOSED MARKETED TABLET WAS NOT INVESTIGATED IN ANY OF THE BA/PK STUDIES SUBMITTED BY THE FIRM.

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs and Biologics

Review by
1/8/85

Attachment I

Date: April 2, 1985

To: Jerome P. Skelly, Ph.D.
Acting Director, Division of Biopharmaceutics, HFN-220

From: T. Greene Reed, M.D.
Medical Officer, HFN-815

Through: Edward Tabor, M.D. E. Tabor 4/3/85
Director, Division of Anti-Infective Drug Products, HFN-815

Subject: Norfloxacin-induced crystalluria (NDA 19-384)

This request is a follow-up to our Biopharmaceutics Division consultation request regarding norfloxacin, NDA 19-384 from Merck, Sharp and Dohme Research Laboratories which is now under review in this Division. We sent copies of the four volumes which contain pharmacokinetic data, Volumes No. 2.145-2.148, to your Division on March 11, 1985.

In your response to our consultation request, please include your comments regarding the possibility that norfloxacin might precipitate into crystals in the human kidney and cause obstruction there or elsewhere in the urinary tract.

Norfloxacin is an orally absorbed member of the quinolone group of antibacterial agents. Crystalluria has been reported in clinical studies of other members of this class. The presence of drug crystals with one member of this class that was never approved for marketing was so troublesome that several products which would acidify urine in an attempt to increase the drug's solubility were given concomitantly during clinical investigations. Later, the pharmaceutical manufacturer suggested that crystallization occurred after voiding while the urine cooled instead of before voiding within the urinary tract.

In animal studies of norfloxacin, crystalluria, consisting of the dihydrate and the magnesium salts of norfloxacin, occurred in rats at 200 and 600 mg/kg/day doses. Crystalluria occurred in beagle dogs given norfloxacin at 50, 150, and 300 mg/kg/day for 26 weeks but not in the 25 mg/kg/day dose group. The incidence was dose related. Three dogs, one in the 150 mg/kg/day and two in the 300 mg/kg/day dose groups, were found dead or were sacrificed due to urinary obstruction from drug crystals. Since emesis occurred in all dose groups in dogs and occurred frequently after dosing, one cannot be sure what proportion of the dose was retained and absorbed. The crystalluria in dogs and rats was attributed to low solubility of the drug in alkaline urine. Crystalluria decreased when urine was acidified by the administration of ammonium chloride. Drug crystals shaped as sea urchins and/or fine needles were occasionally seen in urine from dogs in each of the drug-treated groups.

Norfloxacin is a new drug entity. We are two months into the 180-day new-NDA time period and the application has high priority.

Theresa Greene Reed

cc Orig NDA 19-384, HFN-815, HFN-815/Reed, HFN-815/Buko, HFN-815/CSO 3585b

21329

*cc: V. K. ...
Review by 1/8/85
Dr. Vert ...
Set up ...
KC: 4/2
Thurs 5/15 2:30*

Correspondence

Reduced Enteral Absorption of
Ciprofloxacin in the Presence of
Antacids

Sir,

Ciprofloxacin, a new quinolone carboxylic acid derivative, has high *in vitro* activity against a wide range of pathogens including members of the family *Enterobacteriaceae* and *Pseudomonas aeruginosa* (1). The pharmacokinetics after oral administration of the drug are characterized by rapid absorption, good diffusion into the extracellular space, and elimination by biliary excretion, hepatic metabolism, glomerular filtration and tubular secretion (2).

In a study in fasting volunteers the absolute bioavailability ranged from 0.63 to 0.77, and the cumulative urinary excretion of unmetabolized drug in 24-hour-urine accounted for approximately 35% of the initial oral dose (2). To assess the effect of antacids on intestinal absorption of orally administered ciprofloxacin, we performed a randomized study in ten healthy volunteers (5 females, 5 males, mean age 30 years, mean body weight 67.5 kg) who were given 500 mg ciprofloxacin orally either in a fasting state or 24 h after administration of the antacid 10 X 600 mg Mg-OH + 900 mg Al-OH (Maalox). Serum and urine concentrations were determined by a bioassay and high performance liquid chromatography. The pharmacokinetic parameters were calculated using an open two-compartment model. Administration of the antacid led to a pronounced decrease of the peak serum concentration from a mean of 1.7 mg/l (range 1.3-2.6 mg/l) after ciprofloxacin alone to a mean of 0.1 mg/l (range 0.06-0.2 mg/l) after ciprofloxacin plus antacid ($p < 0.001$). The time after which the serum concentration peaked was only slightly prolonged (73 ± 13 min versus 87 ± 21 min). The cumulative urinary excretion of unmetabolized ciprofloxacin in 24-hour-urine after ciprofloxacin administered alone accounted for 24% (range 19-34%) of the administered dose as against only 2.1% (range 0.9-4.7%) after prior administration of the antacid.

A possible explanation for the reduced absorption rate of ciprofloxacin administered after the antacid is that Mg⁺⁺ or Al⁺⁺⁺ chelates form. In fact, chelate complexes of the drug with Mg⁺⁺ have been reported to reduce bactericidal concentrations of ciprofloxacin tested in nutrient broth against *Escherichia coli* KL16 (3). In addition, association constants for Mg⁺⁺ complexes of nalidixic and oxolinic acid, analogous substances, were reported to be 3.0 and

3.3 respectively. The diminished absorption of ciprofloxacin seen in our study could be explained by a reduced rate of absorption of the Mg⁺⁺ and Al⁺⁺⁺ ciprofloxacin chelate complexes. To date it has been difficult to assess the significance of the chelates on absorption. Nevertheless, the pronounced effect of antacids on the bioavailability of ciprofloxacin should be considered if both these drugs are administered to a patient. Furthermore, all other new quinolone derivatives should be tested for such interaction with antacid drugs.

G. Höffken

K. Börner

P. D. Glatzel

P. Koepe

H. Lode*

Section for Chemotherapy and Infectious Diseases, Medical Department, Klinikum Steglitz, Hindenburgdamm 30, 1000 Berlin 45, FRG

References

1. Wingender, W., Graefe, K. H., Gau, W., Förster, D., Beerman, D., Schacht, P.: Pharmacokinetics of ciprofloxacin after oral and intravenous administration in healthy volunteers. *European Journal of Clinical Microbiology* 1984, 3: 355-359.
2. Wise, R., Lockley, M., Webberly, M., Deam, J.: Pharmacokinetics of intravenously administered ciprofloxacin. *Antimicrobial Agents and Chemotherapy* 1984, 26: 208-210.
3. Ratcliffe, N. T., Smith, J. T.: Effects of magnesium on the activity of 4-quinolone antibacterial agents. *Journal of Pharmacy and Pharmacology* 1983, 35: 61.

In Vitro Activity of Ciprofloxacin
against Mycobacteria

Sir,

Ciprofloxacin is a new broad-spectrum quinolone derivative with activity against many gram-positive and gram-negative bacterial species. As little is known about its activity against mycobacteria we decided to investigate the antimycobacterial activity of ciprofloxacin in comparison with enoxacin, another quinolone derivative.

One hundred mycobacteria strains were tested for sensitivity to ciprofloxacin and 30 of these strains were also used for the comparative study with enoxacin. The 100 strains consisted of 69 strains of *Mycobacterium tuberculosis*, 12 of *Mycobacterium*

Appendix B

Tables and Figures

1 Page(s)

Redacted

Table 1b

Study 13
Zinny Study 13

Dissolution Profiles - Kyorin Tablet Formula

pH 4 Acetate Buffer, Paddles, 50 RPM

200 mg - Lot 002-B03

15 min 30 min 45 min 60 min

$\bar{x}$ = 68% 98% 101% 100%

400 mg Lot 001-C01

15 min 30 min 45 min 60 min

$\bar{x}$ = 41% 96% 104% 105%

200mg 400mg

Source : Kyorin Kyorin

Study 59 - Dissolution Profiles

Kyorin 400 mg vs Merck 400 mg NOROXIN Tablets

pH 4 Acetate Buffer, Paddles, 50 RPM

Kyorin Formula - Lot 006-C01 (400 mg)

15 min 30 min 45 min 60 min

$\bar{x}$ = 59% 75% 85% 91%

Merck Formula - Lot 020-C017 (400 mg)

15 min 30 min 45 min 60 min

$\bar{x}$ = 98% 99% 99% 99%

Kyorin MSD (blue)

Kyorin MSD-USA

[- "developed for overseas markets" - International Blue]

Dissolution Profiles

Merck NOROXIN Tablets 400 mg (Iron Oxide Colors)

pH 4 Acetate Buffer, Paddles, 50 RPM

Lot 029-C010

15 min 30 min 45 min

$\bar{x}$ = 102% 103% 103%

Lot 029-C012

15 min 30 min 45 min

$\bar{x}$ = 99% 100% 101%

MSD (pink) 029-C010 MSD (pink) 029-C012

MSD-USA MSD-USA

- same composition
- Direct Compression
- "USA-pink"

Table 1b (cont)

<u>Batch No.</u>	<u>Dissolution (30 minutes) †</u>	<u>Average</u>
850261A		90
850261B		90
850449A		93
850449B		96
850450A		94
850450B		90
850514A		94
850514B		96
850638A		94
850638B		95

~~XXXXXXXXXX~~
 NOROXIN Tablets - Final Market Image 400 mg
 Lot 0366 PCT 029-C013
 First Production Demonstration Lot
 † Dissolved

	<u>15 Min.</u>	<u>30 Min.</u>	<u>45 Min.</u>
Mean	100	100	100
Rel. Std. Dev.	2%	1%	2%

Mean	100	100	100
Rel. Std. Dev.	2%	1%	2%

Source :

MSD Italy
 - Direct Compression

MSD - USA
 - Direct Compression
 - USA

Table 2

Identity of All Oral Formulations Used in Clinical Studies of
Norfloxacin Pharmacokinetics and Bioavailability

Study Description	Pivotal (P) or Supportive (S)	Type of Formulations Used	Formulation and Batch Number	Batch Size	Number of Subjects Studied
Single, Rising Dose Study (ref. #15, Study #1)	P	Capsule (200 mg)	0336-DVC-001-B01		14
Multiple (BID) Dose Study (ref. #16, Study #45)	S	Kyorin Tablets (400 mg)	0366-FCT-005-C02		26
Multiple (TID) Dose Study (ref. #17, Study #66)	S	Kyorin Tablets (400 mg)	0366-FCT-006-C01		26
Tablet Bioavailability vs. Oral Solution (ref. #18, Study #13)	P	Kyorin Tablets (200 mg) Kyorin Tablets (400 mg)(A) Oral Solution	0366-FCT-002-B03 0366-FCT-001-C01 0366-080-001-A01		15
Tablet Bioavailability; Kyorin Tablet vs. Merck Direct Compression Tablet (ref. #21, Study #59)	P	Kyorin Tablets (400 mg)(B) Merck Direct Compression Tablet (400 mg)	0366-FCT-006-C01 0366-FCT-020-C017		20

Tablets from the particular batch of 200-mg Kyorin tablets identified in Table I were used in pivotal clinical studies in acute uncomplicated urinary tract infections (Study #3, #6, #7) and acute urinary tract infections (Study #8, #10, #12). Likewise, tablets from the largest batch of 400-mg Kyorin tablets were used in key clinical studies in acute urinary tract infection (Study #28) and to suppress aerobic bowel flora in patients with granulocytopenia (Study #15, #19). Similarly prepared batches of Kyorin tablets were used in other key studies to define efficacy in these areas (#2, #5, #11, #9, #14, #505, #543, #521, #16, #17, #37, #38, #27, #25, #36, #40, #35, #554, #545, #535, #539, #549, #538, #565, #542, #564, #530, #518, #551, #534, #533, #541, #528, #537, #532, #519, #555, #548, #53, #24, #507, #508, #512, #509, #512, #509, #510, #511, #568, #567, #693, #573, #694, #574, #692), as well as in pivotal studies in acute bacterial gastroenteritis (#14, #588, #591, #595, #609, #590, #589, #634, #31) and in uncomplicated gonorrhoea (#30, #48, #49).

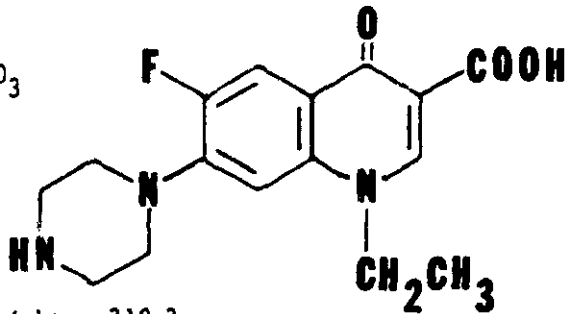
Figure 1

Physical and Chemical Information for Norfloxacin.

Physical and Chemical Information

Structure:

$C_{15}F_1H_{18}N_3O_3$



Molecular Weight: 319.3

Description: White odorless powder

Melting Point: 220-224°C

Metabolites of Norfloxacin.

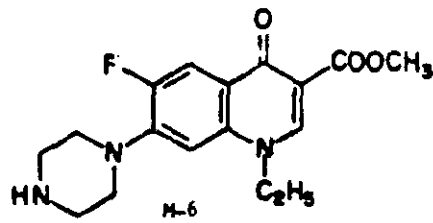
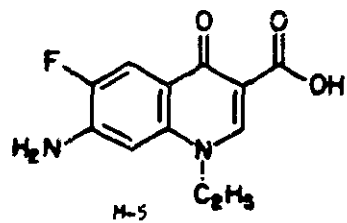
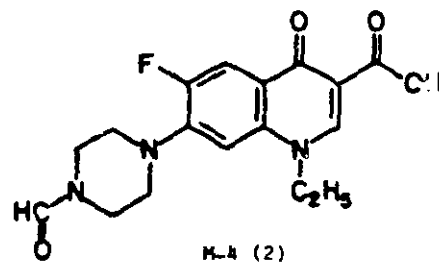
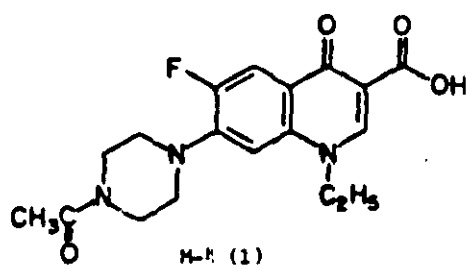
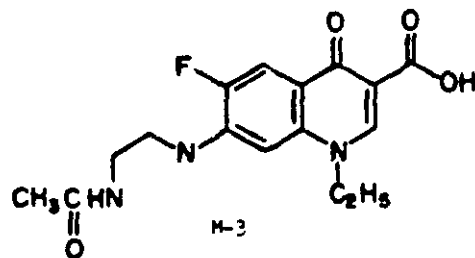
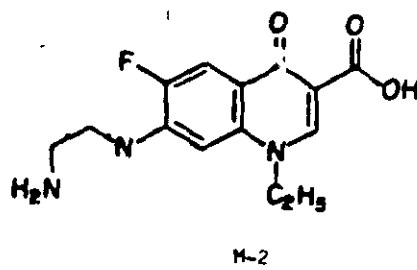
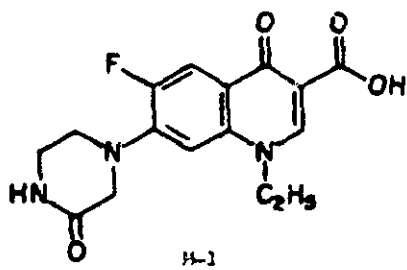


Table 3

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TABLE 3 Urinary excretion of AM-715 after oral administration of 200 mg of AM-715 in humans

Treatment	Subject no.	Clearance period (h)	Creatinine clearance (ml/min)	AM-715 clearance (ml/min)	Clearance ratio	Urinary recovery (% dose ^a)
Without probenecid	1					
	2					
	3					
	4					
	5					
Mean ± S.E.		3-5	111.6 ± 10.6	266.0 ± 32.6 (72.1)	2.4 ± 0.3	28.0 ± 6.9 (S.D. = 15.5)
		5-7	135.3 ± 11.7	387.5 ± 65.3 (146)	3.4 ± 0.5	
		7-9	125.8 ± 7.4	351.1 ± 19.9 (39.8)	2.8 ± 0.3	
				$\bar{x}$ 334.9 ± 62.4 (S.D.)		
With probenecid	1					
	2					
	3					
	4					
	5					
Mean ± S.E.		3-5	150.1 ± 23.4	164.8 ± 22.9	1.2 ± 0.2	13.9 ± 2.1 (S.D. = 4.7)
		5-7	119.9 ± 8.1	144.3 ± 12.9	1.2 ± 0.1	
		7-9	118.9 ± 4.7	121.8 ± 19.7	1.5 ± 0.1	

^a Recovery of AM-715 12 h after administration.
^b ND, No detectable serum concentration of AM-715.

$\bar{x}$ 163.6 ± 18.8
(S.D.)

Figure 3

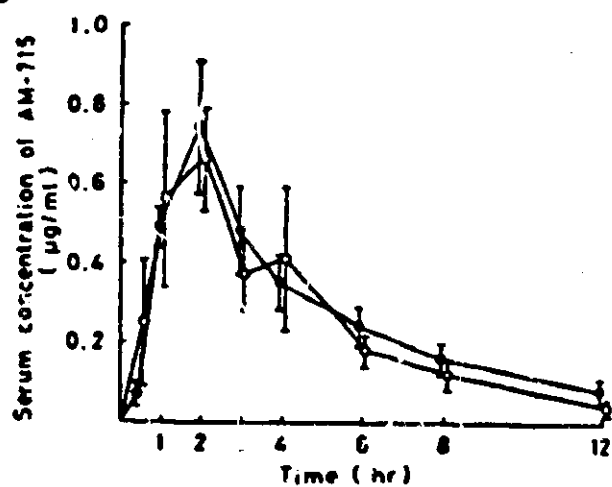


Figure 3. Mean ± standard error serum concentration of AM-715 after oral administration of 200 mg of AM-715 without (O) and with (●) probenecid in human volunteers.

1 Page(s)

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N19-384 2 of 2

Table 9-1

~~Table 1~~ Serum concentration of AM-715 after oral administration of 200mg of AM-715 to healthy human subjects (µg/ml)

Name	Time after administration (hr.)							
	0.5	1	2	3	4	6	8	12
SU								
SA								
AO								
IT								
Mean	2.5	6	10.8	8	7.3	5	4	2.5
SD	2.6	3	2.6	2.9	1.7	1.7	0.8	0.5

Table 9-2

~~Table 2~~ Urinary concentration of AM-715 and its metabolites after oral administration of 200mg of AM-715 to healthy human subjects (µg/ml)

Name	Time (hr.)	AM-715	M-1	M-2	M-3	M-4	M-5
OZ							
SU							
UC							

Table 9-3

~~Table 3~~ Urinary concentration of AM-715 and its metabolites after oral administration of 1,600mg of AM-715 to healthy human subjects (µg/ml)

Name	Time (hr.)	AM-715	M-1	M-2	M-3	M-4	M-5
SU							
SA							
AO							
IT							

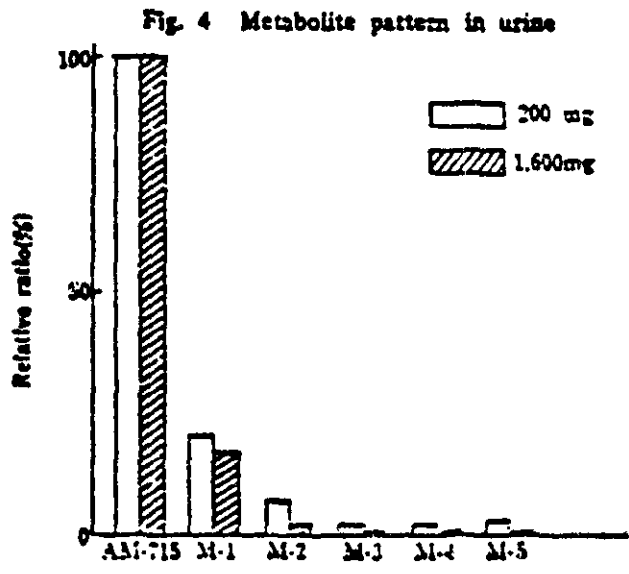
Table 9-4

Table 4 Urinary excretion of AM-715 and its metabolites after oral administration of 200mg of AM-715 to healthy human subjects (mg) -

Name	Time (hr.)	AM-715	M-1	M-2	M-3	M-4	M-5	Total	% of dose
OZ	0-2.5								
	2.5-5								
	5-9								
	9-24								
	Total								
		Reduced to AM-							
		% of dose							
SU	0-2.5								
	2.5-5								
	5-9								
	9-24								
	Total								
		Reduced to AM-							
		% of dose							
UC	0-2.5								
	2.5-5								
	5-9								
	9-24								
	Total								
		Reduced to AM-							
		% of dose							

$\bar{x}$ = 26.6 5.1 1.5 0.33 ≤ 0.5 0.7 34.7
 S.D. 9.05 0.78 0.36 0.15 0.1 9.4
 range

Figure 9-3



This figure shows the mean ratio of urinary excretion of each metabolite during 24 hours when the ratio of excretion (% of dose) of unchanged form was taken as 100.

Table 9-5

Table 5 Urinary excretion of AM-715 and its metabolites after oral administration of 1,500mg of AM-715 to healthy human subjects (mg)

Name	Time (hr.)	AM-715	M-1	M-2	M-3	M-4	M-5	Total	% of dose
SU	0-2.5								
	2.5-5								
	5-9								
	9-24								
	<u>Total</u>								
		<u>Reduced to AM</u>							
		<u>% of dose</u>							
SA	0-2.5								
	2.5-5								
	5-9								
	9-24								
	<u>Total</u>								
		<u>Reduced to AM</u>							
		<u>% of dose</u>							
AO	0-2.5								
	2.5-5								
	5-9								
	9-24								
	<u>Total</u>								
		<u>Reduced to AM</u>							
		<u>% of dose</u>							
IT	0-2.5								
	2.5-5								
	5-9								
	9-24								
	<u>Total</u>								
		<u>Reduced to AM</u>							
		<u>% of dose</u>							

$\bar{X}$ = 23.0 3.6 0.57 0.15 0.05 0.145 27.5
 S.D. 8.0 0.7 0.25 0.06 0.04 0.06 8.8

Fig. 5 Urinary excretion rate of AM-715 and its metabolites after oral administration of 1,500mg of AM-715

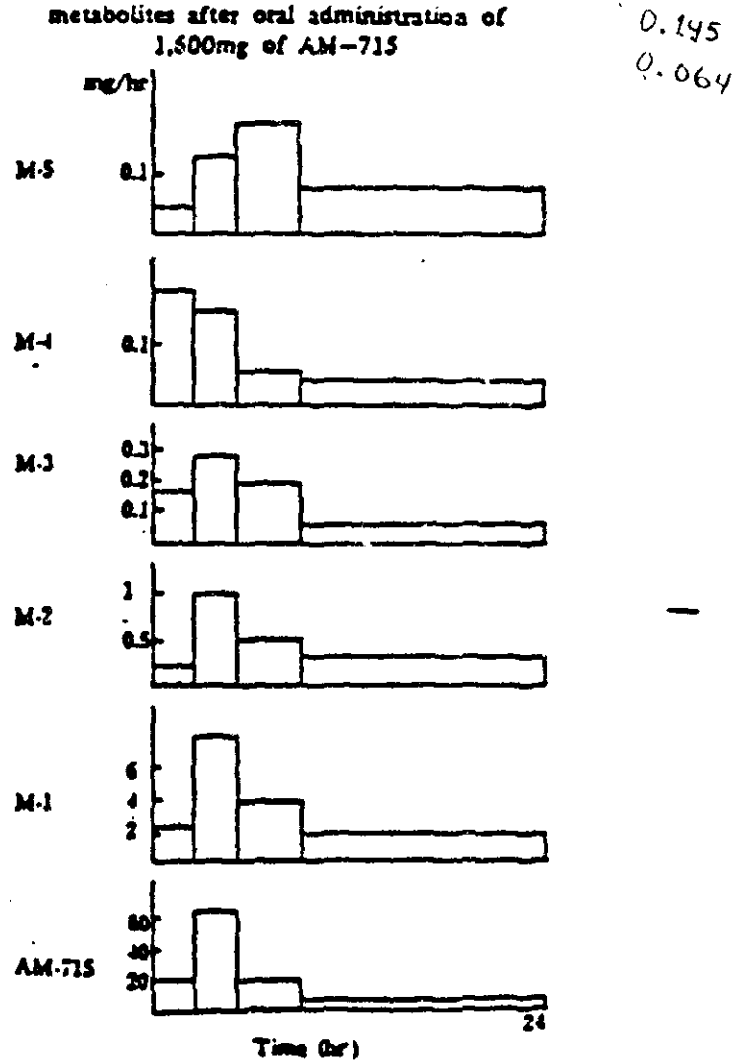


Figure 12-1

Fig-48 Urinary excretion of AM-715 in healthy male adults (200mg/person, p.o. single administration)

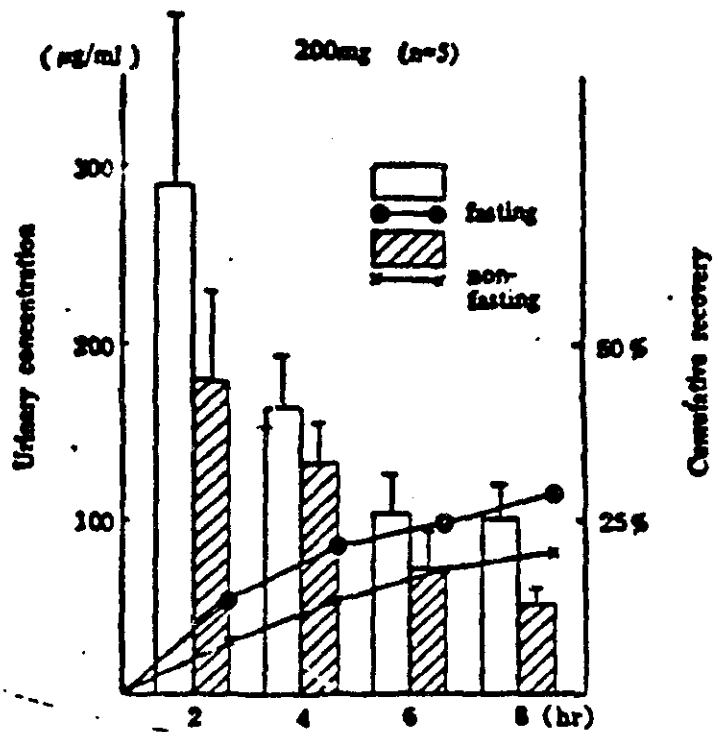


Table 12-1

Group	Volunteer	Urinary excretion				Recovery
		0-2h	2-4h	4-6h	6-8h	
fasting	O.U. 35y.M.	(µg/ml)				100
		mg				5
	T.O. 31y.M.	µg/ml				100
		mg				5
	Y.K. 28y.M.	µg/ml				100
		mg				5
non-fasting	H.N. 26y.M.	µg/ml				100
		mg				5
	H.K. 26y.M.	µg/ml				100
		mg				5
	A.K. 26y.M.	µg/ml				100
		mg				5

Volunteer
fasting
non-fasting

% Recovery
 $\bar{x} = 28.3$
 $S.D. = 8.19$
 $C.V. = 28.9$

$\bar{x}$ 181.6 134.8 72 53.2
 $S.D.$ 109.5 53.8 44.2 24.1

% Recovery
 $\bar{x} = 19.9$
 $S.D. = 3.2$
 $C.V. = 16.1 \%$

Table 12-2Table 1 Plasma levels of AM-715 in healthy male adults
(200mg/person, p.o. single administration)

Group	Volunteer	Serum concentration ($\mu\text{g/ml}$)					
		1/2	1	2	4	6	8 (hr)
fasting	O.U. 35y.M. 57kg.						
	T.O. 31y.M. 69kg.						
	Y.K. 28y.M. 65kg.						
	H.K. 26y.M. 68kg.						
	A.K. 26y.M. 67kg.						
non-fasting	O.U. 35y.M. 57kg.						
	T.O. 31y.M. 69kg.						
	Y.K. 28y.M. 65kg.						
	Yi.N. 26y.M. 68kg.						
	A.K. 26y.M. 67kg.						

Table 15-1

~~Subject~~
Serum Concentration of MK-366 (mcg/ml)
After a Single 200 mg Oral Dose

Subject No.	Time After Dose (Hr.)									
	0	0.5	1	1.5	2	3	4	6	8	12
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
n =	13	14	14	12	14	13	14	14	13	13
mean	0.00	0.48	0.75	0.61	0.52	0.38	0.32	0.22	0.15	0.10

* Insufficient sample for analysis.

Table 15-2

Serum Concentration of MK-366 (mcg/ml)
After a Single 400 mg Oral Dose

Subject No.	Time After Dose (Hr.)									
	0	0.5	1	1.5	2	3	4	6	8	12
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
n =	14	14	14	14	14	13	13	14	14	14
mean	0.00	0.44	1.39	1.32	1.07	0.78	0.55	0.42	0.29	0.20

* Insufficient sample for analysis.

Table 15-3

Serum Concentration of MK-366 (mcg/ml)
After a Single 800 mg Oral Dose

Subject No.	Time After Dose (Hr.)									
	0	0.5	1	1.5	2	3	4	6	8	12
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
n =	14	14	14	13	13	14	14	14	14	14
mean	0.00	1.13	2.12	2.06	2.03	1.50	1.16	0.76	0.61	0.40

* Insufficient sample for analysis.

Table 15-4

Serum Concentration of MK-366 (mcg/ml)
After a Single 1200 mg Oral Dose

Subject No.	Time After Dose (Hr.)									
	0	0.5	1	1.5	2	3	4	6	8	12
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
n =	14	14	13	13	12	13	14	14	14	14
mean	0.00	1.33	2.76	2.70	3.05	2.36	1.90	1.28	1.00	0.62

* Insufficient sample for analysis.

Table 15-5

Serum Concentration of MK-366 (mcg/ml)
After a Single 1600 mg Oral Dose

Subject No.	Time After Dose (Hr.)									
	0	0.5	1	1.5	2	3	4	6	8	12
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
n =	14	14	13	14	14	14	14	14	14	14
mean	0.00	1.44	2.68	3.22	3.65	2.87	2.19	1.55	1.19	0.76

* Insufficient sample for analysis.

Figure 15-1

Figure 1
MK-366 Study #1
Mean Serum Concentration

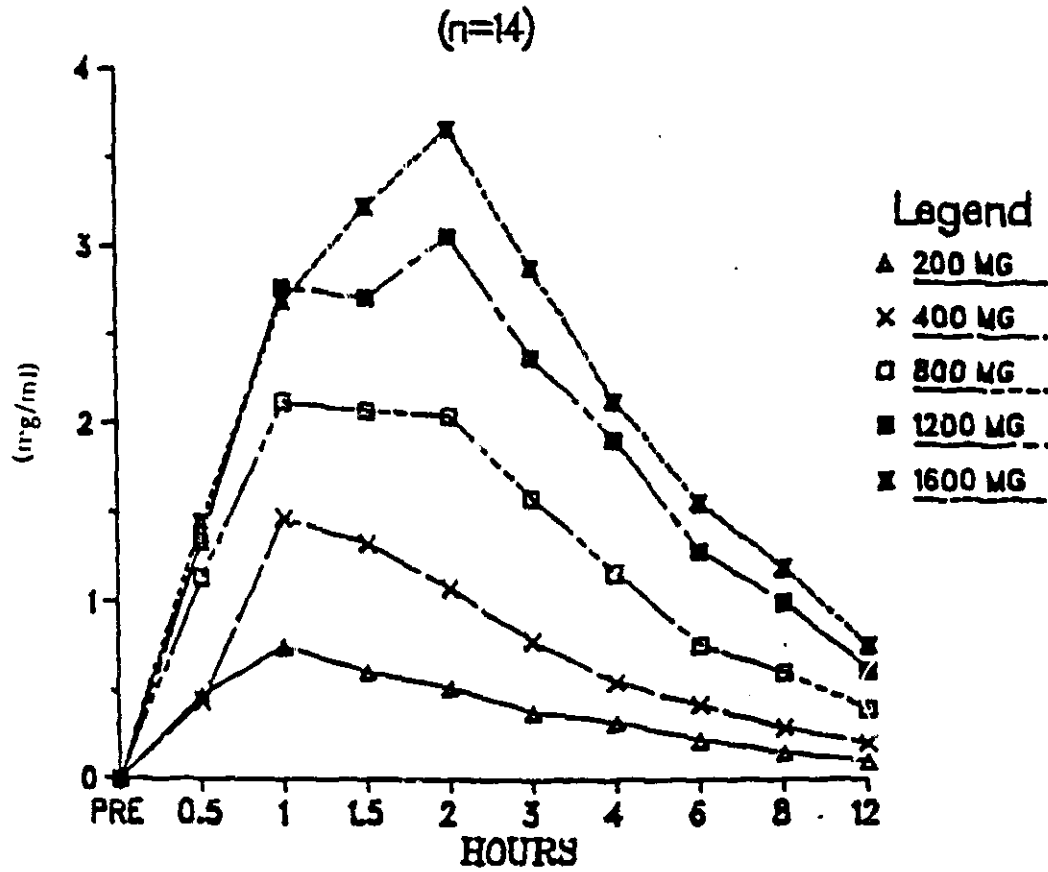


Table 15-6

Subject No.	Dose (mg) MK-366									
	200		400		800		1200		1600	
	C _{max} (µg/ml)	t _{max} (hr)	C _{max} (µg/ml)	t _{max} (hr)	C _{max} (µg/ml)	t _{max} (hr)	C _{max} (µg/ml)	t _{max} (hr)	C _{max} (µg/ml)	t _{max} (hr)
1 ⁵										
2 ⁵										
3										
4										
5										
6										
7										
8 ⁵										
9										
10										
11 ⁵										
12 ⁵										
13 ⁵										
14										
Mean	0.79	1.1	1.55	1.1	2.38	1.4	3.64	1.7	3.67	1.8

Individual Peak Serum Levels of MK-366 and Time to Peak Following Single Oral Doses of Drug

- 1 Insufficient sample for analysis at 1.5 hr.
- 2 Insufficient sample for analysis at 2 hr.
- 3 Insufficient sample at 1, 1.5, 2, and 3 hr.
- 4 Insufficient sample at 1 hr.
- 5 Excluded from mean.

400 mg
 C_{max} $\bar{x}$ 1.57
 (n=14) S.D. 0.45
 T_{max} $\bar{x}$ 1.1
 (n=14) S.D. 0.35

Table 15-7

Effective Serum Half-Life (t_{1/2}) of MK-366 Following Single Oral Doses of Drug

(For a dosing interval of 8 hours)

Subject No.	t _{1/2} (hr) Following...Dose MK-366				
	200 mg	400 mg	800 mg	1200 mg	1600 mg
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
Harmonic Mean	2.18	2.19	2.29	2.39	2.48

- 1 Incomplete urinary recovery.
- 2 Insufficient serum data.

Individual 8-Hour Area Under the Curve, $[AUC]_0^8$,
for MK-366 Following Single Oral Doses of the Drug

Table 15-8

Subject No.	$[AUC]_0^8$ (mcg·hr/ml) Following...Dose of MK-366				
	200 mg	400 mg	800 mg	1200 mg	1600 mg
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
Mean	2.77 (±0.59)	5.19 (±1.31)	9.57 (±1.91)	14.34 (±3.51)	16.71 (±5.17)

¹ Insufficient serum sample for analysis at 1, 1.5, 2, 3, 4, and/or 8 hr. Serum concentration estimated.

² Insufficient serum data.

Table 15-9

Individual Estimates of Total Area Under the Curve,
 $[AUC]_{\infty}$, for MK-366 Following Single Oral Doses of the Drug

Subject No.	$[AUC]_{\infty}$ (mcg·hr/ml) Following...Dose MK-366				
	200 mg	400 mg	800 mg	1200 mg	1600 mg
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
Mean	3.36 (±0.78)	6.20 (±1.78)	12.19 (±2.63)	19.09 (±5.42)	24.06 (±8.03)

¹ Incomplete urinary recovery.

² Insufficient serum data.

Table 15-10

Urinary Excretion of MK-366 (mg)
After a Single 200 mg Dose, p.o.

Subject #	Collection Intervals (hr)							12-24	24-48	Total 0-48	
	0-1	1-2	2-3	3-4	4-6	6-8	8-12				Total 0-12
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
13											
14											
Mean	8.56	14.8	7.83	6.80	7.62	5.38	3.97	53.8	5.93	1.93	61.9
S.D.	4.30	3.05	3.43	2.64	2.18	3.60	1.87	10.3	2.21	0.96	12.6

† - probable incomplete collection
* - repeatable assay value

Table 15-11

Urinary Excretion of MK-366 (mg)
After a Single 400 mg Dose, p.o.

Subject #	Collection Intervals (hr)							Total 0-12	12-24	24-48	Total 0-48
	0-1	1-2	2-3	3-4	4-6	6-8	8-12				
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
13											
14											
Mean	11.9	31.6	14.5	13.0	14.6	11.6	8.21	104.26	10.42	64.94	119
S.D.	6.86	7.18	7.07	7.46	5.03	3.79	3.39	21.7	5.44	3.16	27.2

† - probable incomplete collection
* - repeatable assay value

Table 15-12

Urinary Excretion of MK-366 (mg)
After a Single 800 mg Dose, p.o.

Subject #	Collection Intervals (hr)							Total 0-12	12-24	24-48	Total 0-48
	0-1	1-2	2-3	3-4	4-6	6-8	8-12				
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
13											
14											
Mean	16.9	46.8	28.0	29.1	30.1	18.4	16.8	186	23.5	10.1	219
S.D.	10.5	9.28	13.1	14.6	12.2	5.55	5.96	40.6	9.25	5.0	50.4

? - probable incomplete collection
* - repeatable assay value

Table 15-13

Urinary Excretion of MK-366 (mg)
After a Single 1200 mg Dose, p.o.

Subject #	Collection Intervals (hr)							12-24	24-48	Total 0-48	
	0-1	1-2	2-3	3-4	4-6	6-8	8-12 Total 0-12				
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
13											
14											
Mean	22.3	60.6	45.0	37.6	44.8	34.5	30.5	273	41.9	14.6	337
S.D.	13.7	14.5	17.4	15.0	24.2	14.2	9.44	64.8	17.5	7.24	77.3

† - incomplete collection.
* - repeatable assay value

Table 15-14

Urinary Excretion of MK-366 (mg)
After a Single 1600 mg Dose, p.o.

Subject	Collection Intervals (hr)							Total 0-12	12-24	24-48	Total 0-48
	0-1	1-2	2-3	3-4	4-6	6-8	8-12				
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
13											
14											
Mean	24.9	65.6	70.1	49.9	61.8	40.2	46.6	353	56.5	18.9	448
S.D.	16.2	25.4	25.3	25.0	35.8	14.9	20.6	115	22.0	11.8	139

† - probable incomplete collection
 * - sample lost
 • - repeatable assay value

Table 15-15

Concentration of MK-366 ($\mu\text{g/ml}$) in Urine
After a Single 200 mg Dose, p.o.

Subject #	Pre-drug	Collection Intervals (hr)								
		0-1	1-2	2-3	3-4	4-6	6-8	8-12	12-24	24-48
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
Mean		133	124	88.5	75.9	48.1	44.0	19.7	10.3	2.35
S.D.		139	67.0	92.9	68.5	24.5	27.2	12.0	3.70	1.78

† - probable incomplete collection
* - repeatable assay value

Table 15-16

Concentration of MK-366 ($\mu\text{g}/\text{ml}$) in Urine
After a Single 400 mg Dose, p.o.

Subject	Pre-Drug	Collection Intervals (hr)								
		0-1	1-2	2-3	3-4	4-6	6-8	8-12	12-24	24-48
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
Mean		168	417	299	211	141	100	46.9	22.5	5.93
S.D.		159	589	369	168	98.3	81.0	37.3	12.5	3.07

† - probable incomplete collection

§ - probable sample mix-up with placebo for subject #13, 1-2 hr. Actual assay value was zero

* - repeatable assay value

Table 15-17

Concentration of MK-366 ($\mu\text{g/ml}$) in Urine
After a Single 800 mg Dose, p.o.

Subject	Pre-Drug	Collection Intervals (hr)								
		0-1	1-2	2-3	3-4	4-6	6-8	8-12	12-24	24-48
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
Mean		280	582	365	358	243	184	84.4	45.9	12.1
S.D.		257	470	280	206	138	97.7	53.1	21.0	10.3

† - probable incomplete collection
* - repeatable assay value

Table 15-18

Concentration of MK-366 ($\mu\text{g/ml}$) in Urine
After a Single 1200 mg Dose, p.o.

Subject #	Pre-Drug	Collection Intervals (hr)								
		0-1	1-2	2-3	3-4	4-6	6-8	8-12	12-24	24-48
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
Mean	0.53	359	897	657	550	424	272	143	73.5	15.7
S.D.	1.47	444	750	411	350	299	162	98.9	54.5	6.93

† - incomplete collection
* - repeatable assay value

Table 15-19

Concentration of MK-366 ($\mu\text{g/ml}$) in Urine
After a Single 1600 mg Dose, p.o.

Subject #	Pre-Drug	Collection Intervals (hr)								
		0-1	1-2	2-3	3-4	4-6	6-8	8-12	12-24	24-48
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
Mean	0.37	250	881	625	421	518	405	188	101	19.1
S.D.	1.33	217	720	550	335	491	404	128	60.0	8.75

• - no sample

† - probably incomplete collection

* - repeatable assay value

Table 15-20

Individual 48-hour Urinary Recovery of MK-366
Following Single Oral Doses of Drug

Subject No.	Z-Dose* Urinary Recovery Following...Dose MK-366					Mean
	200 mg	400 mg	800 mg	1200 mg	1600 mg	
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
Mean	32.2 (±6.4)	31.5 (±7.2)	28.7 (±6.4)	29.0 (±7.3)	29.2 (±9.1)	

- ¹ Low urine volume 12-24 hr or 24-48 hr. Included in mean.
² No Void 4-6 hrs. Renal clearance indicates incomplete recovery. Excluded from mean.
³ Questionable urinary collection 12-24 hr. Excluded from mean.
⁴ No void 3-4 hrs. Renal clearance indicates incomplete urinary recovery. Excluded from mean.
⁵ Urine sample lost (12-24 hr). Excluded from mean.
* See Table IX for average capsule dose of MK-366.

Table 15-21

Individual Cumulative Renal Clearance ($V_{CL,R}$) of MK-366
Following Single Oral Doses of Drug

Subject No.	$V_{CL,R}$ (ml/min) Following...Dose MK-366					Mean
	200 mg	400 mg	800 mg	1200 mg	1600 mg	
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
Mean	313.4 (±55.0)	319.6 (±50.0)	305.8 (±92.3)	290.8 (±50.2)	308.5 (±39.8)	

- ¹ Insufficient serum data for analysis.

		MK-366 TREATMENTS														
		A 200 MG			B 400 MG			C 800 MG			D 1200 MG			E 1600 MG		
VARIABLE (UNITS)	RESULT	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD
48-H UR RECOVERY (% dose)	NS	14	32.4	6.2	14	31.3	6.7	14	29.7	6.4	14	29.0	7.3	14	28.0	9.7
CUM RENAL CLEAR (ml/min)	NS	14	313.4	55.0	14	319.6	50.0	14	305.0	92.3	13	290.8	50.2	14	308.5	39.0
0-HOUR AUC (mcg x hr x ml)	AA	14	2.0	0.6	14	5.2	1.3	14	9.6	1.9	13	14.3	3.5	14	16.7	5.2
TOTAL AUC (mcg x hr x ml)	AA, PP	13	3.4	0.8	12	6.2	1.0	14	12.2	2.6	13	19.1	5.4	13	24.1	8.0
PEAK SERUM LEVEL (mcg/ml)	AA	14	0.8	0.2	14	1.6	0.5	14	2.4	0.5	14	3.3	1.0	14	3.0	1.2
TIME TO PEAK (hr)	"	14	1.1	0.4	14	1.1	0.3	14	1.4	0.4	14	2.0	1.0	14	1.9	0.5
SERUM HALF-LIFE (hr)	"	13	2.2	0.2	12	2.2	0.2	14	2.3	0.2	13	2.4	0.2	13	2.5	0.2

NS NO SIGNIFICANT LINEAR TREND AND NO SIGNIFICANT DIFFERENCE BETWEEN TREATMENTS.
 " RESPONSE WAS HIGHER FOR THE HIGHER 2 DOSES THAN FOR THE LOWER 3 DOSES (P<0.01).
 AA A LINEAR TREND WAS PRESENT BETWEEN RESPONSE AND DOSE LEVEL (P<0.01).
 PP A PROPORTIONAL DOSE-RESPONSE RELATIONSHIP WAS OBSERVED.

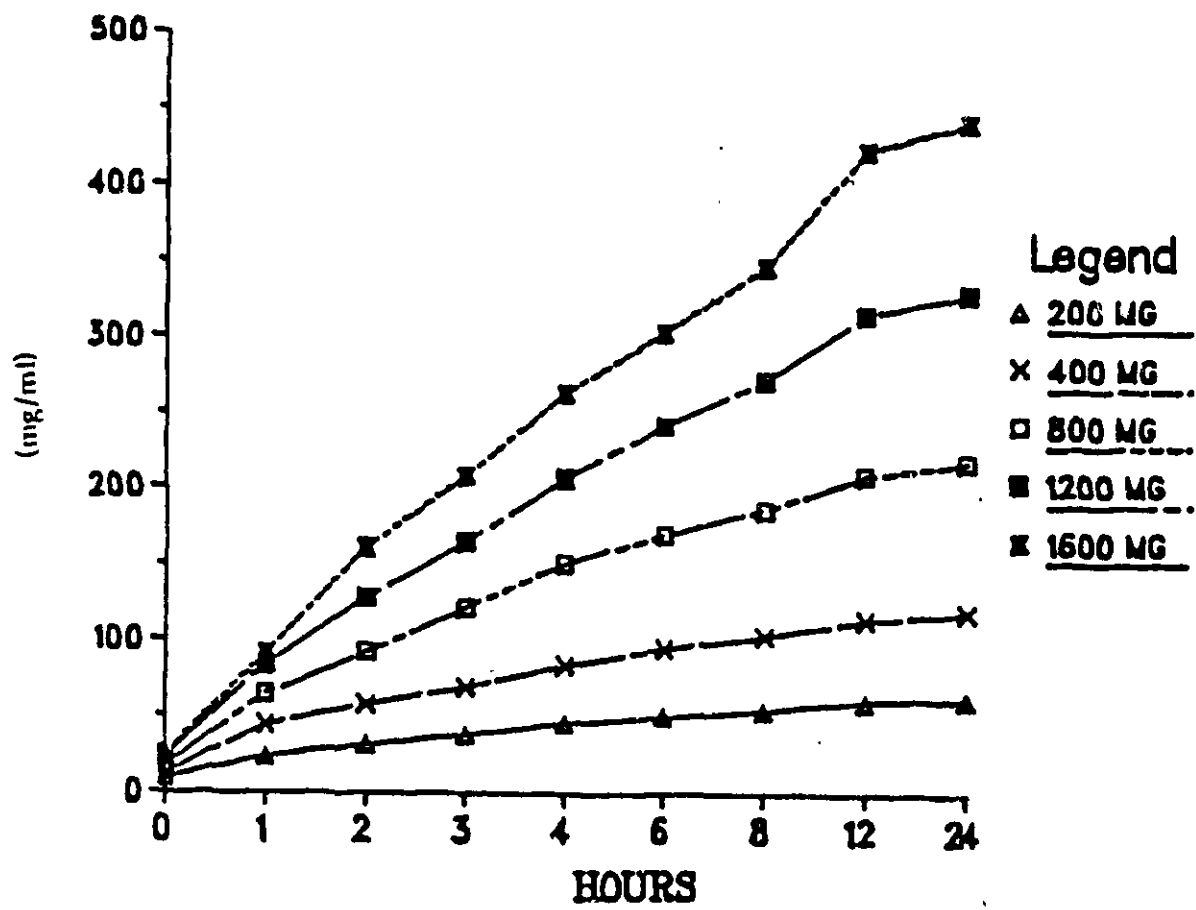
	POSTERIOR PROBABILITY PR(TRUE DIFFERENCE <20%)	POWER OF DETECTING 20 % DIFFERENCE AT α=0.05
48-HOUR URINARY RECOVERY	0.937	0.967
CUMULATIVE RENAL CLEARANCE	0.999	> 0.999
0-8 HR AREA UNDER CURVE (dose adjusted)	0.852	0.956
TOTAL AREA UNDER CURVE (dose adjusted)	0.961	0.935

Mean MK-366 Biopharmaceutical Parameters

Table 15-22

Figure 15-2

MK-366 Study #1
Mean Cumulative Urine Excretion



ble 16-1

Figure 16-1

Mean Norfloxacin Plasma Concentration Profiles

Table 16-1 is a listing presenting the demographic data of the 27 volunteers at entry into this study.

VOLUNTEER DEMOGRAPHIC DATA

Vol. No.	Sex	Age (yrs.)	Height (in.)	Weight (lbs.)	Race
1	M	41	71	157	Caucasian
2	M	29	69	160	Caucasian
3	M	27	71	155	Caucasian
4	M	21	71	202	Caucasian
5	M	39	70	170	Caucasian
6	M	24	72	179	Caucasian
7	M	31	65	148	Caucasian
8	M	23	70	150	Caucasian
9	M	21	69	166	Caucasian
10	M	44	70	155	Caucasian
11	M	20	76	180	Caucasian
12	M	21	71	155	Caucasian
13	M	45	72	159	Black
14	M	36	72	163	Caucasian
15	M	20	76	190	Caucasian
16	M	34	68	146	Caucasian
17	M	24	74	170	Caucasian
18	M	19	71	150	Caucasian
19	M	31	72	204	Caucasian
20	M	24	71	162	Caucasian
21	F	31	61	124	Caucasian
22	M	24	70	171	Caucasian
23	F	34	68	164	Caucasian
24	F	50	67	164	Black
25	M	27	68	143	Caucasian
26	M	19	66	148	Caucasian
27	M	31	69	155	Caucasian

Ranges: Age - 19 - 50 years
Height - 61-76 inches
Weight - 124-204 pounds

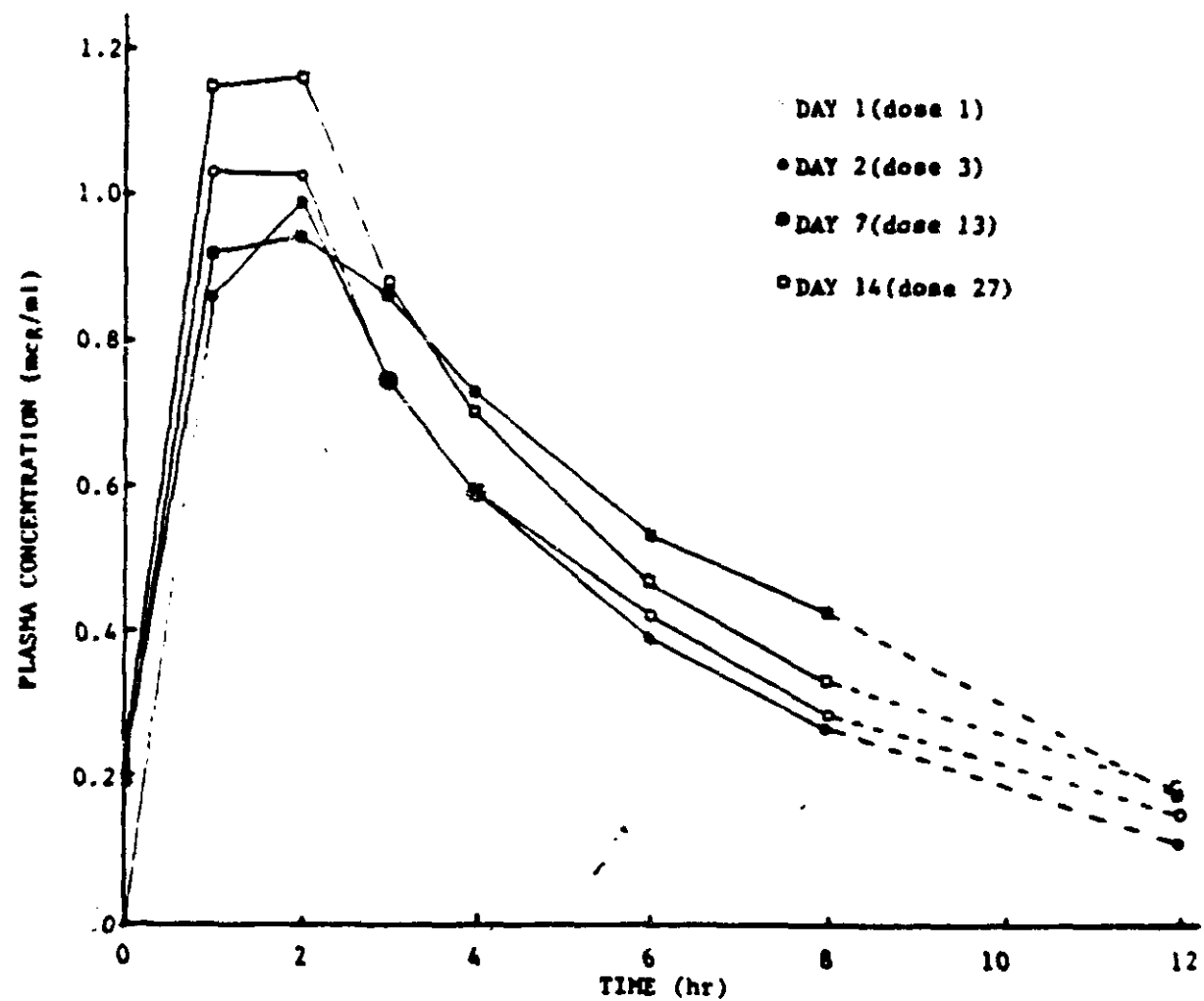


Table 1b-1

Below is a listing presenting the demographic data of volunteers at entry into this study.

VOLUNTEER DEMOGRAPHIC DATA

<u>Vol. No.</u>	<u>Sex</u>	<u>Age (yrs.)</u>	<u>Height (in.)</u>	<u>Weight (lbs.)</u>	<u>Race</u>
1	M	41	71	157	Caucasi
2	M	29	69	160	Caucasi
3	M	21	71	155	Caucasi
4	M	21	71	202	Caucasi
5	M	39	70	170	Caucasi
6	M	24	72	179	Caucasi
7	M	31	65	148	Caucasi
8	M	23	70	150	Caucasi
9	M	21	69	166	Caucasi
10	M	44	70	155	Caucasi
11	M	20	76	180	Caucasi
12	M	21	71	155	Caucasi
13	M	45	72	159	Black
14	M	36	72	163	Caucasi
15	M	20	76	190	Caucasi
16	M	34	68	146	Caucasi
17	M	24	74	170	Caucasi
18	M	19	71	150	Caucasi
19	M	31	72	204	Caucasi
20	M	24	71	162	Caucasi
21	F	31	61	124	Caucasi
22	M	24	70	171	Caucasi
23	F	34	68	164	Caucasi
24	F	50	67	164	Black
25	M	21	68	143	Caucasi
26	M	19	66	148	Caucasi
27	M	31	69	155	Caucasi

Ranges: Age - 19 - 50 years
Height - 61-76 inches
Weight - 124-204 pounds

Table 16-2

Individual 12-Hour Urinary Excretion (U_{0-12}) of Norfloxacin Following Twice Daily Administration

$$\% \text{ of Dose} = \frac{X}{400} = (\quad)$$

U_{0-12} (mg) Following 1st Dose on Day . . .

Subject No.	1 (% Dose)	2	7	14
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				

	Day 1	Day 7	Day 14
1	Estimated from cumulative urinary excretion profile.		
	using all data (n=26)	(n=26)	(n=25)
	$\bar{x} = 16.5$	$\bar{x} = 17.75$	$\bar{x} = 18.9$
	S.D. = 6.7	S.D. = 6.2	S.D. = 8.2
	C.V. = 40.6%	C.V. = 34.9%	C.V. = 43.4%
	* Range: 1.0 - 27.75%	Range: 6.2 - 27.6%	Range: 7.1 - 40%

Table 16-3

Individual Cumulative Renal Clearance ($V_{Cl,R}$) of Norfloxacin Following Twice Daily Administration

$\dot{V}_{Cl,R}$ (ml/min) Following First Dose on Day . . .

Subject No.	1	2	7	14
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
Mean (S.D.)	276.6 (112.0)	330.4 (39.0)	239.6 (39.5)	266.0 (78.6)

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Table 16-5

Individual Peak Plasma Concentrations (C_{max}) of Norfloxacin Following Twice Daily Administration

Subject No.	C_{max} (mcg/ml) Following 1st Dose on Day . . .			
	1	2	7	14
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
Mean (S.D.)	1.15 (0.41)	1.18 (0.55)	1.27 (0.50)	1.35 (0.39)

- 1 No blood samples taken as per protocol.
- 2 Unusually low plasma concentrations.
- 3 Dose not administered.

Table 16-6

Individual Times (T_{max}) that Peak Plasma Concentrations of Norfloxacin Occurred Following Twice Daily Administration

Subject No.	T_{max} (hr) Following 1st Dose on Day . . .			
	1	2	7	14
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
Mean (S.D.)	1.5 (0.6)	2.2 (1.6)	2.2 (2.0)	2.4 (0.6)

- 1 Blood samples not taken.
- 2 Unusually low plasma concentrations.
- 3 Dose not administered.

Table 16-7

Individual Minimum Plasma Concentrations (C_{min}) of Norfloxacin Following Twice Daily Administration

Subject No.	C_{min} (mcg/ml) following dose no. . . .							
	Pre	1	2	3	12	13	26	27
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								
15								
17								
18								
19								
20								
21								
22								
23								
24								
25								
26								
27								
Mean (S.D.)	0	0.12 (.09)	.20 (.21)	.15 (.05)	.20 (.14)	.17 (.11)	.23 (.21)	.18 (.13)

- 1 No blood samples taken as per protocol.
- 2 Dose not administered.
- 3 Unusually low plasma concentrations.

Table 16-8

Individual 12-Hour Area Under the Plasma Concentration-Time Curve, $[AUC]_{0-12}$, for Norfloxacin Following Twice Daily Administration

Subject No.	$[AUC]_{0-12}$ (mcg-hr/ml) following the first dose on Day . . .			
	1	2	7	14
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
Mean (S.D.)	5.23 (2.02)	5.69 (1.99)	6.57 (2.99)	6.52 (2.86)

- 1 $[AUC]$ estimated using norfloxacin half-life.
- 2 Drug not detectable at 12 hr. $[AUC]_{0-12}$ only. Excluded from mean.
- 3 Unusually low plasma concentrations. N. estimate of $[AUC]$.
- 4 Dose not administered.

Table 16-9

LISTING OF VOLUNTEERS WHO RECEIVED MEDICATIONS
OTHER THAN STUDY DRUG

<u>Vol. No.</u>	<u>During Assigned Regimen</u>	<u>Period No.</u>	<u>Medication</u>	<u>Reason for Use</u>
2	Norfloxacin	1	Anusol	Hemorrhoids
	Placebo	2	Haley's MO	Laxative
	Placebo	2	Ducolax	Laxative
10	Placebo	2	Tylenol	Headache
15	Placebo	2	Polysporin Ointment	Swelling on left inguinal area
22	Norfloxacin	1	Mylanta	Burning stomach
18	Placebo	1	Penicillin VK	Strep throat
19	Placebo & Norfloxacin	1 & 2	Cortisporin	Boil in external right meatus
	Placebo	1	Tylenol	Headache
20	Post Study	*	Tetracycline	Palpable lymph node
24	Placebo	2	Tylenol	Sore throat & earache

* Seven days after terminating Period 1 and being dropped from study.

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Table 17-1

Individual Plasma Concentrations (C_p) of Norfloxacin Following Administration of 400 mg Every 8 Hours for 5 Days

Subj. No. (Period)	Day	C_p (mcg/ml) at . . . hr						
		0	1	2	3	4	6	8
101 (1)	1							
	2							
	5							
102 (2)	13							
	14							
	17							
103 (1)	1							
	2							
	5							
126 (1)	1							
	2							
	5							
Mean	1	0	1.74	1.37	0.994	.746	.535	.364
	2	.622	1.28	1.46	1.29	1.02	.707	.518
	5	.771	1.32	1.41	1.01	.824	.626	.436

Table 17-2

Individual Maximum Plasma Concentrations (C_{max}) and Times Those Peaks Occurred (t_{max}) for Norfloxacin Following Administration of 400 mg Every 8 Hours for 5 Days

Subject No.	Day 1 (Dose 1)		Day 2 (Dose 4)		Day 5 (Dose 13)	
	C_{max} (mcg/ml)	t_{max} (hr)	C_{max} (mcg/ml)	t_{max} (hr)	C_{max} (mcg/ml)	t_{max} (hr)
101						
102						
103						
126						
Mean	1.50	1.3	1.73	1.8	1.49	1.5
(S.D.)	(0.40)	(0.5)	(0.33)	(1.0)	(0.38)	(0.6)

Table 17-3

Individual 8-Hour Area Under the Plasma Concentration-Time Curve, $[AUC]_0^8$, for Norfloxacin Following Administration of 400 mg Every 8 Hours for 5 Days

Subject No.	$[AUC]_0^8$ (mcg·hr/ml) Following First Dose on Day . . .		
	1	2	5
101			
102			
103			
126			
Mean	6.34	7.79	7.04
(S.D.)	(0.88)	(2.36)	(1.97)

Figure 17-1

Mean Plasma Concentrations of Norfloxacin

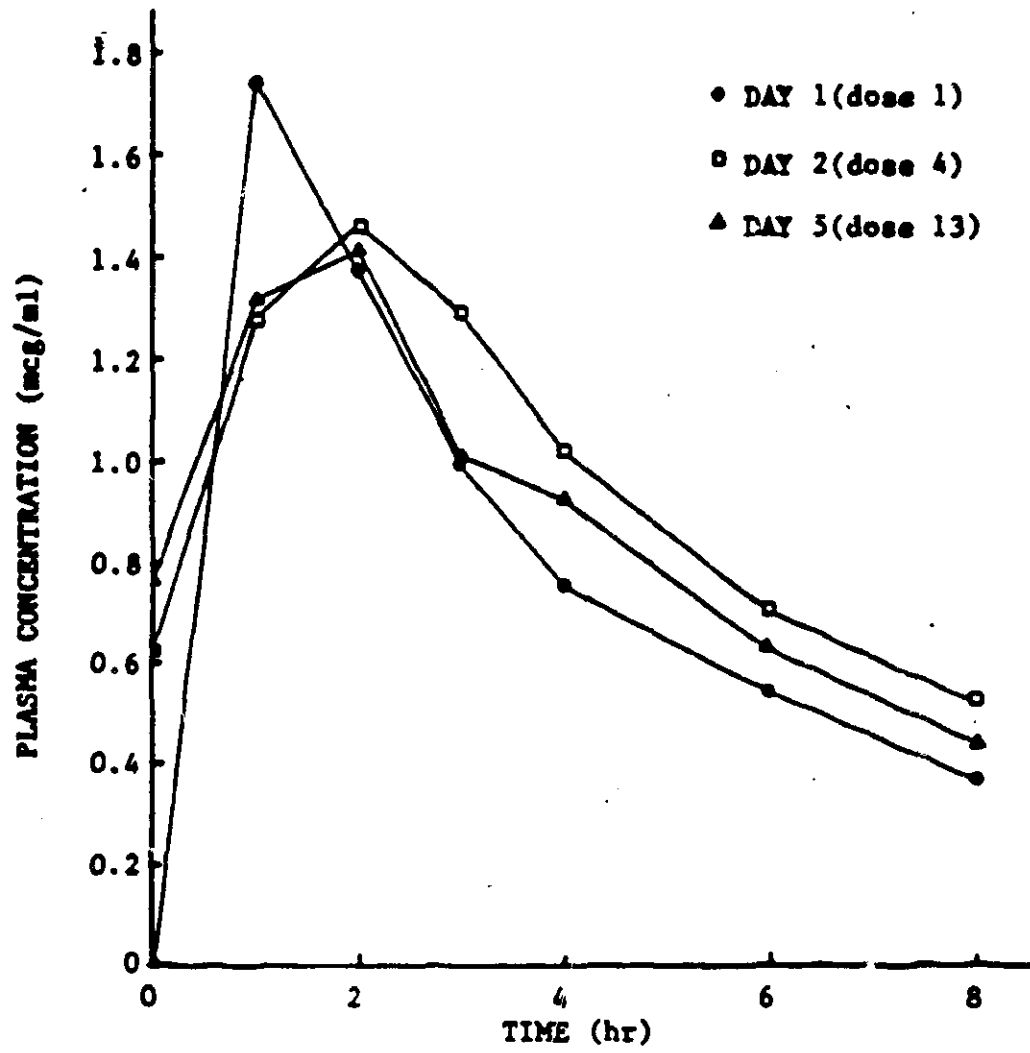


Table 17-4

Individual Minimum Plasma Concentrations (C_{min}) of Norfloxacin Following Administration of 400 mg Every 8 Hours for 5 Days

Subject No.	C_{min} (mcg/ml) Following Dose No. . . .					
	0	1	3	4	12	13
101						
102						
103						
<u>126</u>	—	—	—	—	—	—
Mean (S.D.)	0	.36 (.06)	.62 (.21)	.52 (.29)	.77 (.78)	.44 (.15)

1 Page(s)

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Table 18-1

Individual 8-Hour Area Under the Curve, $[AUC]_0^8$, for MK-366 Following Single Oral Doses of Drug

Subject No.	$[AUC]_0^8$, $\mu\text{g}\cdot\text{hr}/\text{ml}$		
	200-mg Tab	400-mg Tab	430-Soln
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
Mean (SD)	2.66 (±1.12)	3.02 (±2.45)	6.04 (±1.90)



Table 18-2

Individual Estimates of Total Area Under the Curve, $[AUC]_{\infty}$, for MK-366 Following Single Oral Doses of the Drug

Subject No.	$[AUC]_{\infty}$, $\mu\text{g}\cdot\text{hr}/\text{ml}$			400 mg Soln (dose adjustment)
	200-mg Tab Tab 200 Sum 200	400-mg Tab Tab 400 Soln 400	430-mg Soln	
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
Mean SD	3.32 (±1.54)	6.56 (±3.28)	7.58 (±2.08)	7.05 (S.D. ± 1.94)
	% Within 75-125% 3/12 = 25%		5/13 = 38.5%	

$\frac{400}{430} = 0.93\%$

Tab 400 (adj to 200)
Tab 200

¹ Incomplete urinary recovery.

Arith $\bar{x} = .998$
(S.D. ± 0.42)
[CV = 42.1%]

Arith $\bar{x} = .987$
(S.D. ± 0.49)
[CV = 49.6%]

$\bar{x} = 1$
S.D. = 0.33
% w/in 75-125% 7/12 = 58.3%

Table 18-3

Individual Peak Serum Concentrations (C_{max}) of NK-366 Following Single Oral Doses of Drug

$\frac{400}{430} = 0.93$

Subject No.	C_{max} ($\mu\text{g/ml}$)		
	200-mg Tab Tab 200	400-mg Tab Tab 400 / Sub 200 (Adj)	430-mg Soln Sol 430 (Adj)
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
Mean ($\pm$ SD)	0.76 (0.32)	1.50 (0.58)	1.87 (0.66) $\bar{x} = 1.74$ SD = 0.61
	CV 42.1% % w/in 75-125%	38.7% $\frac{5}{15} = 33.3\%$	CV = 35% $\frac{6}{15} = 40.0\%$

Table 18-4

Effective Serum Half-Life ($t_{1/2, \text{eff}}$) of Norfloxacin Following Single Oral Doses of Drug

(For 8 hr dosing Interval)

Subject No.	$t_{1/2, \text{eff}}$ (hr)		
	Treatment A	Treatment B	Treatment C
1	1	..	..
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
Harmonic Mean	3.3	3.2	3.0

Tab 400 (adj) q 12, 20
Tab 200

- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10
- 11
- 12
- 13
- 14
- 15

$\bar{x} = 1.1$
SD = 0.52
CV = 47.3%

% w/in 75-125%
 $\frac{5}{15} = 33.3$

¹ No estimate of [AUC]_{0-∞} because of incomplete urinary recovery of drug

Table 18-5

Individual 48-Hour Urinary Recovery (U_{0-48}) of MK-366
Following Single Oral Doses of Drug

Subject No.	200-mg Tab.		400-mg Tab.		430-mg Soln	
	U_{0-48} (mg)	% Dose ⁴	U_{0-48} (mg)	% Dose ⁴	U_{0-48} (mg)	% Dose ⁴
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
Mean (SD)		25.5 (±9.1)		26.5 (±9.1)		28.4 (±6.7)

- 1 Renal clearance estimates indicate incomplete urinary recovery of drug 1-2 hr and 4-6 hr. Excluded from mean.
- 2 Renal clearance estimates indicate incomplete urinary recovery of drug 0-1 hr. Excluded from mean.
- 3 Renal clearance estimates indicate incomplete urinary recovery of drug 1-2 hr. Excluded from mean.
- 4 For dose estimates see Table 13.

Table 18-6

MEANS OF BIOAVAILABILITY PARAMETERS
MORFLOXACIN STUDY 813-- DR. ZIDOVY

RELATIVE BIOAVAILABILITY	200 MG TAB/STANDARD	400 MG TAB/STANDARD	200 MG TAB/400 MG TAB
N	12	13	12
MEAN (S)	0.89 (0.89)	0.90 (0.90)	1.00 (1.00)
95% C.I.	0.70-1.16	0.72-2.13	0.79-1.26
POWER (95% DIFFERENCE)	0.77	0.70 (0.78)	0.80 (0.80)
POSTERIOR PROB. (10%)	0.43	0.47	0.65
(15%)	0.65	0.70	0.84
(20%)	0.82	0.86	0.94
(25%)	0.93	0.95	0.98
(30%)	0.97	0.98	0.99

(S) - GEOMETRIC MEANS TABULATED.

None of the above ratios is significantly different from unity.

Table 18-7

Individual Estimates of Norfloxacin Relative Bioavailability from 200-mg and 400-mg Market Image Tablets as Compared to Solution Administration of the Drug

Based on the method of Kwan and Till (as modified by Huang & Kwan)

Subject No.	Tab 200 / Soln 400	Tab 400 / Soln 400	Tab 200 / Tab 400
	F _A /F _C	F _B /F _C	F _A /F _B
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
Geometric Mean	0.89	0.90	1.00

Subscripts A, B and C refer respectively to the 200-mg tablet, the 400-mg tablet, and the 400-mg solution treatments.

- ¹ Incomplete urinary recovery Treatment A.
- ² Incomplete urinary recovery Treatment C.
- ³ Based on the ratio of 1-dose urinary recovery.
- ⁴ Incomplete urinary recovery Treatment B.

Table 18-8

Individual Cumulative Renal Clearance ($\dot{V}_{Cl,R}$) of NK-366 Following Single Oral Doses of the Drug

Subject No.	$\dot{V}_{Cl,R}$ (ml/min)		
	200-mg Tab	400-mg Tab	430-mg Soln
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
Mean (SD)	263.4 (±76.1)	299.3 (±93.0)	276.4 (±71.3)

Table 18-9

MEANS OF BIOAVAILABILITY PARAMETERS
NORFLOXACIN STUDY 813-- DR. 23097

48-HR URINARY RECOVERY		UNITS	430 MG SOL'N (STANDARD)	200 MG TABLET	400 MG TABLET
TOTAL			MG (UMADJ)		
N			14	13	14
MEAN			121.91	52.15 ^{0.05}	105.14
S.D.			28.96	18.63	36.22
X DOSE					
N			14	13	14
MEAN			28.28	25.45	26.48
S.D.			6.76	9.66	9.12
0-HR AUC			MCB-MG/ML (A)		
N			15	15	15
MEAN			6.04	5.57	5.44
S.D.			1.90	2.36	2.65
ESTIMATED TOTAL AUC			MCB-MG/ML (A)		
N			14	13	14
MEAN			7.58	6.96	7.10
S.D.			2.06	3.23	3.56

(A)--DOSE ADJUSTED UP TO 430 MG.

0.05 SIGNIFICANTLY LOWER THAN STANDARD 430 MG SOL., P<0.05, 0.01 RESPECTIVELY.
0.05 SIGNIFICANTLY LOWER THAN 400 MG TABLET, P<0.05, 0.01 RESPECTIVELY.

CUR. RENAL CLEARANCE		UNITS	430 MG SOL'N (STANDARD)	200 MG TABLET	400 MG TABLET
			ML/100		
N			15	15	15
MEAN			876.37	863.39	879.26
S.D.			71.31	76.15	94.96
PEAK SERUM CONC--C _{MAX}			MCB/ML (A)		
N			15	15	15
MEAN			1.87	1.68	1.62
S.D.			0.44	0.66	0.62
TIME TO PEAK SERUM CONC--T _{MAX} HR					
N			15	15	15
MEAN			0.70	1.03 ⁰	1.03 ⁰
S.D.			0.37	0.35	0.35
HALF-LIFE			HR		
N			14	13	14
MEAN (M)			2.99	3.26	3.22
95% C.I.			2.63-3.47	2.85-3.81	2.92-3.89

(A) - DOSE ADJUSTED UP TO 430 MG.

(M) - HARMONIC MEAN TABULATED.

0.05 - SIGNIFICANTLY DIFFERENT FROM STANDARD 430 MG SOL., P<0.05, 0.01, RESPECTIVELY.
NO SIGNIFICANT DIFFERENCES WERE FOUND BETWEEN THE TWO TABLETS.

Table 19-1

INDIVIDUAL 24-HOUR URINARY RECOVERY (U_{0-24})
TOTAL URINARY RECOVERY (U_{∞}), AND RENAL CLEARANCE
($\dot{V}_{Cl,R}$) OF NORFLOXACIN IN HEALTHY ELDERLY VOLUNTEERS

SUBJECT NUMBER	URINARY RECOVERY			$\dot{V}_{Cl,R}$ (ML/MIN)
	U_{0-24} (MG)	U_{∞} (MG)	% OF DOSE ¹	
1				
2				
3				
4				
5				
6				
Mean (S.D.)			22.3 (6.9)	154.0 (15.7)

1 Assay content was 405 mg of norfloxacin per tablet
2 Questionable urinary recovery three to twelve hours: U_{0-24} estimated from renal clearance (zero to three hours) and AUC_{0-12} plus U_{12-24}

Table 19-2

INDIVIDUAL PHARMACOKINETIC PARAMETERS FOR NORFLOXACIN
IN PLASMA OF HEALTHY, ELDERLY VOLUNTEERS*

SUBJECT NUMBER	$[AUC]_0^8$ (MCG.HR/ML)	$[AUC]_{\infty}$ (MCG.HR/ML)	C_{max} (MCG/ML)	T_{max} (HR)	$t_{1/2, n}$ (HR)
1					
2					
3					
4					
5					
6					
Mean	7.48	9.80	2.02	1.3	3.9 (harmonic mean)
(S.D.)	(2.24)	(2.83)	(0.77)	(0.4)	(0.3)

(98° dosing interval)

* Plasma parameters:
[AUC] = Area under the plasma concentration-time curve
 C_{max} = Maximum plasma concentration
 T_{max} = Time to peak, (C_{max})
 $t_{1/2, n}$ = Effective plasma half-life

Figure 19-1

MEAN NORFLOXACIN PLASMA CONCENTRATION IN HEALTHY ELDERLY SUBJECTS GIVEN A SINGLE 400 MG TABLET

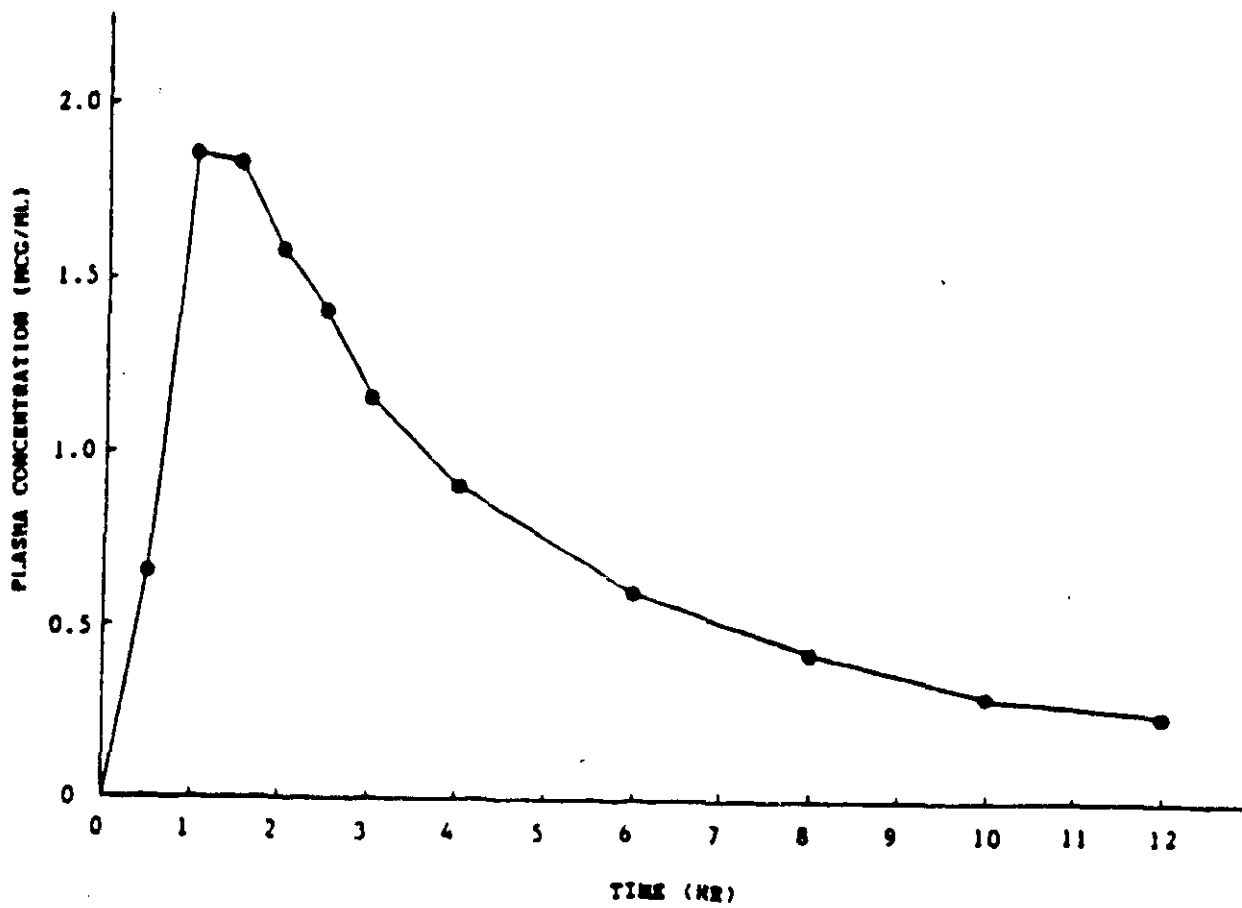


Table 19-3

DEMOGRAPHIC DATA FOR SUBJECT POPULATION

SUBJECT NUMBER	SEX	AGE, YR	WEIGHT, KG	HEIGHT, IN.	CREATININE CLEARANCE ML/MIN/1.73 m ²
<u>Individual Data</u>					
1	F	69	56.8	64	86
2	F	68	69.1	68	115
3	M	69	60.9	65	95
4	M	74	69.5	66	72
5	F	67	60.0	62	88
6	F	68	58.2	63	90
<u>Averages By Sex</u>					
1,2,5,6	F	68.0	61.0	64.3	94.8
3,4	M	71.5	65.2	65.5	83.5
<u>Overall Average (S.D.)</u>					
1 to 6	4F,2M	69.2 (2.5)	62.4 (5.5)	64.7 (2.2)	91 (14.1)

Table 20-1

Individual Demographic Data

Subject No.	Sex	Age (Yr)	Wt (Kg)	GFR (ml/min/1.73m ²)	Other Medication
Group I					
1	M	51	72	96 ¹	None
2	M	35	74	117 ³	None
7	M	23	103	131 ⁴	None
9	M	27	53	115	None
10	M	16	63	125	None
14	M	27	70	110 ²	None
20	M	31	73	111	None
8	M	49	89	148 ³	Warfarin, Pimozide
21	M	21	65	94	Hydroxychloroquine, Prednisolone
Group II					
5	M	60	62	60 ⁴	Furosemide, Slow K
6	M	51	88	31	Mixard, Furosemide, Spironolactone
12	M	56	64	46	Atenolol
25	F	55	75	56	Atenolol, Moduretic
26	F	45	43	60 ⁵	Captopril, Nifedipine, Diazide, Nitrazepam
27	M	53	73	74 ⁵	None
Group III					
3	M	69	62	12 ⁶	Salmophylline, Salbutamol, Furosemide, Aludrox
11	M	52	78	28	Chlorpropamide, Prednisolone, Furosemide
13	F	52	64	13	Flurbiprofen, Slow K, Insulin, Vit. B
15	M	65	57	17	Captopril, Hydralazine, Furosemide, Ampicillin, Erythromycin
17	M	72	55	11	Allopurinol, Lactulose, Alucaps, Temazepam
18	M	51	80	15	Alfacalcidol, Aluminum hydroxide

$\bar{x} = 54.5$ S.D. 14.6

Individual Demographic Data (Continued)

Subject No.	Sex	Age (Yr)	Wt (Kg)	GFR (ml/min/1.73m ²)	Other Medication
Group IV					
19	F	23	54	9.2	Atenolol, Bendrofluazide
23	F	69	68	7.5	Nifedipine, Hydralazine
16	M	54	53	6.6	Prednisolone, Isosorbide dinitrate, Allopurinol, Furosemide, Slow K
4	F	54	49	8.0 ³	Ferrous sulphate, Prazosin, Furosemide, Alucaps
22	M	43	77	7.6	Furosemide, Aludrox, Slow sodium
24	F	62	61	9.1	Aluminum hydroxide, Thyroxine

GFR = Glomerular Filtration Rate as determined on study days by Cr⁵¹-EDTA clearance unless otherwise noted.

1 ¹³¹I/¹²⁵I Hippuran clearance (assuming a filtration factor of 0.7)

2 Creatinine Clearance

3 Determined 2 months after the study

4 Determined 1 month after the study

5 Determined 1 month before the study

6 ⁵¹Cr-EDTA clearance determined 2 months after the study. Creatinine clearance was 4 ml/min 3 days before the study.

Table 20-2

Individual Total Urinary Recovery (U_u) and Cumulative Renal Clearance ($\dot{V}_{CL,R}$) of Norfloxacin In Renal Insufficiency Study

Subject No	U_u (mg)	Z Dose	$\dot{V}_{CL,R}$ (ml/min)
<u>Group I</u>			
1			
2			
7			
8 ⁴			
9			
10			
14			
20			
21 ⁵			
Mean		28.2	297.1
(± S.D.)		(12.8)	(117.4)
<u>Group II</u>			
5 ⁴			
6 ⁵			
12			
25			
26			
27			
Mean		35.3	264.5
(± S.D.)		(9.2)	(83.2)
<u>Group III</u>			
3			
11 ¹			
13			
15 ²			
17 ³			
18			
Mean		6.7	17.8
(± S.D.)		(4.1)	(4.4)

Individual Total Urinary Recovery (U_u) and Cumulative Renal Clearance ($\dot{V}_{CL,R}$) of Norfloxacin In Renal Insufficiency Study (Continued)

Subject No.	U_u (mg)	Z Dose	$\dot{V}_{CL,R}$ (ml/min)
<u>Group IV</u>			
4			
16 ⁴			
19 ⁴			
22 ³			
23			
24			
Mean		2.4	14.7
(± S. D.)		(1.1)	(8.4)
1 Questionable urinary recovery 0-2 hr. No estimate of $\dot{V}_{CL,R}$ possible. Excluded from mean. 2 Questionable urinary recovery 4-8 hr. Urinary recovery 4-6 estimated from $\dot{V}_{CL,R}$ and AUC. 3 No drug detectable in urine. 4 Questionable urinary recovery 0-2 hr. Urinary recovery estimated from $\dot{V}_{CL,R}$ and AUC. 5 Questionable urinary recovery. Excluded from mean. 6 Questionable urinary recovery. No drug detectable in urine after 12 hr but serum levels detectable through 24 hr. Excluded from mean.			

Table 20-3

Individual Area Under the Serum Concentration-Time Curve, [AUC],
for Norfloxacin in the Renal Insufficiency Study

Subject No.	[AUC] ₀₋₈ (mcg·hr/ml)	[AUC] ₀₋₂₄ (mcg·hr/ml)
<u>Group I</u>		
1		
2		
7		
8		
9		
10		
14		
20		
21		
Mean (±S.D.)	<u>5.38</u> (1.93)	<u>6.94</u> (2.73)
<u>Group II</u>		
5		
6		
12		
25		
26		
27		
Mean (±S.D.)	<u>7.62</u> (2.00)	<u>9.53</u> (2.47)
<u>Group III</u>		
3		
11		
13		
15		
17		
18		
Mean (±S.D.)	<u>9.18</u> (2.41)	<u>24.01</u> (13.49)
<u>Group IV</u>		
4		
16		
19		
22		
23		
24		
Mean (±S.D.)	<u>7.79</u> (5.31)	<u>16.46</u> (14.52)

1 See Table 20-2.

2 Excluded from mean.

Table 20-4

Individual Maximum Serum Concentration (C_{MAX}) of Norfloxacin
and the Time that Maximum Occurred (T_{MAX}) in the Renal
Insufficiency Study

Subject No.	C_{MAX} (mcg/ml)	T_{MAX} (hr)
<u>Group I</u>		
1		
2		
7		
8		
9		
10		
14		
20		
21		
Mean ($\pm$ S.D.)	$\overline{1.51}$ (0.56)	$\overline{1.4}$ (0.4)
<u>Group II</u>		
5		
6		
12		
25		
26		
27		
Mean ($\pm$ S.D.)	$\overline{1.91}$ (0.71)	$\overline{1.3}$ (0.4)
<u>Group III</u>		
3		
11		
13		
15		
17		
18		
Mean ($\pm$ S.D.)	$\overline{1.70}$ (0.43)	$\overline{1.8}$ (1.1)
<u>Group IV</u>		
4		
16		
19		
22		
23		
24		
Mean ($\pm$ S.D.)	$\overline{1.70}$ (0.92)	$\overline{1.8}$ (1.2)

Table 20-5

Individual Effective Serum Half-life ($t_{1/2, n}$) of Norfloxacin in the Renal Insufficiency Study

Subject No.	$t_{1/2, n}$ (hr)	Subject No.	$t_{1/2, n}$ (hr)
<u>Group I</u>		<u>Group III</u>	
1		3	
2		11	
7		13	
8		15	
9		17	
10		18	
14		Mean ¹	6.57
20			
21		<u>Group IV</u>	
Mean ¹	3.47	4	
		16	
<u>Group II</u>		19	
5		22	
6		23	
12		24	
25		Mean ¹	6.40
26			
27			
Mean ¹	3.38		

¹ Harmonic Mean

² See Table 9.

Figure 20-1

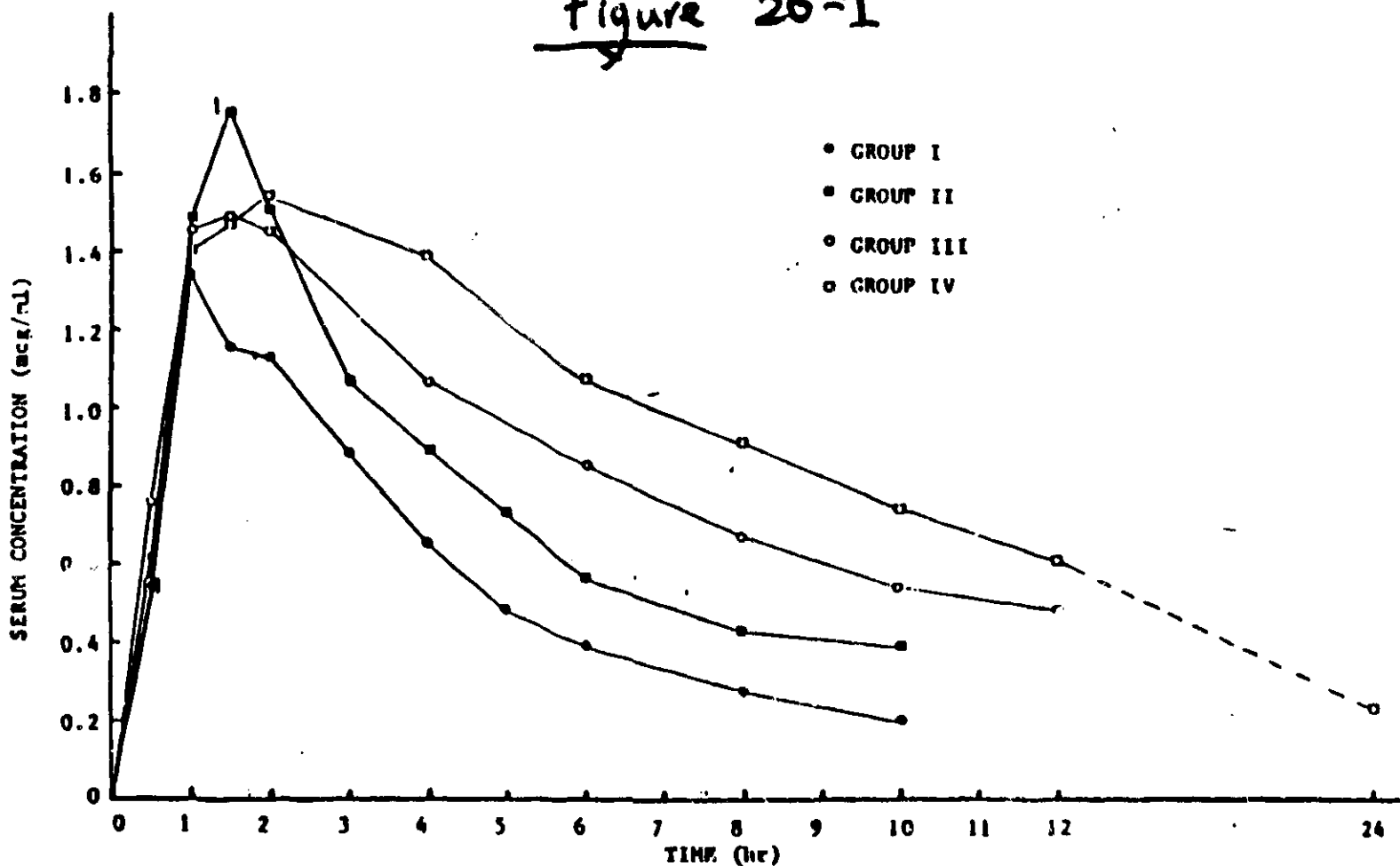


Figure 5. Mean norfloxacin serum concentration profiles.

Table: 21-1

Individual Plasma Concentrations (C_p) of Norfloxacin Following Administration of One 400-mg Tablet (Old Formulation)

Subject No.	C_p ($\mu\text{g/ml}$) at ...hr.									
	0	0.5	1.0	1.5	2	3	4	6	8	12
51										
52										
53										
54										
55										
56										
57										
58										
59										
60										
61										
62										
63										
64										
65										
66										
67										
68										
69										
70										
Mean	-	0.48	1.17	1.35	1.29	0.96	0.78	0.53	0.40	0.23

Table: 21-2

Individual Plasma Concentrations (C_p) of Norfloxacin Following Administration of One 400-mg Tablet (New Formulation)

Subject No.	C_p ($\mu\text{g/ml}$) at ... hr									
	0	0.5	1.0	1.5	2	3	4	6	8	12
51										
52										
53										
54										
55										
56										
57										
58										
59										
60										
61										
62										
63										
64										
65										
66										
67										
68										
69										
70										
Mean	-	0.94	1.48	1.29	1.05	0.80	0.67	0.48	0.36	0.22

C_{max}
75-125

Table 21-3

Ratio Eval (MSD/Kyorin)

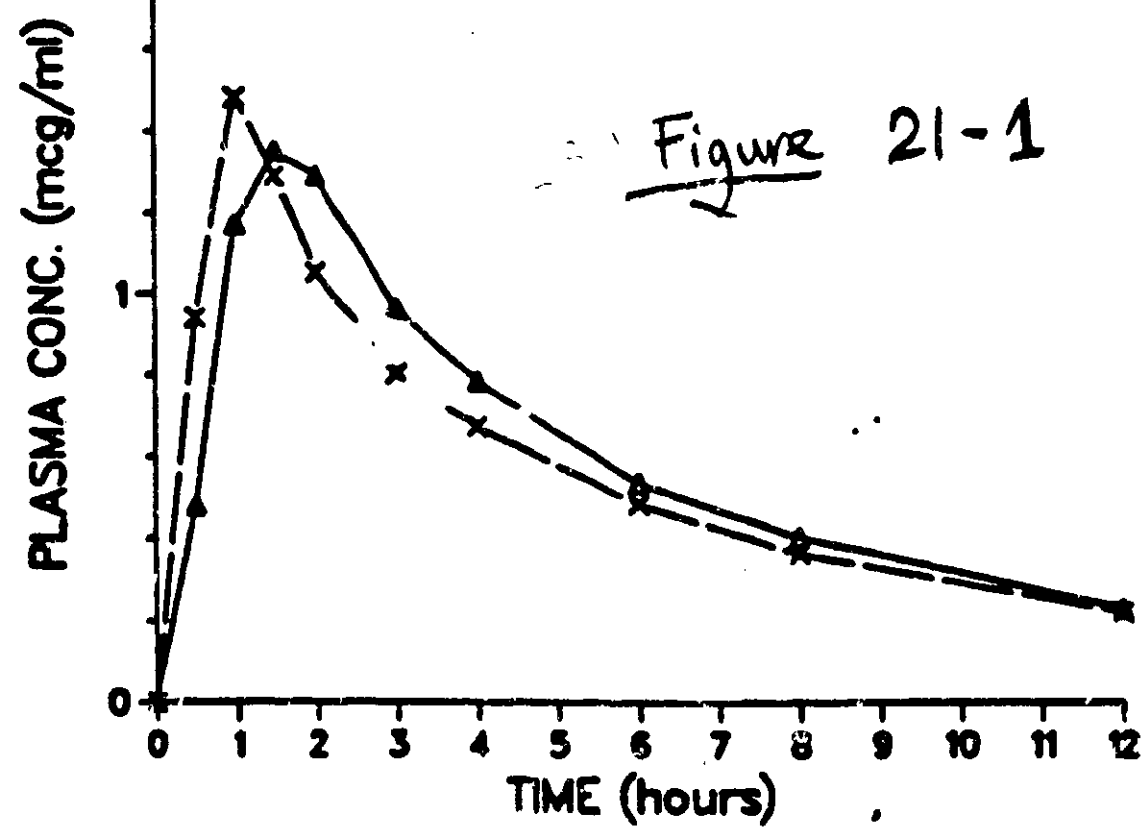
Individual Peak Plasma Concentration (C_{max}) of Norfloxacin and Time that Peak Occurred (T_{max}) After Tablet Administration

- Sub#
- 1 - 1.19
- 2 - 1.03
- 3 - 1.44* (H)
- 4 - 0.77
- 5 - 1.28* (H)
- 6 - 1.03
- 7 - 0.45* (L)
- 8 - 0.81
- 9 - 0.97
- 10 - 1.19
- 11 - 0.67* (L)
- 12 - 1.21 (1.2058)
- 13 - 0.90
- 14 - 1.05
- 15 - 1.78* (H)
- 16 - 1.40* (H)
- 17 - 1.43* (H)
- 18 - 1.08
- 19 - 0.90
- 20 - 0.48* (L)

Subject No.	(Kyorin)		(MSD)		T _{max} Ratio Eval
	C _{max} (ug/ml)	T _{max} (hr)	C _{max} (ug/ml)	T _{max} (hr)	
1 - 51					
2 - 52					
53					
54					
55					
56					
57					
58					
58 (L)					
60					
61					
62					
63					
64					
65					
66					
67					
68					
69					
70					
Mean (±S.D.)	1.56 (0.48)	1.4 (0.4)	1.54 (0.42)	1.1 (0.4)	% w/ 75-125
CV (%)	(30.8%)	(28.6%)	(27.3%)	(36.4%)	10/20

% withm 75-125 12/20 (0.62)

[5 Hi]
[3 L]



Legend
 Δ OLD FORM.
 X NEW FORM.

1 Page(s)

Redacted

Table 21-5

Individual Total Urinary Recovery (U) of Norfloxacin Following Single-Dose Administration of Old and New Tablet Formulations

Subject No.	Kyorin - 412 mg		MSD - 414 mg		Rate $\frac{U}{D}$
	U (mg)	X-Dose	U (mg)	X-Dose	
51					
52					
53					
54					
55					
56					
57					
58					
59					
60					
61					
62					
63					
64					
65					
66					
67					
68					
69					
70					
Mean		27.9		27.0	
(±S.D.)		(8.9)		(8.5)	
		(CV 31.9%)		(CV 31.5%)	

- 1 No sample or no void 1-2, and 6-8 hr. Excluded from mean.
- 2 No void 0-1 hr. Renal clearance indicates drug retrieved in 1-2 and 2-3 hr collection.
- 3 No sample or no void 4-6 hr.
- 4 No sample or no void 8-12 hr. Urinary excretion estimated from $\bar{V}_{CL,R}$ and AUC.
- 5 No void 1-7 and 3-4 hr. Renal clearance indicates drug recovered in 2-3 hr collection.
- 6 No sample 12-24 hr. Excluded from mean.
- 7 No sample or no void 8-12 and 24-48 hr. Urinary excretion 8-12 estimated from $\bar{V}_{CL,R}$ and AUC. Later sample assumed insignificant.
- 8 Five urine collections covered the interval 24-48 hr. One sample missing or no volume recorded.
- 9 Three and 7 urine collections covered the interval 12-24 and 24-48 hr., respectively. No volume given for 1 sample 12-24 and 2 samples missing 24-48 hr.
- 10 Four urine collections covered the interval 24-48 hr. No volume given for 1 sample or 1 sample missing.
- 11 No sample or no void 2-3 hr. Excluded from mean.

Table 21-6

Individual Estimates of Norfloxacin Relative Bioavailability
From 400-mg New Formulation Tablets (F_{NEW}) as Compared to
Old Formulation Tablets (F_{OLD})

Subject No.	F_{NEW}/F_{OLD}
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
Geometric Mean	0.94

¹ Incomplete urinary recovery

Cont 9

REL. BIOAVAILABILITY	NEW FORM/OLD FORM
$\bar{X}$ GEOMETRIC MEAN 95% C.I.	0.94 — 0.94 0.80-1.09 — 0.80-1.09
POWER (10% DIFFERENCE) .27 (15% DIFFERENCE) .34 (20% DIFFERENCE) .61 (25% DIFFERENCE) .99	0.27 0.54 0.81 0.99
POSTERIOR PROB. (10%) .68 (15%) .89 (20%) .97 (25%) .99	

NOTE: PATIENTS 9, 14, 60 AND 68 WERE EXCLUDED FROM BIOAVAILABILITY CALCULATIONS.
ALL INCLUSIONS/EXCLUSIONS WERE CARRIED OUT IN ACCORDANCE WITH THE BIOPHARMACEUTICS REPORT.

Table 21-7

Individual Cumulative Renal Clearance ($\dot{V}_{CL,R}$) and Total Area Under the Plasma Concentration-Time Curve, $[AUC]_{\infty}$, for Norfloxacin

Subject No.	Kyorin		MSD		Ratios MSD/Kyorin
	Old Formulation		New Formulation		
	$\dot{V}_{CL,R}$ (ml/min)	$[AUC]_{\infty}$ (mcg.hr/ml)	$\dot{V}_{CL,R}$ (ml/min)	$[AUC]_{\infty}$ (mcg.hr/ml)	
51					
52					
53					
54					
55					
56					
57					
58					
59					
60					
61					
62					
63					
64					
65					
66					
67					
68					
69					
70					
Mean	261.9	7.82	270.0	6.94	
(±S.D.)	(80.7)	(2.53)	(63.4)	(1.69)	
CV (%)	30.5	32.3	23.3	24.3	

¹ Incomplete urine collection

$\frac{412}{414} = 0.995 \rightarrow 1$
 $\frac{414}{412} = 1.0049 \rightarrow 1$
 $\bar{x} = 0.967$
 $S.D = 0.313$
 $CV \bar{x} = 32.4\%$
 $\% \text{ within } 75-125 = \frac{10}{17} = 58.8$

Norfloxacin
 Study No. 59
 Dr. Ziny

BASED ON SUBJECTS WITH COMPLETE URINARY RECOVERY ON B O T H FORMULATIONS

PARAMETER	N	OLD FORMULATION		NEW FORMULATION		CHANGE (NEW-OLD)		
		MEAN	S.D.	MEAN	S.D.	MEAN	S.D.	
PEAK SERUM CONC.--MCG/ML	20	1.56	0.48	1.54	0.42	-0.02	0.50	NS
TIME TO PEAK CONC.--HR	20	1.35	0.43	1.07	0.37	-0.27	0.57	*
AUC--MCG/ML X HR	17	7.71	2.58	6.90	1.73	-0.82	2.14	NS
RENAL CLEARANCE--ML/MIN	18	266.10	83.98	269.98	63.44	3.88	61.25	NS
URINARY RECOVERY--MG (UNADJ)	20	117.43	37.78	106.55	36.94	-10.88	36.74	N/A
URINARY RECOVERY--X DOSE (A)	17	27.74	8.98	26.72	8.62	-1.02	7.60	NS

NOTE: BASED ON 412 AND 414 MG FOR THE OLD AND NEW FORMULATIONS RESPECTIVELY.

NOTE: SUBJECT 060 WAS EXCLUDED FROM MEAN OF UR-X DOSE BECAUSE OF INCOMPLETE URINARY RECOVERY FOLLOWING TREATMENT A (OLD FORMULATION)
 SUBJECTS 054 AND 060 WERE EXCLUDED FROM MEAN OF UR-X DOSE BECAUSE OF INCOMPLETE URINARY RECOVERY FOLLOWING TREATMENT B (NEW FORMULATION).
 RENAL CLEARANCE CALCULATIONS WERE AVAILABLE FOR SUBJECT 060 BUT NOT FOR SUBJECTS 054 & 060.
 ALL THREE SUBJECTS WERE EXCLUDED FROM AND ANALYSES ON AUC AND RELATIVE BIOAVAILABILITY.

ALL EXCLUSIONS WERE CARRIED OUT IN ACCORDANCE WITH THE BIOPHARMACEUTICS REPORT.

NS-- NOT STATISTICALLY SIGNIFICANT.

N/A--NOT ANALYSED.

*--DIFFERENCE IS STATISTICALLY SIGNIFICANT, P<0.05

ANALYSES ADJUSTED FOR PERIOD.

Means of Pharmacokinetic Parameters

Table 21-8

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs and Biologics
Office of Drug Standards

DATE : MAY 6 1986

TO : Edward Tabor, M.D., Director
Division of Anti-Infective Drug Products, HFN-815

FROM : Jerome Skelly, Ph.D., Director
Division of Biopharmaceutics, HFN-220

SUBJECT : Biopharmaceutics Recommendation of Approval
NDA-19,384 ; Norfloxacin - 400 mg tablet
Merck, Sharp & Dohme Research Labs

Background:

Norfloxacin is a quinoline carboxylic acid antibacterial agent structurally related to compounds such as nalidixic, oxolinic, and pipemidic acids. The proposed indications are for the treatment of infections caused by susceptible strains of micro-organisms, in complicated and uncomplicated cystitis, gonococcal urethritis, acute gastroenteritis and prophylactically in profound neutropenia. The proposed dosing follows.

Uncomplicated UTI - 400 mg BID X 7-10 days
Complicated UTI - 400 mg BID X 10-60 days
Uncomplicated GC urethritis - 600 mg followed by 600 mg 4 hours later
Acute gastroenteritis - 400 mg BID X 5 days
Prophylaxis in neutropenia - 400 mg TID for duration of neutropenia
(no recommendations available beyond 8 weeks)

There is no record of any previous submissions to the Division of Biopharmaceutics concerning norfloxacin, the subject of NDA 19-384. Norfloxacin is licensed by Merck from Kyorin Pharmaceutical Co., Ltd. (Japan).

Results:

Dose proportionality was determined by administration of 200, 400, 800, 1200 and 1600 mg single doses to 14 subjects. Based on AUC, dose proportionality across the single dose range 200-1600 mg exists for norfloxacin. However, the peak concentration (Cmax) of norfloxacin does not increase proportionately with the increase in a single dose beyond 800 mg. After a 400 mg single dose (capsule), mean Cmax was approximately 1.6 ug/ml (Tmax about 1 hour), whereas following a single 1600 mg dose, Cmax was approximately 3.8 ug/ml (Tmax about 2 hours). The mean Cmax observed after a single 400 mg dose (MSD direct compression tablet) was 1.5 ug/ml with a corresponding mean Tmax of about 1 hour.

Because clinical studies utilized products manufactured by different processes and with different formulations (Kyorin vs MSD), Zinny conducted a bioequivalency study with the MSD direct compression tablet and the Kyorin product. Based on this study, the MSD and clinically studied Kyorin tablet products have equivalent extents of absorption. Based on mean Tmax, the rate of absorption of the MSD formulation is faster than the Kyorin formulation (1.07 vs 1.35 hrs). The MSD-400 mg tablet proposed for marketing is very slightly different from that studied in the bioavailability and bioequivalency studies. Dissolution data on both dosage forms indicate the equivalence of both dosage forms. The relative bioavailability of the 400 mg tablet compared to a solution showed a mean dose adjusted AUC(0-infinity) ratio of 0.99 (C.V. 49 %). While the power is inadequate to establish statistical equivalence to the administered solution, it is adequate to define the pharmacokinetics. About 30-35 % of the administered dose of norfloxacin is recovered in the urine over 24-48 hours as parent (25-30 %) and metabolites (4-8 %). Fecal recovery accounts for approximately 30 % of the administered dose but may be much greater. Although fecal recovery is difficult to quantitate because of analytical assay difficulties, it may be accounted for by incomplete GI absorption, biliary excretion and/or other factors. Thus while the fraction of the administered dose orally absorbed cannot be determined on the basis of the data submitted, one may conclude that it is at least 30-35 percent. The elimination half-life of the parent drug norfloxacin is about 5 hours. Protein binding of norfloxacin measured by ultrafiltration is about 14 %. The "effective half-life for accumulation" for an 8 hour dosing interval is about 3 hours. The renal clearance of norfloxacin measured in adults with normal renal function is about 300 ml/min.

Because of the effect of pH on the solubility of norfloxacin, as well as data from an inconclusive study by Kumasaka where the administration of norfloxacin with food appeared to alter the absorption characteristics of the drug, the effect of food on the proposed marketed product needs investigation. If food effects are not resolved with a controlled study, then this issue should be addressed in the labeling. In addition, since reduced enteral absorption of ciprofloxacin (a quinoline carboxylic acid derivative) has been demonstrated, coadministration of norfloxacin and antacids should be discouraged in the labeling because of the possibility of complexation resulting in a decrease in absorption.

The dose of norfloxacin needs to be adjusted in the elderly and patients with renal dysfunction. We recommend that dosing guidelines provided by the firm be clarified because of drug accumulation/decreased clearance.

Our concerns about crystalluria which were discussed in a meeting with HFN-815 on March 13, 1986 are outlined in Section IX of the attached biopharmaceutics review. It appears that with the recommended doses of norfloxacin, crystallization should not be a problem with the parent compound in most patients. However, concern is expressed about the potential for formation of crystals under conditions commonly seen (e.g. low urine flow, alterations in urine pH), when receiving doses greater than those recommended, and in vegetarians who characteristically have a high urine pH. Crystallization has been reported in subjects given 1200 and 1600 mg as a single dose. Although drug crystals were not reported in the bioavailability studies submitted, the fluid loaded condition of the subjects prevents interpretation of the clinical results of these studies for resolving safety issues by the Division of Biopharmaceutics. Labeling should include specific instructions concerning maintenance of a good fluid intake in all patients so as to prevent crystallization of drug in the urinary tract.

The proposed dissolution method and specification are the following,

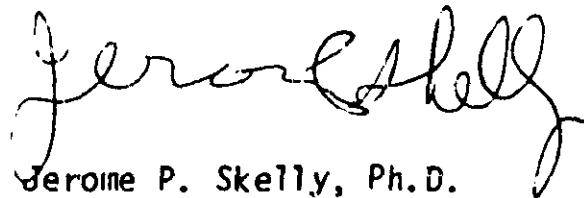
USP Apparatus II, 50 rpm, 37 degrees centigrade,
750 ml of 0.05 M sodium acetate buffer (pH 4.0)
Q specification of [REDACTED]
Assay via HPLC methodology

The dissolution method and specification are acceptable from a biopharmaceutics perspective.

Overall Conclusion:

The data provided in NDA 19,384 for the 400 mg tablet is acceptable from a Division of Biopharmaceutics point of view. This submission fulfills the bioavailability and bioequivalence requirements set forth in the regulations of 21 CFR, part 320. However, suggested phase IV commitments (i.e. food/antacids effect study) as outlined in the review should be conveyed to the firm.

Comments in the review pertaining to labeling should be considered by HFN-815 when evaluating the package insert. These issues include food effects, co-administration of norfloxacin with antacids and ensuring adequate hydration in patients.



Handwritten signature of Jerome P. Skelly in cursive script.

Jerome P. Skelly, Ph.D.

Prepared by Gene D. Mason, Pharm.D.
RD Initialed by John Hunt
FT Initialed by C.T. Viswanathan, Ph.D.

N-19384-1

WDA 19384

Best

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REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 19-384 (Original Submission, dated 1/14/85)

Date Review Completed: 2/3/86

Applicant: Merck Sharp & Dohme

Drug: Noroxin™ Coated Tablets

Code Names: Kyorin AM-157; NK-0366

Category: Quinolone urinary antibacterial

Related Drugs: All quinolone urinary antibacterials

For chemical technical data, the reader is referred to my review of IND

PRECLINICAL STUDIES

Labs Performing Studies: Kyorin Pharmaceutical Co., Ltd., Japan; MSD, USA; and various Italian, French, Canadian res. institutes & universities.

Note: "#" is used to designate foreign studies.

ACUTE TOXICITY

These studies follow the order of Vol. 2.43, from page III-00510 on.

Animals Used: Rats; dogs; mice; monkeys

#1. Acute Toxicity [Kyorin]

IV LD₅₀: 220 mpk in mice
Oral LD₅₀: 4000 mpk in rats & mice

#2. Acute Toxicity & Lethality in Rats & Mice

MLD for both species: 3000 mpk, PO; 1500 mpk, SC; 300 mpk, IV

#3. Oral Toxicity of the 6 Metabolites of the Drug [Kyorin]

Oral LD₅₀s: M-1, M-4 (2), M-5: Greater than 2000 mpk
M-2, M-3, M-4 (1): Greater than 4000 mpk

SUBACUTE TOXICITY

#1. 1-Month Oral Toxicity in Rats [Kyorin]

Doses: 250, 500 & 1000 mpk/day. A slight but stat. sig. increase in urinary K excretion was seen in F rats at the MD & HD, but no concurrent decrease in serum K level. Besides enlargement of the cecum at the HD, which is usual in these studies, no toxic signs were seen.

#2. 1-Month Oral Toxicity in Rats [

Doses employed were the same as in the previous study. There was no appreciable toxicity; not even potassuria.

#3. 1-Month Oral Toxicity in Dogs

Doses: 50, 100 & 200 mpk/day. No drug related changes observed.

#4. Subacute Oral Toxicity Study in Dogs [Kyorin]

Doses: 25, 50 & 100 mpk b.i.d. The only abnormality was slightly increased glucose-6-phosphatase activity in the liver of most drug-treated groups; the biological sig. of this change is not known. No other drug-induced changes were observed.

Reviewer's Comment: Regarding the enzyme changes, I don't know how to interpret this finding either.

5. 14-Week Oral Toxicity in Dogs Receiving NH₄Cl [MSDRL, USA]

This is a repetition of a study in which, at the same doses as in this study, crystalluria and/or urinary obstruction occurred. Based on the knowledge that in vitro, the solubility of the drug is substantially increased under pH 6, the study was repeated in the USA with simultaneous administration of NH₄Cl (oral). No detailed write-up of that study was provided. Since the MSD study is pivotal, a detailed review will be presented here.

Animals, Doses, Route & Duration: Beagles, 43-45 wks of age; 4 groups, 3/sex/gp - Controls, 50, 150 & 300 mpk/day; oral (gavage); 14 wks, with acidification by adding 1% ammonium chloride to the drinking water.

Results

Mortality: Four in all gps due to aspiration.

<u>Week 3</u>	<u>Week 6</u>	<u>Week 8</u>
T M @ 300mpk	T M @ 150mpk	T F @ 150mpk; 1 F @ 300 mpk

The following dogs had aspiration pneumonia as a result of vomition and regurgitation: Controls, 2/6; LD, 5/6; MD, 4/6; HD, 4/6. [Reviewer's Comment: Since the controls did not receive the drug, but only the vehicle, apparently the vehicle itself was irritating to the stomach of some control dogs, resulting in this reaction.]

Body Wt: All animals at the HD and several from other gps (including controls) lost body wt. The mean total wt change (kg/gp) was: Controls, +0.2; LD, -0.4; MD, -0.1; HD, -0.8.

Crystalluria: The admin. of ammonium chloride to drinking water was routinely effective in reducing urine pH to an approx. range of 5.5-6.5.

Drug crystals shaped like sea urchins and/or fine needles were occasionally seen in urine from dogs in each drug-treated gp. Those found during Drug Weeks 11, 12 & 13 were shown by high performance liquid chromatography to be MK-366. The severity & incidence of crystalluria was greatest in the HD gp.

No evidence of urinary tract obstruction was observed. Chronic tubulointerstitial nephritis (unilateral, slight-moderate) was present in 1 M each in the MD & HD gps. This lesion is not typical of a toxic change and its association to treatment is unknown.

Other: No other drug-related changes were seen in urinalysis, hematology or serum chemistry determinations.

No dose-related changes were seen in organ wts or on gross exam or histomorphologic exam of tissues.

6. Urinary Drug Disposition Study in Dogs [MSDRL, USA]

An oral study was initiated in beagle dogs with MK-366 to determine whether crystals of MK-366 or its metabolites can be isolated from the urine. The drug was administered to 4 dogs (2/sex) @ 300 mpk/day for 4 days, by oral gavage (as a suspension in aq. methylcellulose). A similar gp of dogs received 0.5% methylcellulose and served as controls. Urine samples were collected 2, 4, 6 & 24 hrs following dosing and were analyzed for undissolved MK-366-related material; 24-hr urine samples were also examined microscopically for crystals & cells. All dogs were killed at termination and both kidneys & urinary bladders removed and samples from each fixed in 10% neutral buffered formalin.

Results: One drug-treated dog showed large numbers of needle-shaped crystals on microscopic exam, suggestive of drug crystals. Three or 4 types of crystals were detected by HPLC in the urine of the dogs. The majority of the crystals seen were MK-366.

#7. Subacute Toxicity Study in Monkeys [Kyorin]

Material Tested: MK-366 administered as oral suspension

Animals, Doses & Duration: Macaca fascicularis; 4 groups, 2 M/gp; Controls (sterile dist. water), 25, 50 & 100 mpk b.i.d.; 4 wks

Schedule of Parameters Measured: Food & water intake, daily; body wt prior to treatment and day of sacrifice; hematological & serum biochem. parameters, pretest and after 2 & 4 wks of treatment; urinalysis, at necropsy. The following enzyme activities were determined in all animals at termination: ATP; glucose-6-phosphatase; B-glucuronidase; heart ATP; kidney ATP; bone marrow alkaline phosphatase; skeletal muscle ATP.

Wts of brain, pituitary, submandibular gland, thyroid, thymus, heart, lung, liver, pancreas, cecum, spleen, kidneys, adrenals, testes & epididymides were recorded at necropsy. Various tissues were fixed in

10% formalin. May-Giemsa stained bone marrow smears were prepared from all monkeys. Microscopic exam was done on hematoxylin- & eosin-stained sections from an extensive list of tissues.

Results: No changes attributable to treatment were seen.

8. Subacute Oral Toxicity Study in Immature Rats

Animals, Doses, Route & Duration: Immature (age under puberty) white laboratory rats (strain not specified); 4 groups - Control, 250, 500 & 1000 mpk/day; orally in suspension; 7 days/week for 4 weeks

Schedule of Parameters Measured: Observation of signs of toxicity & body wt gain daily; food & water intake weekly; hematology, serum biochemistry, enzyme activity of kidney, heart & skeletal muscle, urinalysis, organ wt and gross & microscopic exams of various tissues near or at the end of the study.

Results

Body Wt; Food & Water Intake: No drug-related changes.

Hematologic & Serum Biochemical Parameters; Urinalysis: Stat. sig. changes in some of these parameters; however, the differences were small, within the limits of normal variation, and generally not dose-dependent.

Reviewer's Comment: The applicant does not consider these changes treatment-related. This might be true, but where are the reports on the expected arthropathy, at least clinically?

The following is a verbatim quotation from the report. Note: It does not even mention joint involvement.

"An increase of absolute and relative weights of cecum was found in drug-treated males and females. This is not an uncommon finding in animals treated with antibacterial agents for long periods. There were no other organ weight changes or gross or microscopic changes attributable to treatment with MK-366."

CHRONIC TOXICITY

#1. 6-Month Chronic Toxicity Study in Rats [Kyorin]

Animals, Doses, Route & Duration: Laboratory white rats (strain not specified); 4 gps, 10/sex/gp - Controls, 125, 250 & 500 mpk/day; orally in suspension; 7 days/week for 6 mos. The age of the rats was 7 weeks at the start of the study. [Note: Puberty onset is at the end of the 10th wk of life in rats. Thus, for 3 wks this was a study in immature (juvenile) rats. I wonder if arthropathy was experienced during the first 3 wks of the study. However, since it is difficult to observe it clinically in the rat, and since the histopathology at the end of the 6-mo. treatment period might be negative (if they paid any attention to

the articular cartilage of the weight bearing joints), this study might indicate negative results with respect to arthrosis, although it could occur but remain unnoticed clinically during the first 3 wks of treatment.]

Schedule of Parameters Measured: Body wt, prior to the study and weekly thereafter; clinical signs, daily; food & water intake, once/week; ophthalmic exam, at 3 mos. & 6 mos. after start of treatment; hematology & urinalysis on all rats 2, 4 & 6 mos. after initial treatment; serum biochemistry on all rats 6 mos. after start of the study; glucose-6-phosphatase & B-glucuronidase, kidney ATP, bone marrow alkaline phos. activity in 5/sex rats from control & HD gps at study termination. All animals were terminally necropsied, and organ wts (heart, spleen, thymus, pituitary, adrenal, liver, pancreas, lung, brain, kidneys, testes, epididymides, prostate, ovaries & uterus) were recorded. Various tissues were fixed in 10% formalin. Microscopic exam was done on hematoxylin & eosin-stained sections of extensive tissues of all rats. Samples of liver & kidney were examined by using transmission electron microscopy. In addition, cochlea were examined using a scanning electron microscope to determine ototoxic potential.

Results: Slight body wt retardation was seen in M rats at the MD & HD. This did not occur in F. Serum albumin/globulin ratio showed tendency to increase in M at all dose levels and in F at the MD & HD. This was considered not to be treatment-related. There were no other changes attributable to treatment, including ototoxicity.

#2. Chronic Toxicity Study in Rats L

This study is identical to the previous study, but performed in Italy.

Results: No treatment-related changes in any of the parameters examined.

#3. 26-Week Oral Toxicity Study in Rats

Animals, Doses, Route & Duration: Laboratory white rats, 5 wks of age at study initiation; 4 gps - Controls, 50, 200 & 600 mpk/day; orally (gavage), suspended in aq. methylcellulose; controls received methylcellulose sol'n only.

Results

Signs: Grey feces (unabsorbed drug) in all treated gps; slight salivation occasionally in the HD gp.

Food & Water Intake: No significant effects.

Mortality: None

Body Wt Gain: Slight, but stat. insig. decrease in body wt gain in the HD M which could be treatment-related.

Hematology, Serum Biochemistry & Urinalysis: (weeks 4, 8, 12, 18 & 25)
No drug-related hematological changes. Very slight but stat. sig. dec. in serum proteins were observed in M at the HD at all scheduled exams and in M at the MD in drug wks 8 & 12 (significance unknown).

Crystalluria, consisting of needle-shaped and "sea urchin" shaped crystals (dihydrate & magnesium salt of MK-366), occurred in rats from the MD & HD gps. Crystalluria was most common in M at the HD. There was no crystalluria in LD rats. A high incidence (40-100%) of cecal enlargement was seen at all dose levels. This is not an uncommon finding in rats treated with antibiotics for a prolonged periods. There were no other treatment-related changes seen at necropsy including organ wt & histopathology.

#4. 54-Week Oral Toxicity Study in Rats

Animals, Doses, Route & Duration: Albino rats [Cr:CD (SD) Br strain]; 20/sex - Controls, 50, 200 & 600 mpk/day; orally by gavage as a suspension; up to 54 wks; controls rec'd dist. water. The age of the rats at study initiation was 7 wks. N.B.: This age is one week short of the onset of puberty, i.e., 8 wks.

Schedule of Parameters Measured: Physical exam of all rats, daily; more detailed physical exam of abnormal animals, weekly; body wts twice/week for 2 wks during the pretreatment period, the first 13 wks of feeding, and thereafter once/week & preterminally; ophthalmic exam of all animals prior to treatment and of control & HD rats during drug weeks 27 & 52; hematology, serum biochem. & urinalysis, drug weeks 6, 12, 25 & 51 using the first 10/sex rats of each gp. Necropsy was performed on all rats dead or sacrificed during the course of the study, and on the rest at termination. At necropsy: body wt measurement; histopathology on all dead & sacrificed rats, 10/sex from control & HD gps, and any rat from any group showing gross lesions at necropsy.

Results

Physical Exam: No abnormalities.

Mortality or Sacrifice of Moribund Rats: Total of 19 (controls, 4; LD, 2; MD, 7; HD, 6). None were considered to be treatment-related.

Body Wt: Lower than that of controls in all treated gps at termination; however, it was sig. different in the MD & HD F.

Ophth. Exam: No abnormalities attributable to treatment.

Hematology, Serum Biochem. & Urinalysis: Normal biological variations

Gross Pathology: Findings not indicative of drug treatment (normal abnormalities).

Organ Wt: Stat. sig. dec. in mean abs. wts of liver, spleen, heart & brain of the HD M, compared to controls. "The differences for the liver, spleen and heart were reflected in the organ weight relative to brain weight. Liver and spleen weights relative to body weight were also statistically significantly decreased. These findings are not considered to be biologically significant since all mean values are within the 95% range of controls values and since there were no histomorphological changes that could account for these organ weight changes."

Histopathology: No drug-related changes.

#5. 13-Month Chronic Toxicity Study in Dogs [Kyorin]

Animals, Doses, Route & Duration: Dogs (breed not specified), 6 mos. old; 4 gps, 4/sex/gp - Controls, 25, 50 & 100/200* mpk/day; orally as a coated tablet; 6 days/wk for 13 mos; controls rec'd placebo tablets.

* "Dogs given 100 mpk/day for 10 months of the study were given 200 mpk/day for the remainder of the study."

Schedule of Parameters Measured: Clinical signs, daily; body wt, weekly; hematology, serum biochemistry, prior to study initiation and 3, 6, 9 & 13 mos. after the initial dose; urinalysis, 13 mos. after initial dose; ECG & ophth. exam, 13 mos. after initial dose. Organ enzymes monitored at termination were: liver ATP, glucose-6-phos. & B-glucuronidase, heart ATP, creatinine phosphokinase, kidney ATP, skeletal muscle ATP, creatinine phosphokinase, bone marrow alkaline phos. Similarly, drug metabolizing enzymes of the liver (cytochrome P-450; aminopyrimidenethylase; aniline hydroxylase) were examined at termination. Sera of all dogs were examined for specific antibodies vs. the drug at termination. All dogs were necropsied at termination and examined histologically.

Results: All of the above parameters remained normal.

Reviewer's Comment: The initial age of the dogs is the minimal age of puberty in this species. This explains the lack of degenerative joint disease.

#6. Chronic Oral Toxicity in Dogs

This is a shorter version of the previous (Kyorin) study. However, it lacks the wealth of parameters measured of the Kyorin study. Since this is not a pivotal study, it will be narratively reviewed.

MK-366 was administered orally as a susp. in distilled water, to gps of dogs (1/sex/gp) for 20 wks at dose levels of 25, 50 & 100 mpk/day. A control gp was established and rec'd distilled water. The animals were observed for general condition & behavior. Body wts were recorded weekly. Hematology, blood chemistry & urinalysis were done at the beginning and at the end of treatment. All animals were necropsied and major organs weighed. Histopath. exam of selected organs was performed.

Results: There were no treatment-related changes in any parameter examined. N.B.: No crystalluria.

#7. 26-Week Oral Toxicity Study in Dogs

Animals, Doses, Route & Duration: Beagle dogs, approx. 11 mos. old; 4 gps, 3/sex/gp - Controls, 50, 150 & 300 mpk/day; 7 days/wk for 26 wks. The drug was suspended in 0.5% methylcellulose and administered in gelatin capsules up to Drug Week 6, and thereafter by oral gavage. Controls were treated with empty gelatin capsules or methylcellulose suspension.

Schedule of Parameters Measured: Clinical signs, daily; body wt, 2x/wk up to week 12, then once/week; ophth. exam, ECG, hematology, serum biochemistry & urinalysis, weeks 3, 8, 12, 17 or 18 & 25. F were sacrificed after receiving 182 doses, M after 183 doses. Routine histologic exam was done on all dogs from the control & HD gps, as well as those that died or were sacrificed prior to scheduled termination. In addition, heart, kidneys, and all gross changes observed were examined microscopically in all dogs.

Results

Mortality: Total of 4; 1 & 3 in the MD & HD, respectively - found dead or sacrificed because of deteriorating physical condition.

Clinical Signs

- dose-related emesis post-dose and salivation pre- & post-dose in all treatment gps; less frequent in the LD gp;
- gray or clay-colored feces (unabsorbed drug) in all treatment gps;
- anorexia in HD dogs that died or were sacrificed during the study;
- dehydration in 2 HD dogs;
- marked wt loss in the same 2 HD dogs;
- slight retardation of body wt gain in surviving MD & HD dogs.

Ophthalmologic Exam; EKG: No changes or abnormalities attributable to treatment.

Hematology; Serum Biochemistry: Treatment-related changes characteristic to uremia & nephropathy, secondary to intra-renal or urethral obstruction (MK-366 crystals). These changes occurred in those dogs that were sacrificed during the study, e.g., (1) neutrophilic leucocytosis & slight lymphopenia; (2) monocytosis & slight lymphopenia.

Biochemical studies in sacrificed dogs showed moderate-marked increases in BUN & creatinine and moderate decreases or increases in serum electrolytes. Slight-moderate increases in activity of SGOT, SGPT, and/or alkaline phos. were also seen in these dogs and were probably secondary to uremia. There was also slight-moderate stress-related inc'd serum glucose in these dogs.

There were very slight transient inc's in BUN & creatinine in one surviving HD dog. Blood was present in the urine of one surviving MD & 2 HD dogs. There were no macroscopic and/or microscopic changes to account for these.

Crystalluria was evident in all treated gps. The crystals were needle-shaped or "sea urchin" shaped and identified as the dihydrate or magnesium salt of MK-366, respectively. Crystalluria was seen in most dogs at the HD & occasionally at the LD & MD. Microscopic changes were seen in the 2 sacrificed MD & HD dogs. Urethral obstruction, as well as hemorrhages in the urinary bladder wall & renal capsule, congestion of renal parenchyma, renal tubular dilatation & hemorrhagic prostatitis were also evident upon gross examination of these dogs. Acute pyelitis, pyelonephritis & nephrocalcinosis were also seen in one of these dogs. The 3rd dog sacrificed, a HD F, had no sig. gross changes in the urinary tract. Renal tubular dilatation, pyelonephritis and very slight unilateral papillary necrosis were apparent in this dog and were considered secondary to obstruction of the ducts of Bellini. Other microscopic changes occurring in the GI tract of one dog, also considered secondary to uremia, included gastritis & a pyloric ulcer. Marked lymphoid depletion in the thymus was apparent in all HD dogs that died or were sacrificed during the study and was considered related to stress.

One HD dog found dead at Week 12, showed no renal or urinary tract changes, but did show slight lymphoid cell depletion related to stress. The changes were present in the lymph node, spleen & Peyer's patches. There were no signs of toxicity in dogs given the MK-366 LD. Crystalluria was seen occasionally in this group.

Reviewer's Comment: Except for occasional crystalluria, the LD appears to be safe. Since crystalluria is an inherent toxic effect of this group of drugs, the final answer should come from human clinical experience. However, in the HD, a new effect surfaced which has not previously been found to be part of the spectrum of toxicity of drugs of this class. This is the lymphoid depletion induction. The sponsor interprets this as a stress-induced change. I question this, since during a 6-month stress period, the adrenal cortex is either exhausted or undergoes hypertrophy. None of these are mentioned in the report. I suspect a peculiar endocrine related effect inherent to the drug or its metabolite(s), since the drug has another endocrine related effect on pregnant Cynomolgus monkeys. The lymphoid depletion, at least of the thymus, can be experimentally accomplished by parenteral admin. of either estrogens or progesterone & its synthetic derivatives, by simultaneous administration of both, or by testosterone alone in F rats. It is also well known that the admin. of exogenous glucocorticoids leads to the same effect, without stress. The importance of this lymphoid-depleting effect of the drug is that it may indicate an, as yet unsurfaced, potentially hazardous effect of this class of drugs. If the lymphoid depletion is a nonspecific stress-related effect, then any carcinogenicity study in laboratory animals should start with a report on "stress-related immunosuppression." Indeed, this is sometimes the case. However, I don't know if, from a sample statement on the presence of "allegedly

indirect immunosuppression" anyone can say that it is strictly stress related. A xenobiotic alone could be directly immunosuppressive, and at the same time, be responsible for the "treatment-induced chronic stress." Who can estimate the rate of contribution of the 2 factors from a simple histologic recognition of lymphoid depression? I wonder what a stress expert would say about this?

#8. 53-Week Oral Toxicity Study in Dogs

Animals, Doses, Route & Duration: Beagle dogs (avg. age = 24-28 wks; age of replacement = 30-32 wks; the 24-28 wks of age coincides with the minimal age of puberty; the replacement dogs were already post-pubertal); 4 groups, 4/sex/gp - Controls, 50, 100 & 150 mpk/day of MK-365; gavage in aq. suspension; 7 days/week for 53 wks; controls rec'd distilled water.

Schedule of Parameters Measured: Physical exam of all dogs, daily; more detailed physical exam of abnormal dogs, weekly; body wt, pretest & weekly during treatment & just before sacrifice; food intake, daily prior to & during treatment; ophth. exam & EKG on all dogs, prior to treatment and at wks 12, 24 & 51; hematology, serum biochem. & urinalysis on all dogs, prior to treatment in at drug wks 6, 12, 23 & 50. At completion of the treatment period, all surviving dogs (except 5, fed by oversight) were fasted overnight, then killed by IV overdose of pentobarbital Na followed by exsanguination via incision of the axillary arteries. In dogs killed at study termination, the adrenals, brain, heart, kidneys, liver & testes were weighed. In addition, a necropsy was performed on all dogs sacrificed during the study. Hematoxylin & eosin-stained sections of tissues from all dogs were prepared for histopathological exams. Oil red O-stained frozen sections of liver & kidney from the same dogs were examined histopathologically by the applicant. Prepared & stained femoral bone marrow smears and reticulocyte counts for all sacrificed dogs were not evaluated, since hematological findings did not warrant these examinations.

Results

Clinical Signs: Silver-gray colored feces (unabsorbed drug) daily in the HD M & F, from wk 27 to termination.

Mortality: One HD M at wk 7, attributed to intussusception of cecum into the colon; one control F at wk 5, [dermatitis (demodicosis), undefined pulmonary pathology (abnormal respiratory sounds & congestion)].

Body Wt Gain: The HD dogs had lower wt gain than controls; wt gain in the LD & M dogs was comparable to controls.

Food Intake: No adverse effect in any gp.

Ophth.; FXG; Hematology; Serum Biochem.; Urinalysis: No treatment-related effects.

Gross Path.; Organ Wts; Histopath.: No treatment-related findings.

Reviewer's Comment: This study contradicts the French study. The dose levels, except for the 300 mpk dose of that study (French), are identical.

The duration of treatment in this study is approx. double that of the French study and the age range of the animals is the same; yet this study is incredibly clean. Where is the crystalluria, nephropathology, lymphoid depletion, at least at 150 mpk? The applicant should explain this. [Is the French dog (whichever breed) reacting differently than the Canadian dog? Where is the stress effect?]

I also wish to note that, in my experience, the final outcome of a toxic effect depends not only on the dose, but on the duration of treatment. In other words, toxicity is the result of a multiplication of the daily dose with the no. of the days of admin. In this case, 300 mpk for 26 wks should result in the same sort & severity of toxicity as 150 mpk for 53 wks (in terms of lymphoid depletion). Lymphoid depletion (immunosuppression) is particularly bad for an antimicrobial drug. Although this cosmetic mistake is not severe enough to hold up approval of this drug, an acceptable explanation should be submitted by the applicant. The 50 mpk/day "no effect dose level" is high enough for the calculation of an acceptable and efficacious human dose.

SPECIAL STUDIES

These studies follow the order in Vol. 2.51.

Arthropathy Studies

#1. Effect on the Diarthroidal Joint of Immature Dogs [Kyorin]

Animals, Doses, Route & Duration: Beagle & mongrel dogs, 3-5 mos. of age; 2/group and a neg. control gp. The treated dogs received orally:

- MK-366 @ 30, 60, 100, 250 & 500 mpk/day for 7 days; recovery study - 200 mpk/day for 99 days;
- Pipemidic Acid @ 30, 60, 100, 250 & 500 mpk/day for 7 days;
- Nalidixic Acid: 30, 60 & 100 mpk/day.

Results: This is the best report I have ever seen on this subject. The summary is excellent and worthy of a verbatim quote. [At the end, I will make some comments on certain aspects of this study; however, is there any study which cannot be made better or more comprehensive?]

"Clinical signs of lameness appeared from the second day of treatment in dogs given doses of MK-0366 greater than 60 mpk/day which persisted through the duration of the study (7 days). In the 99-day study there was recovery from clinical signs within 6-8 weeks after initiation of the study. The degree of lameness was related to dose administered. In dogs administered PPA (pipemidic acid) and NA (nalidixic acid), similar dose related lameness was seen at dose levels greater than 30 mpk/day.

An increased amount of synovial fluid was found at necropsy in dogs at doses at 100 mpk/day or greater for all three compounds in the 7-day study. The synovial fluid was sometimes yellow & semiopaque with white suspended matter. The abnormality in the synovial fluid was dose dependent for all three compounds. No abnormality was seen in the synovial fluid of dogs in the 99-day study at the time of necropsy.

The joint lesions were characterized by blister formation in the articular cartilage. At higher doses ruptured blisters (erosions) were common. The chondrocytes adjacent to the blisters and erosions were hypertrophied. Although there was recovery from clinical signs in dogs in the 99-day study, gross and microscopic changes were evident in the articular cartilage at termination. Synovial membranes and epiphyseal plates were not affected by any of the three compounds tested.

No abnormalities related to treatment were detected in the hematologic and serum biochemical parameters, urinalysis or tissue enzymes."

Reviewer's Conclusions

- a) The study shows that the very left-hand ring of the quinolone, which is a fused substituted benzene in MK-366, could be modified by exchanging 1 carbon of the ring with a N-atom (NA) or 2 carbons with 2 nitrogen atoms (PPA) without losing the arthrototoxicity of the drug.
- b) The molar conc'n of the same dose is higher for NA (m.w. 232.23), less for PPA (m.w. 303.33) and even less for norfloxacin. Though the minimal arthropathogenic dose is not known for any of the drugs, from the available data, a conclusion based on the ratio of molecular size (no. of moles) and severity of the lesions cannot be drawn.
- c) No other organs or systems were affected by MK-366 from a 500 mpk/day dose for 7 days, or from 200 mpk/day for 99 days.
- d) Conspicuous is the finding in the synovial fluid at 100 mpk/day and higher. Unfortunately, it is not stated that this change included increased viscosity; cloudiness was due to inflammatory cellular exudate and/or increased protein content. The most important aspect of protein content would be its enzyme activity, which was not investigated.
- e) It is also interesting that minor lesions in the articular cartilage are present, in the case of all these drugs, at doses not inducing changes in the synovial fluid; therefore, it is safe to assume that the synovial fluid change is not essential in the pathogenesis and that it appears to be secondary.
- f) The hypertrophy of the chondrocytes adjacent to blebs & fissures indicates something. Is this a desperate tendency to regenerate, or do these cells only appear to be hypertrophied since, in the neighborhood of the "lakes", they are not compressed as tightly as in normal cartilage?

- g) It is still not clear from this study (or any study) whether or not the chondrocytes or the matrix are primarily affected by the drug or vice versa. From one single photograph of _____ I am unable to conclude that the drug is deposited only in the chondrocytes in the case of NA in the rat.
- h) The drug does not appear to be an enzyme inhibitor in a general sense, since it did not show these effects in a number of visceral enzymes. The 3 enzymes that might play a crucial role in the articular toxicity of these drugs might be Mg-dependent topoisomerase, the Mg-dependent GPT-ase, and the group of lysosomalytic (proteoglycan) enzymes of the chondrocytes, which were not investigated.
- i) This study also proved that only the juvenile cartilage is sensitive to the arthrotoxic effects of the drug. Prior to this study, they tested mature rats & dogs for this purpose, with negative results.
- j) Finally, the study shows that MK-366 is less arthrotoxic (with a factor of 2) than the world-wide (USA involved) marketed NA, and the world-wide (except USA) marketed PPA.
- k) Although the applicant rightly determined the acute toxicity of the individual metabolites, it is unknown whether or not the drug per se, or one or several of the metabolites, with or without the drug in concert, are responsible for the arthrosis.
- l) This study does not identify any objection to the approval of the drug.

#2. Study in Immature Rabbits [Kyorin]

Animals, Doses & Duration: Japanese white rabbits, 8-10 wks old; 250 & 300 mpk/day of MK-0366 for one week or 100 & 300 mpk/day for 21 days; groups of 5-11 rabbits; 4 other groups were treated with NA (150 mpk) & PPA (250 mpk/day) for 7 days, as pos. controls.

Results: No gait abnormalities, hematologic, serum biochemical, urinary or tissue enzyme changes related to treatment in any group.

Pathology: Gross blisters were seen on the articular cartilage of the stifle, hip or elbow joints or some of the rabbits treated with NA, PPA & MK-366 for 7 days. The rabbits given MK-366 for 21 days had no blisters on the articular cartilage. However, 1/5 control rabbits also had blisters on the articular surface of the stifle joint. Histopathologically, activation was seen at the intermediate zone of the cartilage with matrix rarefaction & fibrillation in the immediately surrounding cartilage.

Reviewer's Comment: The study does not indicate the no-arthropathogenic-effect dose level in rabbits.

#3. Antigenicity Studies [Kyorin]

- MK-366 elicited no delayed hypersensitivity reaction on the skin of guinea pigs, whereas under the same conditions, 2,4-dinitrochlorobenzene elicited a positive response.
- Anaphylactic reaction was not observed in guinea pigs sensitized with MK-366 alone or in a mixture with Freund's complete adjuvant (FCA).
- Serum from guinea pigs sensitized with MK-366 induced no passive cutaneous anaphylaxis in recipient guinea pigs.
- Specific antibodies vs. MK-366 were not detected in sera of rabbits immunized with MK-366-BGG conjugate & FCA.

#4. Guinea Pig Skin Maximization Test [Kyorin]

There was no evidence (gross or microscopic) of sensitization in the MK-366 treated groups. On the other hand, the challenge sites of all animals in the DNCB group showed, as expected, characteristic sensitization reactions consisting of slight-marked dermal inflammation and slight-moderate epidermal thickening.

#5. Influence on the Retina of Cats [Kyorin]

Retinal toxicity of MK-366 was evaluated in cats by electroretinogram (ERG) & histopathological exam. NA was used as a reference substance. MK-366 or NA was infused IV (0.8 ml/min) at a dose of 40 mpk and ERGs were recorded during & after dosing. There were no sig. changes in latent times or amplitude of ERG waves during or up to 60 min. after dosing with MK-366, when compared with those before admin. NA, on the other hand, caused a prolongation of latency as early as 15 min. after the start of dosing, followed by complete loss of op- & b-waves of ERG.

In another experiment, MK-366 was administered orally at doses of 50, 100 & 200 mpk/day for 2 wks. NA was administered orally @ 100 & 200 mpk dose levels (varied doses, based on the presence or absence of toxicity) for 2 wks. ERGs were recorded at termination under anesthesia or while the animal was immobilized by a muscle relaxant. All animals were killed after recording of ERG and eyes were collected for histopathology. Results of histopathologic exam were negative.

#6. Auditory Toxicity in Rats [Kyorin]

Schedule: A daily dose of 500 mpk of the drug was given orally to Wistar rats for 7 mos. Other groups of rats were given 200 mpk b.i.d. of kanamycin & 400 mpk b.i.d. of streptomycin for 27 days (pos. controls). All groups were tested for auditory & vestibular function at the end of their period of treatment.

Upon completion of auditory & vestibular function tests, the animals were killed and cochleae were resected & processed for scanning electron microscopic exam.

There were no treatment-related changes in auditory or vestibular function in rats given MK-366 @ 500 mpk/day for 6 mos. There were also no histopathological changes in the organ of Corti.

The rats given streptomycin showed changes in vestibular function characterized by tremor, tilting of the head & decreased ability to balance on a bar; there were no abnormal auditory functions or histopath. changes in the organ of Corti. The rats treated with kanamycin showed auditory dysfunction, but no vestibular dysfunction. Histologically, there were dec's in the number, reaction & size of cilia of the inner hair cells and complete loss of cilia in the outer hair cells.

7. Acute Phototoxicity in Female Mice [Method of E.S. Copeland, et al., J. Invest. Dermatol. 64: 349-356, 1975]

In this study, chlorpromazine was used as a positive control. Oral admin. of MK-366 at doses of 625, 1250 & 2500 mpk produced no perceptible erythema in F mice after 20 hrs of exposure to long wave UV light. However, oral admin. of chlorpromazine, a known phototoxic agent, produced definite erythema of the ears at a dose of 120 mpk. All 6 animals in this group showed moderate erythema 3 hrs following exposure. By the 7th day, 4 of these had slight or no erythema, while the remaining 2 had marked erythema with scarring. Negative control animals (water) showed no evidence of erythema.

8. Ocular Irritation Study in Rabbits (Draize Method)

All rabbits showed a normal body wt gain during the study. Instillation of MK-366 powder into conjunctival sac produced a very slight conjunctival injection & moderate cloudy discharge at 15 min. The severity of ocular effects increased by 24 hrs with a moderate injection & discharge and a marked amount of chemosis; 2/4 eyes had corneal opacification & circumcorneal hemorrhage by the 4th day; 3/4 eyes appeared normal after 10 days; the remaining eye continued to show severe ocular irritation at day 14.

Applicant's Conclusion: MK-366 was found to be severely irritating to the rabbit eyes in a primary eye irritation study.

9. Drug Deposition Study in Dog

Purpose of the Study: To determine in Beagle dogs (3 gps, 3/sex/gp), the conc'n of MK-366 in the plasma, aq. humor & lens of dogs after 1 & 21 oral doses of 7 days after cessation of treatment.

Conclusions

- a) Once daily oral admin. of 150 mpk of MK-366 for 21 days to dogs resulted in a small, though stat. sig., increase in aq. humor levels, ranging from 0.06-0.11 ug/ml.
- b) Three-week admin. of MK-366 resulted in a small, but stat. sig. inc.

in the lens content of the product. Such an observation would not be unexpected, as the product is present in low conc'ns in the aq. humor. What is clear is that the avidity of the lens for MK-366 is negligible as reflected by the very low value of 0.24 ug/g. The presence of low conc'ns of MK-366 in the lens most probably result from simple diffusion.

- c) The lack of sequestration of MK-366 by the lens is clearly shown by the rapidity of washout following cessation of treatment, conc'ns declining from 0.24 to 0.08 ug/g at 7 days.
- d) Once daily admin. of 150 mpk of MK-366 does not result in a marked, persistent accumulation of the compound in the dog lens.

REPRODUCTION STUDIES

#1. Effect of MK-366 on Fertility in M & F Mice [Kyorin]

Animals, Doses, Route & Duration: White laboratory mice (SLC:ICR strain); 4 gps, 21/sex/gp - Controls, 125, 250 & 500 mpk; oral; Days 6-15 of gestation. Prior to this an equal no. of M & F were kept together (1:1/cage) until the appearance of a vaginal plug (= day 1 of pregnancy).

Parameters observed were: maternal toxicity, embryotoxicity & lethality, functional & behavioral tests of newborn F₁ & F₂ generations and reproduction performance of F₁ & F₂ generations.

Results: No abnormalities were observed in any parameter.

#2. Teratogenic Effects in Mice

Animals, Doses, Route & Duration: Laboratory F white mice; 4 groups, 20/gp - Controls, 100, 200 or 400 mpk/day; oral; Days 5-16 of pregnancy.

Results: There were no drug-induced effects on the dams. There were also no treatment-related differences in gestation period, no. of corpora lutea, no. of implants, no. of resorptions, no. of live or dead fetuses, wts of fetuses or external malformations.

#3. Effects of Oral Admin. on Pregnancy in the Rat (Dose-Range-Finding Study)

Animals, Doses, Route & Duration: Charles River CD rats; 5 groups, 20 F/gp - Controls, 200, 400, 600 & 800 mpk; oral; Days 6-17 of pregnancy.

Results: Treatment with MK-366 had no effect on the general condition of the animals or upon body wt gain during gestation. MK-366 had no adverse effect on pregnancy, as assessed by external exam of the uterine horns. It was concluded from this preliminary study that dose levels up to 800 mpk/day should be suitable for use in a main teratology study in rats.

#4. Effects of Oral Admin. on Pregnancy in Rats

Animals, Doses, Route & Duration: Pregnant F SD/CD rats; 4 groups, 25/gp - Controls, 50, 200 & 800 mg/kg b.i.d.; oral; Days 6-17 of pregnancy.

Results: The general condition & body wt gain of treated animals were similar to those of the controls throughout the study.

At termination on Day 20 of gestation, there were no changes or trends in the nos. of implantations and viable young or in the extent of pre- & post-implantation losses that could be attributed to treatment. Fetal & placental wts were similar in all gps.

Fetal exam at necropsy, by free-hand serial sectioning or following skeletal processing, revealed a small no. of anomalies in all gps, including 4 abnormal fetuses, but no indication of any adverse effects could be related to treatment with MK-366.

#5. Teratogenicity Study of AM-715 in Rats [Kyorin]

AM-715 Chemical Formula: 1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-Pipreaziny)-3-quinolinecarboxylic acid

Animals, Doses, Route & Duration: JCL-SD rats (pregnant F only); 30/gp - Controls, 125, 250 & 500 mpk/day; oral; Days 7-17 of pregnancy. [Max. dose equiv. to 41.7x the proposed clinical dose (12 mpk/day).

Results: AM-175 showed no undesirable effect on pregnant rats. In the F₁ fetuses of the treated gps, it was determined that the gross malformations, visceral & skeletal abnormalities and variations observed were within the limit of spontaneous occurrence.

AM-715 produced no serious effect on growth, differentiation, functions, behavior or reproductive performance of the newborns. The drug showed no toxicity or any effect on F₂ fetuses.

From the above, it was concluded that admin. of AM-175 to rats during organogenesis, at the doses used in this study, had no adverse effect. Therefore, 500 mpk/day was assumed to be the maximum dose producing no overt teratological effect in rats.

#6. Effects of Oral Admin. on Pregnancy in Rabbits (Dose-Range-Finding Study)

Animals, Doses, Route & Duration: Japanese white domestic rabbits (pregnant F only), 8/group; Controls, 50, 100 & 200 mpk; oral; Days 6-18 of gestation. All surviving rabbits were sacrificed on 2 days before expected parturition.

Results: Body wt loss or dec'd body wt gain and premature births or abortions were observed in all dosage gps.

Applicant's Comments: In view of the sensitivity of MK-366, the rabbit was considered unsuitable for use in a full teratology study. This sensitivity is due to the disturbance of the GI flora.

#7. Teratology Study in Rabbits [Kyorin]

Animals, Doses, Route & Duration: White domestic pregnant F rabbits; 4 groups, 12-13/gp; Controls, 25 & 100 mpk/day; oral; Days 6-18 of gestation. On day 29 of gestation, all dams were sacrificed for examination of uterine contents.

Results: Only at the HD, slight dec. in spontaneous movement, sig. reduction of appetite, diarrhea & reduction of body temp. were noted. Sig. wt gain reduction also in the same gp. One dam of this gp aborted dead fetuses on the 27th day of gestation.

Embryotoxicity: Noted in the HD only: inc'd no. of dead embryos and resultant dec. in the no. of surviving fetuses. There were no external, visceral or skeletal malformations that were considered related to the admin. of MK-0366.

8. Exploratory Plasma Profile Study in Rabbits [MSDRL, USA]

Reason for Study: As was suggested in the earlier rabbit studies, the oral route for teratogenicity studies in rabbits is not appropriate. Therefore, it was decided to determine the drug's toxicity in the absence of an effect on intestinal flora by administering the drug parenterally.

A comparative plasma profile study (oral vs. SC) was performed in rabbits, in order to aid in the selection of doses for parenteral admin.

Animals, Doses, Route & Duration: Nonpregnant F NZ albino rabbits; 2 groups, 3/gp; 100 mpk, once, orally; 20 mpk once, SC. Plasma was collected 0.5, 1, 2, 3, 4, 5, 6 & 24 hrs post-dose. Determination of plasma levels were done by microbiological assay. N.B.: This might indicate that in the case of oral admin., a great deal of microbiologically nonactive metabolites entered the blood stream (intestinal microbiological metabolism); but since they don't have antimicrobial effects, the assay does not indicate their presence.

Results: Plasma level of MK-366 peaked at 0.6-1.3 ug/ml within 3 hrs following oral admin. and at 6.8-6.9 ug/ml within 0.5 hr follow SC admin. At 24 hrs post-dose, there was no detectable amount of drug in plasma in either gp of animals.

Based on these results, 20 mpk/day SC is judged to be a more than adequate dose to attain blood levels as high & prolonged as 100 mpk/day orally.

9. Exploratory Biliary Excretion Study in Rabbits [MSDRL, USA]

Reason for Study: As is evident from earlier rabbits studies, oral MK-366 appears to be much more toxic to rabbits than to other laboratory animals (rats, mice). It appears that for teratogenicity studies, the parenteral route is the only available way for the rabbit. To avoid disturbing interference by enterohepatic circulation of the drug, its

biliary excretion had to be explored. The SC route is valuable only if biliary excretion is minimal; therefore, a substantial amount of the SC-administered dose does not enter the intestines, and after being metabolized by the GI bacteria, does not enter the blood stream as a highly toxic metabolite. (Urinary excretion is predominant in most species.)

Animals, Doses, Route & Duration: NZ albino rabbits; 4 groups (1/group) anesthetized; SC; 20 mpk of MK-366. Bile was collected continuously via a cannula in the common bile duct; blood samples were collected periodically for 4-6 hrs after dosing; determinations were done by microbiological assay.

Results: Plasma levels of MK-366 peaked at 3.84-14.4 ug/ml between 10 & 60 min. post-dose. Levels of MK-366 in the bile peaked at 33.3-93.5 ug/ml between 30 & 90 min. post-dose and inc'd & dec'd approx. in parallel with plasma levels. The total amount of drug excreted in bile during the 4-6 hr post-dose period represented 1.2-2.4% of the SC dose. By extrapolating from the decreasing rate of biliary excretion at the end of the collection period, it can be estimated that the total amount excreted in bile would have been 2-4%.

Applicant's Remarks: "The low rate of biliary excretion of MK-0366 in the rabbit makes it possible to design a study to test the hypothesis that the toxicity and fetotoxicity associated with oral dosing may be due to an effect on the intestinal flora."

10. Exploratory Toxicity Study in Nonpregnant Rabbits [MSDRL, USA]

Reason for Study: To prove the hypothesis that the maternotoxicity of MK-366 was secondary to an antibiotic effect on the GI flora, it was decided to administered the drug parenterally, and thereby determine its toxicity in the absence of an antibiotic effect on the intestinal flora. The results of the previous study proved that the biliary excretion rate is low (2-4%); therefore, the potential interference by that portion of the drug that re-enters the circulation after being excreted in the bile is negligible.

Study Objective: To determine whether SC admin. of MK-366 for 13 days at doses up to 20 mpk/day is tolerated in rabbits.

Methods: In this study, which used NZ albino rabbits, MK-366 was given SC to 3 groups of 5 F, at dosage levels of 5, 10 & 20 mpk/day. A 4th group of 5 F received 100 mpk/day of MK-366 orally by rubber catheter in 4 ml/kg of 0.1% methylcellulose. A 5th group of 5 F received 0.9% saline SC and served as controls. The drug (factor = 1.00) or control article was administered once/day for 13 days (day of 1st dose = Day 1). The dosing volume for the SC gps was 0.5 ml/kg. At the beginning of the study, the F were approx. 5-6 mos. of age & weighed 3680-4370 gm.

At the end of the 13-day dosing period, the F were observed for an additional 7 days. Body wts were recorded on Days 1, 4, 7, 10, 13, 14,

17 & 20. Food intake, at 24-hr intervals, was measured the day before the 1st dose and every 3rd day beginning at Day 1. At 0.5 & 3 hrs after the 1st & 13th doses, the rabbits were bled for determination of plasma levels of MK-366 by microbiological assay. On day 14, they were bled for determination of serum levels of urea nitrogen, creatinine, Na, K & Cl. On Day 20, they were sacrificed and discarded without further examination.

Results: There were no deaths. Toxicity was apparent @ 100 mpk/day PO as a mean body wt loss of 354 gm during the dosing period compared to a wt gain of 132 gm in controls. The wt loss was accompanied by dec's in food & water intake. Mean food intake @ 100 mpk/day PO dec'd during the dosing period to 20-30% of controls levels, then inc'd during the post-dose period, but remained below that of controls. Also, on Day 14, there were slight but sig. inc's (Day 14) in serum creatinine (up to 2.0 mg/dl) & urea nitrogen (up to 24.4 mg/dl) levels in the 100 mpk/day orally-treated gp. There was no evidence of toxicity with the SC route.

Orally dosed F had orange urine as early as Day 10 and as late as Day 20. There was no discolored urine in the SC-treated gp.

At 0.5 hr following the 1st dose, plasma levels of MK-366 in the 100 mpk/day PO gp (mean = 1.02 ug/ml) were much lower than those in the 5, 10 & 20 mpk/day SC gps (means = 2.25, 5.33 & 9.25 ug/ml, respectively). Following the 13th dose, however, the oral plasma levels had inc'd compared to those after the 1st dose. At 0.5 hr post-dose (PD), the oral levels (mean = 1.77 ug/ml) were almost as great as those @ 5 mpk/day SC (mean = 2.45 ug/ml). At 3 hrs post-dose, the oral levels (mean = 1.5 ug/ml) were greater than both the 5 & 10 mpk/day SC levels (means = 0.59 & 1.24 ug/ml, respectively). Only the 20 mpk/day SC gp had plasma levels (3.76 & 1.94 ug/ml @ 0.5 & 3 hrs after 13th dose) which exceeded those in the oral gp at all time points tested.

Applicant's Conclusion: "Since the toxicity seen with oral dosing was not seen with SC dosing, even though blood levels of drug were higher following SC dosing, it seems likely that the toxicity seen with oral administration of high doses is not due to a systemic effect of the drug but rather to an effect on the intestinal flora."

11. Exploratory Blood Level Study in Nonpregnant Rabbits

Study Objective: To determine plasma drug levels at many time points after the 1st & 13th doses in order to better define the kinetics of the plasma levels of the drug. In addition, the effect of dec'd food intake on plasma levels of MK-366 was examined in a 2nd gp of F.

Methods

Group A: 5 F NZ albino rabbits received 13 daily oral doses (= Days 1-13) of 100 mpk/day, and were provided with the normal daily allotment of 150 gm/day of food.

Group B: Received a single oral dose of 100 mpk on Day 13 and were provided with an amount of food approx. equal to the max. level consumed

by a gp identical to Group A in a previous study (130 gm, Day 1; 100 gm, Day 2; 70 gm, Day 3; 40 gm, Days 4-13). The base compound of the drug (factor = 1.0) was suspended in 0.1% aq. methylcellulose and administered orally via rubber catheter at a dose volume of 4 ml/kg. At the beginning of the study, the animals were approx. 5-6.5 mos. of age and weighed 3620-4180 gm. Body wts were recorded on Days, 1, 4, 7, 10, 13 & 14. Food intake was measured at 24-hr intervals beginning on Day 1. On Days 1 & 13 (Gp A) & Day 13 (Gp B), the F were bled at 0.5, 1, 2, 3, 4, 6, 8 & 24 hrs PD for plasma drug level determination by a microbiological bioassay procedure. Plasma drug levels were also determined for samples collected from Gp A just before dosing on Day 13. On Day 14, the animals were sacrificed and discarded without further examination.

Results: There were no deaths. Toxicity was apparent in the gp receiving multiple doses (Gp A) as dec'd food & water intake and a mean body wt loss of 266 gm. Some F in Gp A had dark or orange urine as early as Day 9 and as late as Day 13. F in the pair-fed Gp B consumed all food provided and had inc'd water intake, but had approx. the same overall body wt loss (mean = 304 gm) as F in Gp A.

Following the 1st dose, the highest plasma level in Gp A occurred at 0.5 & 1 hr PD (mean levels = 1.25 & 1.24 ug/ml, respectively). No drug was detected at 8 hrs PD. Following the 13th dose, the peak plasma level (mean = 3.5 ug/ml), occurring at 1 hr PD, was approx. 3-fold higher than that following the 1st dose. The drug had not been cleared from plasma, even at 24 hrs after the 12th & 13th doses (mean levels = 0.34 & 0.36 ug/ml, respectively).

In the pair-fed gp B, the highest plasma levels following the single dose on Day 13 occurred at 0.5 & 1 hr PD (mean = 0.92 & 0.89 ug/ml, respectively). The drug had been cleared from plasma by 6 hrs PD. Thus, a low level of food intake for 12 days did not cause inc'd plasma levels of MK-366 in Gp B and is not an explanation for the inc'd plasma level following the 13th dose in Gp A.

Other possible explanations which have not been tested include the following:

- MK-366 may be broken down in the gut to a greater extent with the normal flora than with the antibiotic-altered flora.
- The drug may be bound to intestinal contents to a greater extent with the normal gut flora compared to the antibiotic-altered flora.
- Transit time in the gut may be inc'd in MK-366-treated rabbits.
- The drug may cause an inc'd absorption rate or a dec'd excretion rate.
- The drug may inhibit its own metabolism in the liver.

12. SC/Oral Teratology Study in Rabbits [MSDRL]

Objectives: To determine if the fetal wastage observed with oral MK-366 dosing is also specific to the oral route and not correlated with drug plasma levels, a combined oral/SC teratology study was conducted.

Methods: MK-366 was administered to NZ albino rabbits orally at a dose of 100 mpk/day to a gp of 20 artificially inseminated F and SC @ 20 mpk/day to a 2nd gp of 20 inseminated F. A 3rd gp of 20 F received saline SC and served as controls. For oral dosing, the drug was suspended in 0.1% aq. methylcellulose and administered at a dose volume of 4 ml/kg. For SC dosing, the drug was dissolved in saline. The dose vol. for both SC gps was 0.5 ml/kg. The drug (factor = 1.00) or control article was given once/day on gestational Days 6 thru 18. At the beginning of the study the F were approx. 6-6.5 mos. of age and weighed 3870-4840 gm. Body wts were recorded on Days 0, 8, 10, 12, 14, 16, 18, 19 & 28 of gest. Food intake was measured at 24-hr intervals every 3rd day beginning on Day 3 of gest. At 1, 4, 7 & 24 hrs after the 1st dose on Day 6 of gest., 5/gp were bled for drug plasma level determination. The same F (except for 1 orally dosed F that died after an intubation accident) were bled again for this purpose just prior to the last dose on Day 18 of gest. and at 0.5, 1, 2, 3, 4, 8 & 24 hrs after the last dose. Because of the possibly complicating effects of the bleedings, these F were sacrificed after the last bleeding on Day 19 of gest., then examined grossly. On Day 28 of gestation, the remaining F were sacrificed & evaluated.

Results: There were no treatment-related deaths or abortions. One F at 100 mpk/day PO was found dead on Day 14 of gest. following an intubation accident. There were 2 abortions @ 100 mpk/day PO on Days 26 & 27 of gest. The F @ 100 mpk PO that aborted on Day 27 of gest. had a small amount of blood stained fluid in the thoracic cavity and associated pulmonary telelectaxis? At termination on Day 28 of gest., 4 F at 100 mpk PO had varying amounts of clear fluid in the thoracic and/or abdominal cavities compared to one in controls. The applicant feels that this was due to malnutrition.

In the gp dosed orally, maternotoxicity was seen as mean wt loss during the dosing period and inc'd wt gain at the end of dosing. Embryotoxicity was apparent @ 100 mpk/day PO, as evidenced by inc'd resorption, dec'd fetal wt & delayed ossification. There was no maternotoxicity or embryotoxicity in the SC-dosed group.

Applicant's Comment: Since embryotoxicity occurred in the gp with maternotoxicity & lower peak blood levels (100 mpk PO), it is concluded that embryotoxicity is not a direct effect of the drug on the embryo, but rather secondary to maternotoxicity.

Reviewer's Comment: The above explanation is acceptable.

#14. Fertility Study in Mice [Kyorin]

MK-366 was administered orally as a suspension in sterile distilled water at dose levels of 125, 250 or 500 mpk/day to ICR M mice (20/gp) for 61 days before mating & during mating, and to ICR F mice (20/gp) daily for 15 days before mating until the 6th day of pregnancy.

Two similar gps of mice served as controls and received distilled water.

The mice were examined daily for their general condition. Body wts were taken daily. Food & water intake were measured once/week for M and 2x/wk for F prior to mating. All M mice were sacrificed & necropsied after mating, and their reproductive organs weighed. On Day 18 of pregnancy, the F were sacrificed, and after fetuses were removed, the corpora lutea & no. of implantation sites were counted. The no. of surviving fetuses, dead fetuses & resorption sites were also counted. The body wts of surviving fetuses & placental wts were also counted. The fetuses were examined for external, visceral & skeletal abnormalities.

Results: No treatment-related effects on reproductive performance or differences in growth & differentiation of the fetuses were observed.

15. Peri/Postnatal Study in Mice

MK-366 was administered orally, suspended in distilled water to F mice (21/gp) from Day 15 of gest. to Day 21 postpartum at dose levels of 0, 125, 250 & 500 mpk/day. The purpose of this study was to determine the effect of the test compound on growth, function, behavior & reproductive performance of F₁ & F₂ offspring. General symptoms & body wt were checked daily during gest. and the nursing period. All pregnant F were allowed to deliver. The length of gest., the no. & sex of newborns and their external abnormalities were determined. The newborns (F₁) were tested for growth & various physiological functions, including reproduction. Major organs were weighed. F₂ offspring were treated in the same manner as the F₁ newborn.

Results: No abnormal signs induced by MK-366 were observed in dams. The body wt of the treated gps was similar to that of controls at all times except on day 18 of gest. in the 500 mpk gp. This was not considered biologically sig.

No sig. differences were observed in the newborns in treated gps compared to controls, in gestation length, sex ratio, birth rate & weaning rate. There was no difference in the no. of implantation sites. There were no external or skeletal abnormalities related to treatment in the F₁ or F₂ newborns. There was also normal body wt gain. Also, there were no abnormalities in function, behavior or reproductive performance of the F₁ or F₂ offspring that were considered related to treatment.

Addendum: In the presently ongoing teratology study in cynomolgus monkeys, preliminary evidence indicates embryoletality at relatively high doses (200 mpk). There is, however, no evidence of teratogenicity. The study is continuing to establish a no-effect level.

Reviewer's Comment: Among all the reproductive & teratology studies, the rabbit & the cynomolgus monkey studies are troublesome. The studies elucidating the maternal-toxicity-dependent embryotoxicity of MK-366 are convincing. By learning about this phenomenon, we are introduced to a new concept in teratology. The rabbit studies do not affect the approval of the drug.

Much more important are the results of the cynomolgus monkey studies which are only briefly mentioned in the NDA and therefore not reviewed above. We have discussed the findings with the applicant. In the present submission, the summary indicates that the drug decreases the serum progesterone level in this species so drastically that dead and/or aborted feti will be delivered by a sizeable portion of the treated group, or if the embryolysis happens quite early, the uterus appears empty at study termination in monkeys which, prior to study initiation, were definitely pregnant.

Since I do not have the final report of the study, I cannot commit myself to anything at this time. However, as I already mentioned, the serum progesterone level reducing effect of the drug should be tested in nonpregnant women. I understand that the progesterone level during pregnancy is much higher than before pregnancy, and that a female body might react differently during pregnancy. I cannot imagine the testing of the effect of the drug in pregnant women, unless it could be done in such cases where the woman is determined to have an abortion anyway. Without saying more about the medical problem, I leave the decision to the medical fora. I anticipate that the monkey findings will call for Pregnancy Category "C", but I cannot offer a final decision on labeling until all the monkey data are submitted (and/or the drug is tested in pregnant women, if this is determined to be ethically feasible by the reviewing MO.)

MUTAGENICITY

MK-366 was tested for mutagenicity in the following tests:

In Vivo Studies: Dominant Lethal Test; Chromosomal Test

In Vitro Studies: V-79 Mammalian Cell Mutagenesis; Rec-Assay; Ames Test; Cytotoxicity Test; Chromosomal Aberration Test; Sister Chromatid Exchange; Unscheduled DNA Synthesis in Rat Hepatocytes; Autoradiographic Assay.

Results: Only the Rec-Assay was weakly positive. In view of this single positive finding, the applicant decided to run a special rat carcinogenicity study, using Fisher rats, 5 wks of age; 3 groups, 50/sex/gp - Controls, 0.05% & 0.2% MK-366 in the diet. Feeding period was 19 mos. followed by withdrawal period of 12-14 wks. Results: No evidence of carcinogenic effect has been observed thus far.

PHARMACOLOGY

MK-366 appears to be without marked pharmacological action in the central & peripheral nervous, GI, and cardiovascular systems. In general, activity was only observed at doses well in excess of those necessary for antimicrobial activity. Therefore, these results suggest that MK-366 is a well-tolerated antibacterial agent.

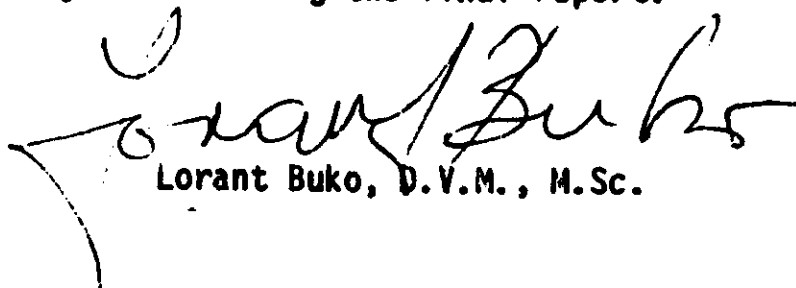
METABOLIC & PHARMACOKINETIC STUDIES

These subjects were already discussed during the review of the original IND. The spectrum of the metabolites (7) is very similar in various species to those of man. The toxicity of the mixture of the metabolites gives the same LD50 value as the parent drug.

CONCLUSIONS & RECOMMENDATION

This drug appears the least troublesome of all in its group. The total lack of functional & morphological eye toxicity is an encouraging quality. The enigmatic studies are the rabbit & cynomolgus monkey teratogenicity studies. The answer is easy for the rabbit, since the peculiarity of the GI tract flora and its unexpected reaction to the drug make this species unfit as an animal model.

The study which aroused my concern with respect to its abortifacient effects in the cynomolgus monkey, implicitly expresses the great hazard for pregnant women. The final report of this study has not been submitted to us yet. I will recommend a Pregnancy Category only after seeing the final report.


Lorant Buko, D.V.M., M.Sc.

cc: Orig. NDA

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HFN-815/MO

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HFN-340

HFN-815/LBuko/smc/3/24/86

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NDA 19-384

NDA 19-384

David W. Blois, Ph.D.
Merck Sharp & Dohme Laboratories
West Point, PA 19486

Dear Dr. Blois:

Reference is made to your New Drug Application (NDA) dated January 14, 1985 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Noroxin (norfloxacin) Tablets, 400 mg.

We also acknowledge your additional correspondence dated February 7, February 11, March 15, March 21, April 2, April 3, April 23, July 3, July 11, July 23, August 1, September 13, October 3, October 10, October 18, November 4, November 6, December 19, 1985, January 20, February 12, February 14, February 14, February 24(3), March 11, March 17, March 18, March 21, March 31, April 4, April 22, May 1, May 8(2), May 15, May 19, July 25, August 26, and September 19, 1986.

We have completed our review of your submission and the application is approved.

However, prior to marketing, you must submit final printed labeling identical to draft labeling dated September 19, 1986, except that the subsection in the Dosage and Administration labeled "Renal Impairment (including the Elderly with Renal Impairment)" should be changed to "Renal Impairment." The first sentence of this section should also have the parenthetical removed.

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

Sincerely yours,

cc: PHI-DO
ORIG. NDA 19-384
HFN-82
HFN-220
HFN-710
HFN-815
HFN-815/RLinkous/8/29/86/sdj/9/5/86
HFN-815/MO R No. 10/11/86
HFN-815/PHARM
HFN-815/CHEM Arc 10/11/86
F/T: 9/26/86/9/29/86

Elaine C. Esber, M.D.
Director
Office of Biologics Research and Review
Center for Drugs and Biologics

APPROVABLE 0476u

OCT 31 1986

NDA 19-384

David W. Blois, Ph.D.
Merck Sharp & Dohme Laboratories
West Point, PA 19486

Dear Dr. Blois:

Reference is made to your New Drug Application (NDA) dated January 14, 1985 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ibroxin (norfloxacin) Tablets, 400 mg.

We also acknowledge your additional correspondence dated February 7, February 11, March 15, March 21, April 2, April 3, April 23, July 3, July 11, July 23, August 1, September 13, October 3, October 10, October 18, November 4, November 6, December 19, 1985, January 20, February 12, February 14, February 24(3), March 11, March 17, March 18, March 21, March 31, April 4, April 22, May 1, May 8(2), May 15, May 19, July 25, August 26, and September 19, 1986.

We have completed our review of your submission and the application is approved as of the date of this letter.

However, prior to marketing, you must submit final printed labeling identical to draft labeling dated September 19, 1986, except that:

1. The title of the subsection in the DOSAGE AND ADMINISTRATION labeled "Renal Impairment (including the Elderly with Renal Impairment)" should be changed to "Renal Impairment;" the first sentence of this section should also have the parenthetical statement removed;
2. Recommended dosage for elderly patients should be added to a different part of the DOSAGE AND ADMINISTRATION section;
3. The footnote after the asterisk in the INDICATIONS AND USAGE section must read: "Efficacy for this organism in this organ system was studied in fewer than 10 infections."
4. An asterisk must be placed after each of the indole positive Proteus species in the INDICATIONS.

These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as requested, in the product's final printed labeling (FPL) may render the product misbranded and an unapproved new drug.

Please submit twelve copies of the revised FPL when it is available. This submission should be designated for administrative purposes an "FPL Supplement" to the approved NDA 19-304. Approval of the supplement by FDA is not required before the labeling is used.

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

Please submit one market package of the drug when it is available.

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

Sincerely yours,

J. Bilstad 10/31/86

Elaine L. Esber, M.D.
Director
Office of Biologics Research and Review
Center for Drugs and Biologics

cc: PHI-DO
ORIG. NDA 19-384
HFN-82
HFN-220
HFN-710
HFN-815
HFN-815/RLinkous/8/29/86/sdj/9/5/86
HFN0815/MO
HFN-815/PHARM
HFN-815/CHEM
F/t: 9/26/86/9/29/86
F/t: JMBilstad:pec:10/31/86:1038S

Letter retyped to include
a couple of standard
paragraphs. See copies of
earlier versions of the letter
for divisions sign-off for
the other content of the letter.
J. Bilstad

NDA 19-384

David W. Blois, Ph.D.
Merck Sharp & Dohme Laboratories
West Point, PA 19486

Dear Dr. Blois:

Reference is made to your New Drug Application (NDA) dated January 14, 1985 submitted pursuant to section 505(b) of the Federal, Food, Drug, and Cosmetic Act for Noroxin (norfloxacin) Tablets, 400 mg.

We also acknowledge your additional correspondence dated February 7, February 11, March 15, March 21, April 2, April 3, April 23, July 3, July 11, July 23, August 1, September 13, October 3, October 10, October 18, November 4, November 6, December 19, 1985, January 20, February 12, February 14, February 14, February 24(3), March 11, March 17, March 18, March 21, March 31, April 4, April 22, May 1, May 8(2), May 15, May 19, July 25, August 26, and September 19, 1986.

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Sincerely yours,

cc: PHI-DO
ORIG. NDA 19-384

HFN-82
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HFN-815/MO
HFN-815/PHARM
HFN-815/CHEM
F/T: 9/26/86/9/29/86
APPROVABLE 0476u

Elaine C. Esber, M.D.
Director
Office of Biologics Research and Review
Center for Drugs and Biologics

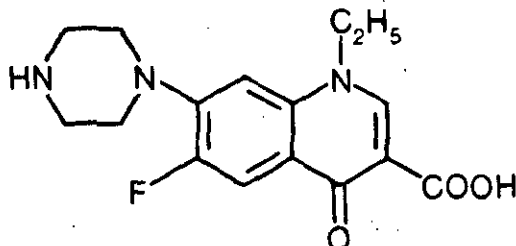
*Pages re retyping, this was
initialed by all supervisors except
Dr. Stanley, who was on sick leave.
See attached copy.*

TABLETS

MSD | **NOROXIN®**
 (NORFLOXACIN, MSD)

NOROXIN®
 (Norfloxacin, MSD)
DESCRIPTION

NOROXIN® (Norfloxacin, MSD) 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-quinolincarboxylic 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, iron oxide, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, and titanium dioxide.

Norfloxacin, a fluoroquinolone, differs from quinolones by having a fluorine atom at the 6 position and a piperazine moiety at the 7 position. Examples of antibacterial drugs which are quinolones include nalidixic acid and cinoxacin.

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 and 400 mg. At the respective doses, mean peak serum and plasma concentrations of 0.8 and 1.5 mcg/mL are attained approximately one hour after dosing. The presence of food may decrease absorption. The effective half-life of norfloxacin in serum and plasma is 3 - 4 hours. Steady-state concentrations of norfloxacin will be attained within two days of dosing.

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

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

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

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

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

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

Microbiology

Norfloxacin has *in vitro* activity against a broad spectrum 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 NOROXIN 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). Resistance of the organism has developed 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
 Enterococci

For this reason, when there is a lack of satisfactory clinical

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response, 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 demonstrates activity against indicated organisms resistant to the aminoglycosides (including gentamicin), penicillins, cephalosporins, tetracyclines, macrolides, and sulfonamides, including combinations of sulfamethoxazole and trimethoprim. Antagonism has been demonstrated *in vitro* between norfloxacin and nitrofurantoin.

While *in vitro* studies have demonstrated the susceptibility of most strains of the following organisms, clinical efficacy for infections other than those included in the INDICATIONS AND USAGE section has not been documented.

Aerobic Bacteria

Gram-positive bacteria including:

Streptococcus faecalis (enterococcus)
Staphylococcus aureus (including both penicillinase-producing and methicillin-resistant strains)
Staphylococcus epidermidis
Staphylococcus saprophyticus
Bacillus cereus

Gram-negative bacteria including:

Acinetobacter calcoaceticus
Aeromonas species
Alcaligenes species
Campylobacter species
Citrobacter diversus
Citrobacter freundii
Edwardsiella tarda
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Flavobacterium species
Hafnia alvei
Klebsiella oxytoca
Klebsiella pneumoniae
Klebsiella rhinoscleromatis
Morganella morganii
Neisseria gonorrhoeae
Proteus mirabilis
Proteus vulgaris
Providencia alcalifaciens
Providencia rettgeri
Providencia stuartii
Pseudomonas aeruginosa
Salmonella typhi
Salmonella species
Serratia marcescens
Shigella species
Vibrio cholerae
Vibrio parahaemolyticus
Yersinia enterocolitica

Other

Ureaplasma urealyticum

NOROXIN is not generally active against obligate anaerobes.

Susceptibility Tests

Quantitative methods that require measurement of zone diameters give precise estimates of bacterial susceptibility.

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One such procedure has been recommended for use with discs to test susceptibility to norfloxacin.

Reports from the laboratory giving results of the standard single disc susceptibility test with a 10 mcg norfloxacin disc should be interpreted according to the following criteria.

Susceptible organisms produce zones of 13 mm or greater, indicating that the test organism is likely to respond to therapy.

Resistant organisms produce zones of 12 mm or less, indicating that other therapy should be selected.

A bacterial isolate may be considered susceptible if the MIC value for norfloxacin is equal to or less than 16 mcg/mL. Organisms are considered resistant if the MIC is equal to or greater than 32 mcg/mL.

The standardized quality control procedure requires use of control organisms. The 10 mcg norfloxacin disc should give the zone diameters listed below for the quality control strains.

Organism	ATCC®	Zone Size Range
<i>E. coli</i>	25922	28 - 35 mm
<i>P. aeruginosa</i>	27853	22 - 29 mm
<i>S. aureus</i>	25923	17 - 28 mm

Dilution susceptibility tests should give MICs between the ranges listed below for the quality control strains.

Organism	ATCC®	MIC (mcg/mL)
<i>E. coli</i>	25922	0.03 - 0.125
<i>S. aureus</i>	29213	0.5 - 2.0
<i>S. faecalis</i>	29212	2.0 - 8.0
<i>P. aeruginosa</i>	27853	1.0 - 4.0

Based on urinary concentrations of norfloxacin achieved in man, breakpoint criteria have been established as listed below.

Category	Zone Diameter (mm)	Recommended MIC Breakpoint (mcg/mL)
Susceptible	≥ 13	≤ 16
Resistant	≤ 12	≥ 32

Norfloxacin susceptibility test results should not be used to predict susceptibility to other less potent quinolone antibacterial agents such as nalidixic acid.

INDICATIONS AND USAGE

Treatment

NOROXIN is indicated for the treatment of adults with complicated and uncomplicated urinary tract infections that are caused by susceptible strains of the designated microorganisms listed below:

Escherichia coli; *Klebsiella pneumoniae*; *Enterobacter cloacae**; *Proteus mirabilis*; indole positive *Proteus* species* (which may include the organisms now called *Proteus vulgaris**, *Providencia rettgeri**, and *Morganella morganii*)*; *Pseudomonas aeruginosa*; *Citrobacter freundii**; *Staphylococcus aureus**, *Staphylococcus epidermidis**; and group D streptococci.

NOTE: Specimens for culture and susceptibility testing should be obtained prior to and during treatment if clinical response warrants.

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

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CONTRAINDICATIONS

NOROXIN is contraindicated in patients with a history of hypersensitivity to norfloxacin or the quinolone group of antibacterial agents (e.g., nalidixic acid and cinoxacin).

WARNINGS

Norfloxacin should not be used in children or pregnant women.

The oral administration of single doses of norfloxacin, 6 times the recommended human clinical dose, caused lameness in immature dogs. Histologic examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs (e.g., nalidixic acid and cinoxacin) also produced erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species.

PRECAUTIONS

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).

The effects of norfloxacin on brain function or on the electrical activity of the brain have not been tested. Until more information becomes available, quinolones should be used with caution in patients with known factors which predispose to seizures.

Drug Interactions

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.

The concomitant administration of norfloxacin with antacids is not recommended.

Information for Patients

Patients should be advised to take NOROXIN one hour before or two hours after a meal. Patients should also be advised to drink fluids liberally and not to take antacids concomitantly or within 2 hours after dosing.

NOROXIN may cause dizziness or lightheadedness; 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.

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.

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 dose. Norfloxacin had no mutagenic activity *in vitro* in the Ames microbial mutagen test, Chinese hamster

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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 33 times the usual human dose.

Pregnancy

Pregnancy Category C: Norfloxacin has been shown to produce embryonic loss in monkeys when given in doses 10 times the maximum human dose (400 mg b.i.d.), with peak plasma levels that are 2 to 3 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 human dose. There were no adequate and well controlled studies in pregnant women. Since norfloxacin, like other drugs in this class, causes arthropathy in immature animals, it should not be used in pregnant women (see WARNINGS).

Nursing Mothers

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

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

Pediatric Use

Norfloxacin should not be used in children because it causes arthropathy in juvenile animals (see WARNINGS.)

ADVERSE REACTIONS

In clinical trials, NOROXIN was generally well tolerated.

The incidence of subjects reporting drug related adverse experiences in clinical trials involving 1127 subjects was 3.4%. However, the incidence figures below were calculated without reference to drug relationship.

The most common adverse experiences (1% - 3%) were either gastrointestinal or neurological: nausea 2.8%, headache 2.7%, and dizziness 1.8%.

Additional reactions (0.3% - 1%) were: fatigue, rash, abdominal pain, dyspepsia, somnolence, depression, insomnia, constipation, flatulence, and heartburn.

Less frequent reactions included: dry mouth, diarrhea, fever, vomiting, and erythema.

Visual disturbances have been reported with drugs in this class.

Abnormal laboratory values observed in these 1127 subjects in clinical trials were eosinophilia 1.8%, elevation of ALT (SGPT) and AST (SGOT) 1.8%, increased alkaline phosphatase 1.4%, and decreased WBC or neutrophil count 1.2%. Those occurring less frequently included increased BUN, serum creatinine, and LDH and decreased hematocrit.

OVERDOSAGE

The acute oral LD₅₀ values in male and female mice and male and female rats were greater than 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.

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DOSAGE AND ADMINISTRATION

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

Normal Renal Function

The recommended dosage of NOROXIN is:

Uncomplicated urinary tract infections: 400 mg twice daily for 7 to 10 days.

Complicated urinary tract infections: 400 mg twice daily for 10 to 21 days.

Maximum total daily dosage should not exceed 800 mg per day.

Renal Impairment

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

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

$$\text{Males: } = \frac{(\text{weight in kg}) \times (140 - \text{age})}{(72) \times \text{serum creatinine (mg/100 mL)}}$$
$$\text{Females: } = (0.85) \times (\text{above value})$$

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Elderly

Elderly patients with a creatinine clearance of greater than 30 mL/min/1.73m² should receive the dosages recommended under *Normal Renal Function*.

Elderly patients with a creatinine clearance of 30 mL/min/1.73m² or less should receive 400 mg once daily as recommended under *Renal Impairment*.

HOW SUPPLIED

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

NDC 0006-0705-68 bottles of 100
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.

MSD MERCK SHARP & DOHME
DIV OF MERCK & CO., INC., WEST POINT, PA 19380, USA

MOR

HFN-815

November 14, 1985

MEDICAL OFFICER'S REVIEW OF NDA 19-384

Initial 148-Volume Submission Dated January 14, 1985
and Amendments (

Applicant: Merck Sharp & Dohme Research Laboratories
Division of Merck & Co., Inc.
West Point, Pennsylvania 19486

MOR

Name of Drug: Generic: Norfloxacin, MSD

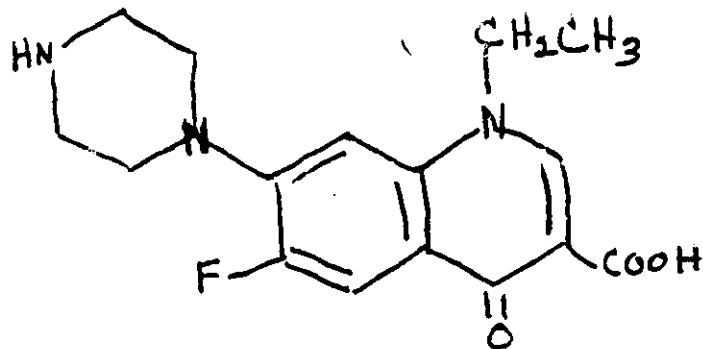
Trade: NOROXINTM

Empirical: C₁₆H₁₈FN₃O₃

Mol. Wt. 319.34

Chemical: 1-ethyl-6-fluoro-1,4-dehydro-4-oxo-7-(1-piperazinyl)
-3-quinoline carboxylic acid

Structural:



Pharmacological Category: Orally absorbed antibacterial agent, a
fluoroquinolone member of the quinolone drug class

Proposed Indications: For treatment of complicated and uncomplicated
infections of the urinary tract, gonorrheal urethritis, bacterial
gastro-enteritis, and for prophylactic use in neutropenia.

Related Submissions: (

Microbiology and Manufacturing Controls: Norfloxacin is a synthetic broad spectrum pyridone carboxylic acid for oral administration. It was discovered and developed by investigators at the Kyorin Pharmaceutical Co., Ltd., in Japan. Norfloxacin is chemically and pharmacologically related to nalidixic acid, oxolinic acid, and pipemidic acid but with a fluoride ion at the 6-position and is much more potent.

Norfloxacin is bactericidal and is active against aerobic gram-negative and gram-positive bacteria including all species of staphylococci, all species of Enterobacteriaceae, N. gonorrhoeae, H. influenzae, G. vaginalis, U. urealyticum, P. aeruginosa, Acinetobacter species, and C. trachomatis. Norfloxacin MIC's are outstanding when compared to MIC's for other nonfluorinated antimicrobial agents shown in the next table. Norfloxacin is not active against anaerobes.

Norfloxacin inhibits bacterial DNA synthesis. It inhibits the ATP-dependent DNA supercoiling reaction by E. coli DNA gyrase. It inhibits the relaxation of supercoiled DNA, an activity that is induced by DNA gyrase in the absence of ATP. It promotes double-stranded DNA breakage in E. coli cells. Collectively, these events cause filamentation of representative gram-negative bacterial cells, swelling of S. aureus, lysis of P. aeruginosa, and shrinkage when the cells are viewed by transmission and scanning electron microscopy.

The applicant has selected a disk content of 10 mcg. Organisms with zones of 17 mm or greater are considered to be susceptible, those with zones of 13-16 mm have intermediate susceptibility, and those with zones of 12 mm or less are considered to be resistant strains. Dilution susceptibility breakpoints are 16 mcg/ml or less - susceptible, and 32 mcg/ml or greater - resistant.

Table of Contents

	Page
Applicant, Name of Drug, Pharmacological Category	1
Proposed Indication, Related Submissions	
Dosage Form and Route of Administration	3
Microbiology and Manufacturing Controls	3
Animal Pharmacology	5
Clinical Background	8
Clinical Studies	
1. Special Studies	9
a) Human Pharmacology and Pharmacokinetics	9
b) Safety and Tolerance (Zimney - diaries)	12
c) Bioavailability (Two trials - Zimney - diaries)	17
d) Renal Function (Asscher)	18
2. Controlled Clinical Trials	
a) Uncomplicated UTI Domestic, Multiclinic	20
b) Complicated & Uncomp. UTI (N vs TMP-SMZ)	
(1) Domestic (Multiclinic)	24
(2) International (Multiclinic)	29
c) Bacterial Gastroenteritis	
(1) N vs Erythromycin vs Placebo (Cohn)	35
(2) N vs TMP-SMZ (Multiclinic)	39
d) Suppression of Bowel Flora in Granulocytopenia	
(1) N + Amphotericin B vs TMP-SMZ + Ampho. B	45
(2) N + Nystatin vs Polymyxin B + Vanco.+Nys.	51
e) Gonorrheal Infection	
(1) N vs Spectinomycin - Subic Bay (Berg)	56
(2) N vs Ampicillin + Probenecid	58
3. Uncontrolled Clinical Studies	
a) Acute Bacterial Gastroenteritis (Kunkel)	61
b) Urinary Tract Infections	
(1) Domestic (Multiclinic)	62
(2) International (Multiclinic)	64
c) Compassionate Treatment	
(1) Salmonellosis (Lyons & Nadworny)	70
(2) Multiple Antibiotic Resistant Infections	70
d) Suppression of Bowel Flora in Granulocytopenia	
(1) Rubin & Talbot	71
(2) LeFrock	74
4. Controlled UTI Trials Filed for Safety Only	
a) N vs TMP-SMZ International (Multiclinic)	75
b) N vs Nalidixic Acid - Un. Kingdom (Multiclinic)	77
c) N vs Nalidixic Acid - Canada (Ronald)	80
Amendments	81
Applicant's Efficacy Summary	88
(Medical Officer's Preliminary Summary of Efficacy)	91
Applicant's Safety Summary	93
Summary of Medical Officer's Comments	102
Biopharmaceutics Consultation	109
Labeling Review	109
Foreign Clinical Data	109
Conclusion and Recommendation	109

I
E

Microbiology and Manufacturing Controls: Norfloxacin is a synthetic broad spectrum pyridone carboxylic acid for oral administration. It was discovered and developed by investigators at the Kyorin Pharmaceutical Co., Ltd., in Japan. Norfloxacin is chemically and pharmacologically related to nalidixic acid, oxolinic acid, and piperidic acid but with a fluoride ion at the 6-position and is much more potent.

Norfloxacin is bactericidal and is active against aerobic gram-negative and gram-positive bacteria including all species of staphylococci, all species of Enterobacteriaceae, N. gonorrhoeae, H. influenzae, G. vaginalis, U. urealyticum, P. aeruginosa, Acinetobacter species, and C. trachomatis. Norfloxacin MIC's are outstanding when compared to MIC's for other nonfluoridated antimicrobial agents shown in the next table. Norfloxacin is not active against anaerobes.

Norfloxacin inhibits bacterial DNA synthesis. It inhibits the ATP-dependent DNA supercoiling reaction by E. coli DNA gyrase. It inhibits the relaxation of supercoiled DNA, an activity that is induced by DNA gyrase in the absence of ATP. It promotes double-stranded DNA breakage in E. coli cells. Collectively, these events cause filamentation of representative gram-negative bacterial cells, swelling of S. aureus, lysis of P. aeruginosa, and shrinkage when the cells are viewed by transmission and scanning electron microscopy.

The applicant has selected a disk content of 10 mcg. Organisms with zones of 17 mm or greater are considered to be susceptible, those with zones of 13-16 mm have intermediate susceptibility, and those with zones of 12 mm or less are considered to be resistant strains. Dilution susceptibility breakpoints are 16 mcg/ml or less - susceptible, and 32 mcg/ml or greater - resistant.

Comparison of Antibacterial Activities

Organism	MIC (mcg/ml)					
	Norflox- acin	Cinoxa- cin	Nalidix- ic acid	Oxolinic acid	Nitrofur- antoin	Trimeth- oprim
<u>L. monocytogenes</u>	4	>128	>128	>128	>128	< 0.03
<u>S. aureus</u>	2	>128	64	1	8	64
<u>S. epidermidis</u>	0.25	128	128	4	>128	2
<u>S. agalactiae</u>	16	>128	>128	>128	32	NT
<u>S. faecalis</u>	4	128	>128	32	32	NT
<u>S. pneumoniae</u>	4	>128	>128	64	4	NT
<u>S. pyogenes</u>	4	>128	>128	>128	4	NT
<u>Acinetobacter iwoffl</u>	0.5	32	8	1	>128	8
<u>Alcaligenes sp.</u>	4	2	4	0.25	64	128
<u>C. diversus</u>	0.015	4	2	0.25	32	0.25
<u>C. freundii</u>	0.03	8	8	1	32	0.5
<u>E. aerogenes</u>	0.06	8	8	1	128	1
<u>E. cloacae</u>	0.06	8	4	0.25	128	2
<u>E. coli</u>	0.5	>128	>128	4	16	0.5
<u>H. influenzae</u>	<0.06	NT	0.5	0.125	NT	NT
<u>K. oxytoca</u>	0.06	8	8	0.5	32	0.5
<u>K. pneumoniae</u>	0.06	4	2	0.125	16	1
<u>Morganella bovis</u>	0.06	32	4	0.25	4	16
<u>N. morganii</u>	0.015	2	1	0.125	8	64
<u>N. gonorrhoeae</u>	0.5	>128	32	2	32	<0.03
<u>P. mirabilis</u>	0.03	16	8	0.125	128	1
<u>P. alcalifaciens</u>	0.125	>128	>128	8	>128	32
<u>P. rettgeri</u>	0.05	4	4	0.25	64	2
<u>P. aeruginosa</u>	0.5	>128	>128	16	>128	>128
<u>S. paratyphi A</u>	4	>128	>128	8	16	2
<u>S. marcescens</u>	0.125	8	4	0.5	>128	16
<u>S. sonnei</u>	0.03	8	4	1	8	0.25

Norfloxacin significantly reduced the mortality of suckling piglets challenged orally with enterotoxigenic E. coli and eliminated diarrhea in surviving animals. Studies in rodents demonstrated that norfloxacin is effective in treating pulmonary infections, skin and skin structure infections, renal abscesses, intradermal abscesses, and in eliminating E. coli from granuloma pouch exudates.

Oral doses of 50 mg/kg for several days in pathogen-free mice lowered the number of enterobacteria in the fecal flora to near zero without affecting the numbers of lactobacilli, Bacteroides species, or gram positive cocci. In rats, norfloxacin significantly decreased both gram-positive and gram-negative bacteria from the ileum to the rectum, while anaerobic bacteria increased

Norfloxacin at a concentration of 2.5 mcg/ml in pooled serum was 13.8% bound to human protein.

Six metabolites identified in human urine, M-1, M-2, M-3, M-4, M-5, and M-6, are all microbiologically active. Eleven bacterial species were tested.

Animal Pharmacology: Animal studies of norfloxacin have been conducted in the rat, mouse, dog, and monkey. Norfloxacin is relatively nontoxic in adult male and female rats and mice. It is poorly absorbed from the gastrointestinal tract. Acute toxicity studies of norfloxacin are summarized as follows:

Species and Sex	LD ₅₀ (mg/kg)			
	PO	Sub Q	IM	IV
Mouse				
Male	Over 4,000	Over 1,500	470	220
Female	Over 4,000	Over 1,500	480	237
Rat				
Male	Over 4,000	Over 1,500	Over 500	270
Female	Over 4,000	Over 1,500	Over 500	245

In mouse and rat studies, six different metabolites were tested orally for their acute toxicities. LD₅₀ values were estimated to be over 2000 mg/kg for M-1, M-4 (2), and M-5 and over 4000 mg/kg for M-2, M-3, and M-4 (1).

One month oral toxicity studies were performed in rats (at doses of 250, 500, and 1000 mg/kg/day), dogs (at 50, 100, and 200 mg/kg/day or 25, 50, and 100 mg/kg bid), and monkeys (at 25, 50, and 100 mg/kg bid). There was no drug-induced toxicity in any species.

Six-month oral toxicity studies in rats conducted by Kyorin revealed body weight retardation in the 250 and 500 mg/kg/day groups but not in the 50 or 125 mg/kg/day group. A similar study in rats conducted by Merck using different doses revealed a slight decrease in body weight gain in the 600 mg/kg/day group. Cecal enlargement was seen in all dose groups. A decrease in body weight gain occurred in females in the 200 and 600 mg/kg/day dose groups in the one-year study in rats. An increase in urinary potassium excretion was seen in female rats given 500 and 1,000 mg/kg/day.

Crystalluria consisting of the dihydrate and the magnesium salts of norfloxacin occurred in rats in the two high dose groups in the Merck study (in the 200 and 600 mg/kg/day dose groups).

Crystalluria occurred in beagle dogs given norfloxacin at 50, 150, and 300 mg/kg/day for 26 weeks but not in the 25 mg/kg/day dose group. The incidence was dose related and was high in the 300 mg/kg/day group. Three dogs, one in the 150 mg/kg/day group and two in the 300 mg/kg/day group, were found dead or were sacrificed due to urinary obstruction from drug crystals.

The crystalluria in dogs and rats was attributed to low solubility of the drug in alkaline urine. This was supported by the observation of a significant decrease in the incidence of crystalluria and in the absence of urinary obstruction when urine was acidified by the administration of ammonium chloride. In this separate study, dogs received 50, 150, and 300 mg/kg/day for three months. Urine acidification to pH range between 5.5 and 6.5 was accomplished by adding ammonium chloride (1%) to drinking water. Emesis

occurred in all dogs and frequently occurred shortly after dosing. Drug crystals shaped as sea urchins and/or fine needles were occasionally seen in urine from dogs in each of the drug-treated groups. Those found during drug weeks 11, 12, and 13 were shown by HPLC to be norfloxacin. The severity and incidence of crystalluria was greatest in the 300 mg/kg/day group. Four deaths due to aspiration pneumonia occurred.

An oral norfloxacin suspension was given to monkeys in doses of 25, 50, and 100 mg/kg bid six days a week for four weeks. There were two monkeys in each group. Controls received sterile distilled water. Monkeys were sacrificed at the end of treatment. The summary says that no findings attributable to treatment were seen.

Medical Officer's Comments:

1. The report indicates that proteinuria was observed in one of two 200 mg/kg/day monkeys and slight hemoglobinuria was observed in one of two 50 mg/kg/day dose monkeys. Upon further review, the report states in regard to urinalysis that, "One monkey in each of the 50 mg/kg/day group and 100 mg/kg/day group, however, were (sic) not examined because urine could not be obtained from the bladder." Therefore, hemoglobinuria occurred in 100% of monkeys at a dose which is 2-3 times the expected human dose. The "no-effect" dose for hemoglobinuria in monkeys is not known. (The higher doses in humans are 800-1200 mg daily or 16-24 mg/kg based upon a human weighing 50 kg.)
2. The presence of drug crystals in the urine of these monkeys cannot be evaluated because urine was not examined microscopically. Crystals may have been present and may have been the cause of the proteinuria and hemoglobinuria. The "no-effect" crystalluria dose in monkeys is not known.
3. Crystalluria occurred in dogs at 50 mg/kg/day, a dose which will be 2-3 times the recommended human dose. The 'no-effect' crystalluria dose is not known. There may be a possibility that crystalluria could occur at the recommended doses in some patients. Labeling should advise about this possibility.

In the cat, intravenous administration of norfloxacin in doses of 10 mg/kg resulted in modestly reduced (less than 30%) contractions of the nictitating membrane elicited by both pre- and post-ganglionic nerve stimulation.

The amplitude of spontaneous contractions of the pregnant and non-pregnant rat uterus and rabbit ileum were slightly reduced.

In vitro, in isolated perfused guinea pig hearts, one-gram bolus injections resulted in a slight increase in coronary flow and decreased heart rate while modestly depressing contractile force. In the isolated rabbit ear artery, a similar 1-mg bolus of norfloxacin produced a weak, transient change in blood flow.

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In vivo, in urethane anesthetized rabbits and barbiturate anesthetized dogs, intravenous doses resulted in an increased respiratory rate. Rabbits received 30 mg/kg and dogs received 10 mg/kg. In these animals and in rats receiving 20 mg/kg IV, blood pressure tended to be reduced without substantial changes in heart rate. In rats, the reduced blood pressure was inhibited by diphenhydramine and was unaffected by atropine, propranolol, or phentolamine. Infusion of norfloxacin in dogs produced an elevation in respiratory rate (60% increase) with only modest changes in blood pressure and heart rate. These doses are well above those which are required for antimicrobial activity.

Results of several teratology studies revealed that rabbits were intolerant of oral doses of norfloxacin. There was, however, fetotoxicity in rabbits that was directly related to maternotoxicity due to its effects on the gastrointestinal flora.

A preliminary report reveals that embryotoxicity and maternal toxicity resulted for 8 of 14 pregnant cynomolgus monkeys that received 300 or 200 mg/kg/day after 10-30 doses. The threshold for embryonic loss is at least 50 mg/kg/day. These doses were not tolerated in all monkeys. This study continues and the applicant is expanding it to evaluate a possible difference in the metabolism of norfloxacin in pregnant and non-pregnant monkeys.

Arthropathy - Lameness appeared on the second day of treatment in 3-5 month old dogs treated for seven days with doses greater than 60 mg/kg/day and persisted during treatment. Similar signs of lameness occurred in dogs given doses of nalidixic acid and pipemidic acid that were greater than 30 mg/kg/day. Lameness did not occur in norfloxacin-treated rabbits but there was blister formation on the articular cartilage in rabbits given 250 mg/kg/day or greater for seven days. In dogs, lameness was usually associated with joint lesions that were characterized by an increased amount of synovial fluid and blister formation and sometimes by erosions of the articular cartilage.

No evidence of retinal toxicity was observed in cats given doses up to 200 mg/kg/day for two weeks. However, cats given nalidixic acid in doses of 100 mg/kg/day showed retinal toxicity as evidenced by electroretinographic changes (prolongation of latency and reduction amplitude) as well as histopathological changes characterized by wave-like arrangements of the outer nuclear layer.

Norfloxacin powder, 100 mg/eye, was found to be severely irritating to rabbit eyes as evidenced by conjunctival injection, discharge, and marked chemosis at 24 hours after treatment.

Serum pharmacokinetics and urinary excretion of norfloxacin suspension and tablets in single doses of 25 mg/kg were studied in three male rhesus monkeys over a period of six months. Peak serum concentrations varied from 1.12-2.35 mcg/ml at one hour. Urinary excretion was variable and ranged from 4.9 mg to 67.5 mg during the first 24 hours. Serum half-life was 165 minutes in monkeys.

The applicant concludes that there is no contraindication to the clinical administration of norfloxacin. However, norfloxacin should not be used in children or during pregnancy unless the benefits outweigh the risks.

Clinical Background:

Norfloxacin has been extensively investigated by Kyorin in Japan. Results of the Japanese studies show that norfloxacin is rapidly absorbed following oral administration. Serum concentrations after a single dose are approximately proportional to the dose in the range of 100 to 800 mg but are higher than expected at 1600 mg. Peak serum concentrations were 0.47, 0.77, 1.38, 2.33, and 9.70 mcg/ml at doses of 100, 200, 400, 800, and 1600 mg, respectively. Drug levels were measured by a microbiological technique and, therefore, include metabolites. The apparent serum half-life is approximately 4 hours and is independent of the dose up to and including 800 mg. At the 1600 mg dose, half-life was prolonged.

No accumulation of the drug in healthy volunteers was found after multiple dosing of 200 mg q 8 h for seven days. The peak serum level on the first day was approximately 0.9 mcg/ml and on the eighth day was approximately 1.0 mcg/ml. Absorption was slightly reduced in post prandial administration.

Urinary concentrations reached approximately 100 times the serum concentration in healthy volunteers. Urinary recovery was 33-48% of the dose within 24 hours after single oral doses.

Studies in five patients with biliary fistulas suggest that norfloxacin levels in bile are 5-10 times serum levels.

The major metabolite, one of six metabolites, was the 2-oxo form which accounted for 10% of the load excreted. Unchanged drug accounted for 70%.

A variety of urinary tract and systemic infections were studied by Kyorin workers but most were urinary tract infections. Outcome in a study of 949 cases is reported as follows:

<u>Diagnosis</u>	<u>No. cases</u>	<u>Treatment Success</u>
Acute, simple cystitis	469	96.2%
Simple pyelonephritis	15	93.3%
Complicated cystitis	307	63.5%
Complicated pyelonephritis	106	50.9%
Gonorrheal urethritis	14	92.9%
Nongonorrheal urethritis	21	42.9%
Prostatitis	13	61.5%
Acute epididymitis	4	100.0%

Of these, Pseudomonas aeruginosa was reported to be the pathogen in 59 and 57.6% of these were resolved with norfloxacin treatment.

Medical Officer's Comment: Adverse effects and abnormal laboratory reports in these 949 cases are not summarized. Also, the report does not say how these patients were monitored.

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Clinical Studies:1. Special Studies

a) Human Pharmacology and Pharmacokinetics: The reader is referred to the Biopharmaceutics Review. Copies of Volumes 2.145-2.148 were sent to Biopharmaceutics on March 11, 1985.

(1) Study No. 1 Roger K. Ferguson, M.D., Clinical Pharmacology Unit, Thomas Jefferson Hospital, Philadelphia, PA, conducted a randomized, double-blind, single-dose escalation, placebo-controlled trial of norfloxacin by the oral route in 14 healthy adult male volunteers. Each subject received 200, 400, 800, 1200, and 1600 mg of norfloxacin in increasing order a week apart and two doses of placebo. Results are shown below.

	Single Norfloxacin Doses				
	200 mg	400 mg	800 mg	1200 mg	1600 mg
C _{max} (mcg/ml)	0.79	1.55	2.38	3.64	3.67
T _{max} (hrs)	1.1	1.1	1.4	1.7	1.8
T _{1/2} (hrs)	2.18	2.19	2.29	2.39	2.48
AUC (mcg/hr/ml)	3.36	6.20	12.19	19.09	24.06
Mean 48 hr. Urinary Recovery (% of dose)	32.2	31.5	28.7	29.0	29.2

Serum levels were never higher than 6 mcg/ml. Maximum levels increased as the dose increased but did not increase in proportion to the dose escalations except at the 200 and 400 mg doses. Since the time to peak increased with higher doses, there may have been some delayed absorption as the dose increased.

The applicant reports that, "Although appreciable quantities of drug were recovered during the 24-48 hour urine collection interval, it appears that little drug would be recovered after 48 hours regardless of dose. The average total urinary recovery of MK-366 represents 30% of the dose administered at all dose levels." For a given individual, renal clearance is constant within a treatment and shows little variability between treatment. There was little change as a function of increasing dose. Renal clearance averaged 300 ml/min.

The applicant concludes that increasing the dose does not affect the total absorption although absorption is somewhat delayed at higher doses. The serum half-life is independent of the dose. The elimination of norfloxacin from serum is linear and the AUC increases in proportion to the dose. The average renal clearance is 300 mg/min. Urinary recovery is 30% in 48 hours. Norfloxacin was well tolerated.

Medical Officer's Comment: This report is incomplete because it fails to report the microscopic examinations of urine sediment examined in order to

ascertain the presence of drug crystals at the peak of the drug excretion period. When the protocol for this study was received, this was one of nine requests from FDA in the initial MOR for protocol revision. The IND was placed "on-hold" status because of this and other deficiencies. These requests were transmitted to the sponsor in a letter. The Agency also asked the sponsor to provide for the examination of urine sediment for the presence of drug crystals in subsequent pharmacokinetic studies until it could be established that drug crystallization was not a problem.

The protocol in this NDA (protocol on page 10, NDA page I-00119, Vol. 2.2) says that, "Following each act of urination, an aliquot (10 ml) of the freshly voided urine will be centrifuged and the resulting sediment examined for the presence of crystalline material." No reports of this examination can be located. Instead, the applicant tells us on page I-00142 of Volume 2.2 that, "In as much as the urinary concentrations of MK-366 can exceed the limits of drug solubility in urine at room temperature (see figure 1), thorough mixing of urine was essential prior to dispensing of urine for assay." Norfloxacin precipitation can probably be diminished by acidification of the urine.

The question as to whether norfloxacin precipitates in the urine and whether drug crystals can cause renal obstruction, as happened in dogs, has not been answered by this study.

Five subjects experienced nine episodes of adverse reactions, seven episodes followed norfloxacin dosing, and two followed placebo dosing. Adverse reactions after norfloxacin dosings were nausea, headache, tiredness, flatulence, and abdominal cramps. Abnormal laboratory values were protein in urine, increased WBC in urine, decreased platelets, elevated SGOT, decreased serum glucose, eosinophilia, and decreased hematocrit. The last two deviations were not considered to be drug related.

(2) Study No. 501 W. R. Kukovetz, Vorstand des Institute for Pharmakodynamik und Toxikologie der Universitat, Universitat Splatz-2, A-8010 Graz 1 Austria, conducted a double-blind, crossover, multiple-dose, placebo-controlled trial of the safety, tolerance, absorption, and excretion of norfloxacin tablets in oral doses of 200 mg three times a day for seven days in twelve healthy male adult volunteers. Treatments for each volunteer were separated by a six-day crossover interval. (The control number for norfloxacin tablets was SOY9890A and the control number for placebo was SOY9890P.)

Three of the twelve subjects experienced the following three adverse reactions after taking norfloxacin: tiredness - 3 subjects, and burning sensation upon voiding - one subject. Five of these reactions appeared on the third day. Two placebo subjects reported tiredness, one of these two had diarrhea.

Serum and urine levels of antimicrobial activity cannot be attributed to norfloxacin alone since the microbiological activities of six metabolites are included in the measurement.

Serum levels were below detectable limits in nearly 60% of the serum samples. Trough levels on the second and eighth days did indicate that antimicrobial activity was accumulating in serum on this eight-hour regimen. Following the last dose, antimicrobial activity persisted in serum for at least four hours with detectable levels in 75% of serum samples. On either the first or the eighth day, serum levels of antimicrobial activity rarely exceeded 1.0 mcg/ml equivalents and were generally near the sensitivity limits of the assay (0.1 mcg/ml).

The amount of antibiotic activity noted for urinary recovery at eight hours after the last dose is nearly twice that found after the first dose. Individual renal clearance appeared constant within a treatment and did not change from the first day to the eighth day. Clearance generally exceeded 400 ml/min. Urine levels of antimicrobial activity were 20 mcg/ml equivalents or higher for approximately 2-3 hours after the first dose and 5-8 hours after the last dose.

A significantly lower mean supine diastolic blood pressure was observed on the fifth day at zero hour for patients on norfloxacin than for those on placebo. Small but significant changes from pretreatment in lymphocytes, monocytes, and basophils were observed for norfloxacin and in WBC, basophils and SGPT for placebo. Significant differences between treatment were observed in lymphocytes, monocytes, and basophils.

The applicant concludes that norfloxacin in doses of 200 mg t.i.d. for seven days is safe and well tolerated.

(3) Study No. 661 Bernard K. Martin, Ph.D., BIOS (Consultancy & Contract Research), Ltd., Pinewood, College Ride, Bagship, Surrey, England, conducted an uncontrolled, single-dose study of pharmacokinetic parameters of norfloxacin in six healthy, elderly volunteers. Subjects were between 67 and 74 years of age. Each subject received one 400-mg film-coated tablet.

Norfloxacin was well tolerated in all subjects. There were no adverse reactions. After a short lag period of 20 minutes, the drug was rapidly absorbed, reaching a mean peak plasma concentration of 2 mcg/ml approximately 1.5 hours after administration.

Highest urine concentrations occurred between two and four hour after dosing and ranged from 79.5 to 254.1 mcg/ml for the six subjects.

The applicant reports that pharmacokinetic parameters indicate elimination of norfloxacin may be slightly reduced in the elderly. This results in small increases in plasma levels and may also result in small increases in drug half-life. Changes in norfloxacin disposition appear attributable to the slightly reduced renal function associated with a normal elderly population. No alteration of dosing regimen appears necessary for elderly subjects whose renal function is normal for this age group (creatinine clearance equal to or greater than 70 ml/min/1.73 m²). The applicant concludes that a single 400 mg tablet of norfloxacin appears safe in healthy, elderly subjects.

b. Safety and Tolerance

(1) Study No. 45 Miguel A. Zinney, M.D., Assistant Professor of medicine at Tufts University School of Medicine, and with Medical and Technical Research Assoc., Inc., Clinical Unit, Jamaica Plain, MA 02194, conducted a randomized, double-blind, multiple-dose, crossover study of norfloxacin and placebo to measure pharmacokinetic parameters and tolerance. Twenty-seven healthy adult volunteers (24 males and 3 females) received either a 400-mg film-coated tablet of norfloxacin q 12 h or placebo for 14 days. There was a seven-day crossover interval.

The applicant reports that nineteen volunteers experienced at least one adverse clinical experience during the course of the study, while on norfloxacin, 5 while on placebo, and 7 while on both regimens. No reactions were considered serious. The most common were central nervous system adverse reactions - 13 (11 of whom reported headache), respiratory tract adverse reactions - 6, and digestive tract reactions - 6. Norfloxacin was discontinued in three male volunteers because of adverse effects and one volunteer did not ingest one placebo dose.

All 27 subjects completed diary sheets for reporting adverse reactions.

Sixteen subjects had at least one adverse laboratory report. The most common were low WBC counts followed by high WBC counts, low hematocrits, and differential WBC's out of range.

Concentrations of norfloxacin in urine averaged 30 mcg/ml or higher during each dosing interval. Cumulative renal clearances ranged between 240 and 330 mg/min from one dosing interval to the next dosing interval. Mean peak plasma norfloxacin concentrations were 1.15, 1.18, 1.27, and 1.35 mcg/ml following the first dose given on Days 1, 2, 7, and 14, respectively. Peak plasma concentrations occurred between 1.5 and 2 hours after the dose while the mean trough concentration determined at 12 hours was 0.12 mcg/ml after the first drug dose. It fluctuated between 0.15 and 0.23 mcg/ml, thereafter. Steady-state conditions were established on a 12-hourly norfloxacin regimen between 2 and 7 days of drug administration.

"There were no norfloxacin crystals found in the urine at 1 to 2 hours post norfloxacin and placebo dosing."

Reviewer's Comment: The report does not say whether drug crystals or crystals of the metabolites were found in other specimens of urine sediment anytime during the study.

The applicant concludes that norfloxacin, when administered twice daily to subjects with normal renal function, produces serum levels 12 hours after dosing on Days 2, 7, and 14 that are similar. Steady state is attained between 2 and 7 days after the beginning of a 400 mg q 12 h schedule. This dose appears to be safe and well tolerated.

Medical Officer's Comment: The medical officer's summary of the positive entries in the 27 patient diaries in this study is shown below:

Norfloxacin

- #3 Sleepy - Day 2. Sluggish after second dose - Day 3. "Clog-noise" and sneezing - Days 5 & 8. Headache - Day 6. Cough - Day 10.
- #8 Headache 1 hr. after dosing for 2 hrs. - Day 1. Massive headache - Day 9.
- #10 Headache 1/2 hr. after first dose for 1 1/2 hrs. - Day 1. Cold - Days 3-4.
- #12 Headache - Day 7.
- #15 "I thought I felt something from the drug, could be psychosomatic, I think" - Day 1. Tired - Day 9, Sleepy - Day 10.
- #16 Tired - Day 5.
- #19 Headache - Day 1. Headache and tension - Day 13.
- #20 Sleepy - Day 1. Dizzy and sleepy - Day 4. Cold - Day 10. Lump in throat - Days 11 and 13-14.
- #21 "Not myself today" - Day 6. Headache - Day 7. Nausea - Day 10.
- #22 Diarrhea - Day 3. Tired - Day 7.
- #23 Headache - Days 4-5. Nausea, sleepy, lightheaded, and dizzy - Day 5. Lightheaded - Day 6. Head swirling - Day 10.
- #27 Cold - Day 6.

Placebo

- #10 Cold symptoms - Day 8
- #11 Headache after dosing for 2 hrs - Day 1. Headache for 30 minutes - Day 2. Headache for 15 minutes - Day 8.
- #21 Tired - Day 1. Headache - Day 6. Nausea & stomachache - Day 9.
- #22 Sour stomach - Day 12.
- #24 Chills and fever, draining sinuses, headache, and dizziness - Day 6. Sore throat - Days 7 & 11.
- #25 Metallic taste in mouth - Day 1. Fever and headache - Day 2. Depressed and suffering from needle withdrawal - Day 7. Headache - Day 9. "I have a strong need for some "coffee" - Day 14.
- #26 Drowsy - Day 1. Soreness in limbs and abdominal pain - Day 2.
- #27 Headache and itching - Day 1. Tired and itching - Day 2. Tired - Day 13. Headache - Day 14.

According to the patient diaries, twelve of 27 subjects (44%) reported one or more adverse reactions while on norfloxacin and 8 of 27 subjects (29.6%) reported one or more adverse reactions while on placebo. This difference is not statistically significant.

(2) Study No. 66 Miguel A. Zinny, M.D., above, conducted a second randomized, double-blind, multiple-dose, crossover pharmacokinetic study. In this study subjects received either placebo or 400 mg q 8 h for 5 days (instead of q 12 h for 14 days). Twenty-six healthy adult subjects participated, one was a female. Only four participated in the pharmacokinetic phase of the study. Subjects completed diary sheets.

The applicant reports that six volunteers experienced adverse clinical

effects: two while on norfloxacin, three while on placebo, and one while on both regimens. None were serious or drug related. One subject had an abnormal laboratory report. These reports followed placebo treatment and were elevations in SGOT and alkaline phosphatase.

Pharmacokinetic parameters are summarized as follows:

	Day 1 (Dose 1)	Day 2 (Dose 4)	Day 5 (Dose 13)
Mean C _{max} (mcg/ml)	1.50	1.73	1.49
Mean C _{min} (mcg/ml)	0.36	0.52	0.44
8-hr AUC (mcg/hr/ml)	6.34	7.79	7.04

Concentrations of norfloxacin in the urine averaged 30 mcg/ml or higher for the duration of each dosing interval. No drug crystals of norfloxacin were found in the urinalysis samples or in the 1-2 hour filtered voidings obtained from the four volunteers who participated in the pharmacokinetic arm of the study.

Neurological examinations were normal.

The applicant concludes that norfloxacin at a dose of 400 mg q 8 h is safe and well tolerated. Too few volunteers (4) participated in the pharmacokinetic phase of this study to demonstrate to what degree norfloxacin accumulation might occur on a 400 mg q 8 h regimen.

Medical Officer's Comment: There is a difference between the investigator's report of the presence of adverse reactions and the patient's report as recorded on the 26 patient diaries. A few of the differences are listed below:

Case No.	Investigator	Patient's Diary
<u>Norfloxacin</u> #102	None	Headache after dosing - Day 1. Headache continues, unable to concentrate on newsprint, lassitude, lightheaded and weak when standing. Impaired vision - Day 2. Same but greatly reduced - Day 3. Very mild residual symptomatic effects - Day 4. Moderate headaches - Day 5.
#103	None	Tired this morning - Day 1. Tired again today - Day 2.
#104	None	Feeling good with slight mild headache in back of head - Day 1. Same as yesterday with mild headache in back of head - Days 2-3. Feeling fine with small headache - Day 4. The effect of second week of study pills, effect was the same

as first but milder with headaches, tiredness and seemed to accept them better each day - Day 5.

- #105 Sclera erythematous rt xl-2 days Sleepy - Day 1. Sleepy and coughing up phlegm - Day 2. Sick to my stomach this morning, sleepy, also, but after lunch felt fine - Day 3.
- #106 None Mild headache today from 1:00 PM to 8:00 PM - Day 4. Felt good today except mild upset stomach from 6:00 PM until 9:00 PM. Otherwise good and no side effects - Day 5.
- #107 None Slight stomachache this afternoon Day 5.
- #112 None Slight headache continuing until 3:00 PM. Slacked off at that time - Day 1. Sleepy most of the day but otherwise I felt well. Am still slightly drowsy at present time (10:00 AM) - Day 2. Drowsy, slight headache until noon. Left at that time, and felt better by 5:30 - Day 4. Very sleepy all day. Still drowsy now at 10:00. Otherwise, I felt in the best of health - Day 5.
- #116 None Lightheadedness - Days 1-5.
- #118 None Very tired and sleepy and very bad headache - Day 1. Very tired and sleepy and was very drowsy and had a small headache - Day 2. Tired, drowsy, headache - Day 3. Tired, drowsy, and very bad headache - Day 4. Tired, drowsy, and small headache - Day 5.
- #120 None Today I felt a little flush in the face with a monotonous headache - Day 1. Headache, a minor one - Day 2. Minor headache - Day 3. Had another one of these headaches but I felt that sleep would remedy the situation by sleeping it off and it really worked - Day 4. No headache but had a little upset stomach - Day 5.
- #122 None Tired - Days 1-2 and 4.
- #123 None Didn't feel any side effects, just dry lips - Day 1. Felt a little cramp in right side - Day 2. Felt a little numb in fingers and hands. A little tired but good - Day 3. A little pain in belly but not bad, outside of fever from cold that everyone has had - Day 4.
- #126 None I have been a little drowsy most of the day and evening but other than that I feel fine as usual - Day 1. I am not so tired or sleepy today and no other problems or side effects - Day 2.

Same as yesterday - Day 3. Same as last 2 days - Day 4..

Placebo

#103	None	Tired this morning - Day 1. Sleepy morning - Day 2. Tired all day, tired AM, all right PM - Day 5.
#104	None	Headache all day - Day 1. Milder headache - Day 2. Headache and very tired - Day 3. Headache gets less and less and still very tired within two hours of taking pills, headache seems to be in temple area- Day 4. Headache and tiredness - Day 5.
#105	Sclera erythematous rt xl-2 days	Sleepy and slight headache - Day 1. Right eye is sore and slightly red - Day 3.
#112	None	Tired and listless in the morning - Day 2. Have felt hyperactive all day - Day 3. Had a slight headache this afternoon but it quit bothering me after a little sleep - Day 4.
#118	None	Headache and very tired - Day 1. Headache and very tired - Day 2. I did not feel very good today because I had a headache and was very tired - Day 3. Very bad headache and not very tired - Day 4. Headache - Day 5.
#120	None	Slight headache. Subsided and felt very tired - Day 1. Slight headache but it subsided at a later time - Day 3.
#122	None	Slight headaches on & off, tired - Day 2. Slight headaches on & off, tired, weight gain - Day 3. Still a bit tired - Day 4. Still tired - Day 5.

The MO's tally shows that 13/26 (50%) of norfloxacin-treated subjects and that 7/26 (27%) of placebo-treated subjects reported one or more effects in their diaries. The difference in rates is not statistically significant but is suggestive of a difference ($p = 0.089$).

In the applicant's summary for these same cases, the applicant reports the following seven adverse events:

Case #108 (Norf.) - Night sweats	Case #102 (Placebo) - Frontal headache
Case #109 (Norf.) - Vomiting	Case #105 (Placebo) - Erythematous sclera with mild pruritis
Case #125 (Norf.) - Pediculosis	Case #109 (Placebo) - Headache
	Case #121 (Placebo) - Cold symptoms

These differences show underreporting of adverse reactions by the investigator and the applicant.

c. Bioavailability

(1) Study No. 13 Miguel A. Zinney's third study was a randomized, three-way crossover-type, single-dose bioavailability study to compare a 200-mg tablet and a 400-mg tablet with a solution containing 430 mg of norfloxacin. The solution was given by a nasogastric tube. Fifteen healthy adult male volunteers participated.

Relative bioavailability ratios were 0.89, 0.90, and 1.0 for the 200 mg-tablet/430 solution, 400-mg tablet/430 mg solution, and 200-mg tablet/400 mg tablet, respectively.

	430-mg sol.	200-mg tab.	400-mg tab.
Mean 48-hr Urinary Recovery % of Dose	121.9 mg 28.38%	52.15 mg 25.45%	105.14 mg 26.48%
Mean 8-hr AUC (mcg/hr/ml)	6.04	5.57	5.44
Mean cumulative renal clear- ance (ml/min)	276.37	263.39	299.26
Mean C _{max} (mcg/ml)	1.87	1.60	1.62
Mean T _{max} (hr)	0.70	1.03	1.03
Mean half-life (hr)	2.99	3.26	3.32

Peak fecal concentrations of norfloxacin-like antimicrobial activity ranged from 144 mcg to 2715 mcg of norfloxacin per gram of feces. While this was the range, most of the 13 volunteers who had bowel movements within 4 hours of drug administration had peak fecal norfloxacin-like antimicrobial activity levels of between 200-750 mcg/gm of feces.

The applicant reports that there was only one adverse clinical effect, soreness of the rectum in one subject. Neurologic examinations performed by a neurologist, and ophthalmologic examinations including tests for visual acuity, field defects, color vision and funduscopic examinations, showed no abnormalities or changes from baseline tests.

The applicant concludes that after the first half-hour after dosing, the tablets show similar bioavailability to each other and to the solution with serum levels and urinary recovery being directly proportional to the dose. All three formulations appear safe.

Medical Officer's Comments:

1. Although the medical officer asked for diaries in pharmacokinetic studies, diaries were not kept in this study. The report that there was only one adverse effect cannot be accepted to mean that other adverse reactions did not occur. It is accepted to mean that the investigator was only aware of one reaction. The differences between the diaries and this investigator's report in the study above (Study No. 66) confirm this

conclusion.

2. The presence or absence of crystals in urine sediment is not addressed in the applicant's narrative. However, Table 14 on pages I-00890-I-00896 shows that non-amorphous crystals per HPF were present as follows:

	Pre		Post		Sign. diff.
	No. cases	%	N. cases	%	
200 mg tablet	3/15	20.0%	3/15	26.7%	NS
400 mg tablet	1/15	6.7%	2/15	13.3%	NS
430 mg solution	4/15	26.7%	6/15	40.0%	NS

It is not known whether these were drug crystals.

(2) Study No. 59 Miguel A. Zinny, M.D. conducted a fourth study. This was a randomized, two-way crossover bioavailability study of single doses of the new 400-mg Merck Sharp & Dohme tablet and the old 400-mg Kyorin tablet. Twenty healthy adult male volunteers participated. There was a one week crossover interval.

Nineteen of the 20 subjects completed diary sheets. None of the comments noted on these diary sheets were assessed by the investigator as adverse experiences. There were no adverse experiences reported by the investigator.

The applicant summarized diary sheet data as follows:

Case #	Period 1 New MSD tab	Period 2 Old Ky. tab	Case #	Period 1 New MSD tab	Period 2 Old Ky. tab
51	Fine	Fine	52	Sleepy	Sleepy
53	Fine	All right	54	OK	Good
			56	OK	OK
58	Lightheaded	Lightheaded	57	No problems	Great
60	Very good	Good	59	Lack of energy	Fine
61	Fine	OK	62	Fine	Fine
63	Drowsy and tired then normal	Normal then tired	64	Normal	Fine
66	Fine	Fine	65	Normal, dry lips	Normal
68	Fine	Fine	67	Dry mouth	Fine
69	Fair	Fine	70	Foggy, tired headache	Fine

Two subjects had an elevated SGOT report.

No crystals of norfloxacin were found in any of the examined urine specimens collected from volunteers who participated in this study. The observation applies to all urine collected for screening before and after the study and to all urine collected through the 48 hours after the dose during the study.

	New MSD tab	Old Ky. tab
Mean Urinary Recovery % of Dose	117.43 mg 27.74%	106.55 mg 26.72%
Mean AUC mcg/hr/ml X hr	7.71	6.90
Mean cumulative renal clear- ance (ml/min)	266.10	269.98
Mean C _{max} (mcg/ml)	1.56	1.54
Mean T _{max} (hr)	1.35	1.07

The new norfloxacin formulation is 94% as bioavailable as the old formulation.

Stool specimens were collected for assay from 18 subjects. Norfloxacin activity was found in stool specimens after the first two hours. Peak concentrations occurred between 12 and 24 hours and ranged from 1,212.17 to 1,916.13.

The applicant concludes that norfloxacin is similarly bioavailable from both 400-mg tablets. Norfloxacin was absorbed faster following the ingestion of tablets manufactured by the new MSDRL process.

Medical Officer's Comments:

1. Diaries from this study cannot be included as part of the minimum 100 diaries that FDA requires for the quinolones because this was a single-dose study. We asked for at least 100 diaries following multiple doses from the longest recommended treatment period.
2. According to the diaries, six of 19 subjects (32%) reported side effects while on the new MSD tablet and three of 19 subjects (18%) reported side effects while on the Old Kyorin tablet.

d. Renal Function

Study No. 576 Prof. A. William Asscher, Welsh National School of Medicine, Renal Unit - Royal Infirmary, Cardiff, Wales, conducted a pharmacokinetic study of single 400-mg oral doses of norfloxacin in patients with varying degrees of renal dysfunction and in subjects with normal renal function. Twenty males and seven females were assigned to four groups based on glomerulo-filtration rate assessed by creatinine clearance as follows:

- Group I (normal renal function - GFR greater than 100 ml/min/1.73 m²)
- Group II (mild renal impairment) - GFR 31-80 ml/min/1.73 m²
- Group III (moderate impairment) - GFR 10-30 ml/min/1.73 m²
- Group IV (severe renal impairment) - GFR less than 10 ml/min/1.73 m²

Urinary recovery and renal clearance of norfloxacin were similar for Groups I and II, but were significantly decreased for Groups III and IV. Mean urinary

recoveries of norfloxacin were 27, 34, 5 and 2% of the dose administered for Groups I to IV, respectively, while mean renal clearances were 280, 254, 17, and 11 ml/min. Peak serum concentrations and time to peak were similar among the groups. Observed differences in total AUC appeared to arise from differences in serum concentrations beginning at about 4 hours after dosing. Mean total AUCs were 7, 9, 20, and 13 mcg/hr/ml for Groups I to IV, respectively. Groups I and II were significantly different from Group III, and Group I was different from Group IV ($p = 0.06$). Groups I and II had significantly shorter mean serum half-lives (3.5 hours) compared to Groups III and IV.

The applicant reports that there were no adverse experiences during this study.

The applicant concludes that a single 400 mg dose of norfloxacin appears to be safe in renally-impaired patients. Based on the renal elimination rate of norfloxacin, no change is needed in the dosing regimen for subjects whose GFR exceeds 30 ml/min/1.73 m². When the rate is 30 ml/min/1.73 m² or greater, the regular dose should be given once a day rather than twice a day.

2. Controlled Clinical Efficacy Studies

(a) Protocol No. 001 Domestic Multiclinic Study of Uncomplicated Urinary Tract Infections

A randomized, controlled, multiclinic trial to compare norfloxacin and trimethoprim-sulfamethoxazole (TMP-SMZ) in the treatment of uncomplicated urinary tract infections in adults was conducted at five clinical centers. The following investigators participated in this trial and treated the number of patients shown:

Study No. 3 Charles E. Cherubin, M.D., Chief, Microbiology Laboratories, Jewish Hospital of Brooklyn, 555 Prospect Place, Brooklyn, NY 11238. (Qualified for efficacy evaluation: 6/7 norfloxacin patients and 3/3 TMP-SMZ patients.)

Study No. 6 Clair E. Cox, M.D., College of Medicine, Dept. of Urology, University of Tennessee, 956 Court Avenue, Box 10, Memphis, TN 38163. (Qualified for efficacy evaluation: 22/23 norfloxacin patients and 22/22 TMP-SMZ patients.)

Study No. 7 Ellie J. C. Goldstein, M.D., 11980 San Vicente Blvd., Suite 103, Los Angeles, CA 90049. (Qualified for efficacy evaluation: 21/23 norfloxacin patients and 22/22 TMP-SMZ patients.)

Study No. 2 Anthony J. Schaeffer, M.D., Northwestern University, The Medical School, Ward Memorial Bldg., 303 E. Chicago Avenue, Chicago, IL 60611. (Qualified for efficacy evaluation: 21/25 norfloxacin courses and 20/25 TMP-SMZ patients.)

Study No. 5 Richard L. Sweet, M.D., Room 6J2, San Francisco General Hospital, 1001 Potrero Avenue, San Francisco, CA 94110. (Qualified for efficacy evaluation: 2/6 norfloxacin patients and 0/7 TMP-SMZ patients.)

(Jack L. LeFrock, M.D., Hahnemann Medical College, Hospital of Philadelphia, 230 N. Broad Street, Philadelphia, PA 19102. Dr. LeFrock did not admit any patients into the study and the study was suspended.)

Norfloxacin-treated patients in Studies Nos. 2, 3, and 5 received four 100-mg tablets twice daily for seven to ten days. Patients in Studies Nos. 6 and 7 received two 200-mg tablets twice daily. These studies were initiated at a time when the 100 mg tablets were no longer being produced.

Ambulatory patients with a diagnosis of uncomplicated urinary tract infection were selected. Clinical symptoms included dysuria, frequency, urgency, etc. of less than one week's duration prior to therapy. All patients were required to have a positive urine culture within 48 hours prior to initiation of therapy. A colony count by either the pour plate or streak method was obtained and uropathogens were speciated. Patients received a history and physical examination that included visual acuity tests, examination of the eye, and tests of neurological function. Ophthalmological and neurological tests were repeated when the patient returned at one week after treatment. Routine follow-up evaluations were made again at 4-6 weeks after the completion of therapy. Urine specimens for culture were obtained during the first 48-72 hours of therapy, 5-9 days after completion of therapy, and 4-6 weeks after completion of therapy. Vaginal-vestibular and anal cultures were optional. Laboratory studies included routine hematology, blood chemistry, and urinalyses which included microscopic examination of the urine sediment for the presence of crystals,

Exclusions included patients with a history of allergy to nalidixic acid, oxolinic acid, trimethoprim, or any sulfa drug; patients under 21 or over 75 years of age; patients with a temperature greater than 101°F, flank pain, chills or any other manifestation suggestive of upper urinary tract infection; patients with complicated UTI; comatose patients or those with a high probability of death; patients with impaired renal function; patients with serious concurrent infections; patients with resistant uropathogens; patients on or just completing other antimicrobial therapy; patients with indwelling urinary bladder catheters; and patient with a history of visual disturbance or psychiatric or CNS illness.

The clinical outcome categories were: cured, improved, did not improve, and other. The bacteriological outcome categories were eradication, suppression, and persistence. Suppression and persistence were considered to be bacteriological failures. The investigator also noted the presence of colonization, superinfection, and at 4-6 weeks, relapse and reinfection.

Guidelines for susceptibility or resistance in all studies are

	Disc Diffusion Zone Size	MIC
Susceptible	17 mm or greater	Greater than 16 mcg/ml
Intermediate	13-16 mm	
Resistant	12 mm or less	Under 16 mcg/ml

Intermediate zone sizes were considered as susceptible for urinary tract pathogens.

In this study, 160 patients received 163 courses, 81 patients received norfloxacin and 79 patients received TMP-SMZ. Only the first entries of the three patients who were treated more than once were counted in the analysis of data. Of the 160 patients, there were 136 evaluable cases, 69 norfloxacin cases and 67 TMP-SMZ cases.

Reasons for Efficacy Disqualification

	Norfloxacin	TMP-SMZ
Causative pathogen not proven	4 (33%)	7 (58%)
Other effective treatment	2 (17%)	0
Course too short	1 (8%)	1 (8%)
Inadequate cultures	5 (42%)	4 (33%)

Characteristics for evaluable patients are shown in the following table:

Age (yrs.)	Norfloxacin			TMP-SMZ		
	Males	Females	Total	Males	Females	Total
18-21	1	2	3		4	4
22-30	2	22	24		25	25
31-40		11	11	2	11	13
41-50	2	5	7	1	3	4
51-60	1	7	8		3	3
61-70	3	7	10	7	6	13
71-80	2	1	3	3	1	4
81-90	2	1	3		1	1
Total No.	13	56	69	13	54	67
Mean Age	56.5	39.3	42.6	61.3	36.5	41.2
Minimum	19	20	19	35	19	19
Maximum	82	81	82	75	82	82

The primary diagnosis was cystitis for about 95% of patients in each treatment group. Four patients had pyelonephritis, three had urinary tract infections not otherwise identified, two had vaginitis, and one had leukocyturia. There was a secondary diagnosis for 42% of norfloxacin-treated patients and for 46% of control patients. Other non-antimicrobial drugs were given to 23% in the norfloxacin group and 31% in the TMP-SMZ group. The mean length of therapy was 10.7 and 10.4 days for the norfloxacin and TMP-SMZ groups, respectively. Roughly, just over one-third of the number in each group were minority.

Of all pathogens tested, 100% (148/148) were susceptible to norfloxacin and 95% (140/148) were susceptible to TMP-SMZ. The eight pathogens which were not susceptible to both drugs were 3/123 E. coli strains and 5/5 P. aeruginosa strains.

Clinical outcome for evaluable patients is shown below:

Diagnosis	Cured	Norfloxacin		# Pts	TMP-SMX		# Pts
		Impro-ved	Not Impro-ved		Cured	Not Impro-ved	
UTI Lower or Upper	65	1	2	68	63	1	65
UTI, NOS	1	0	0	1	2	0	2

The percentage of patients who were cured or improved was 97% (67/69) in the norfloxacin group and 99% (66/67) in the TMP-SMZ group.

Bacteriological outcome for evaluable patients is given below (number eradicated/number isolated):

Pathogen	Norfloxacin	TMP-SMZ
<u>Staphylococcus aureus</u>	2/2	0/0
<u>Staphylococcus saprophyticus</u>	1/1	0/0
<u>Citrobacter species</u>	0/0	1/1
<u>Citrobacter diversis</u>	1/1	0/0
<u>Enterobacter aerogenes</u>	0/1	2/2
<u>Enterobacter agglomerans</u>	1/1	0/0
<u>Enterobacter cloacae</u>	1/1	0/0
<u>Escherichia coli</u>	53/54	58/58
<u>Klebsiella pneumoniae</u>	2/2	3/3
<u>Proteus mirabilis</u>	3/3	1/1
<u>Pseudomonas aeruginosa</u>	4/5	0/0
<u>Pseudomonas fluorescens</u>	0/0	1/1
Total	67/69 (97%)	66/66 (100%)

Adverse clinical and laboratory experiences for all patients are shown below:

Adverse Reactions	Norfloxacin		TMP-SMZ	
	No.	No. Discon- tinued	No.	No. Discon- tinued
Drug Related				
Dyspepsia	1		0	
Nausea, headache, & insomnia	1	1	0	
Total	2 pts			
Not Drug Related				
Pain and insomnia	1	1	0	
Headache	1		3	1
Dyspepsia	1	1	0	
Nausea and anorexia	0		1	
Nausea	0		1	
Diarrhea	0		1	
Total	3 pts		6 pts	
No. pts with AR	5 pts		6 pts	
Total No. Patients	81		79	

Diagnosis	Cured	Norfloxacin			TMP-SMX			# Pts
		ved	Not ved	Impro- ved	ved	Not ved	Impro- ved	
UTI Lower or Upper	65	1	2	68	63	1	1	65
UTI, NOS	1	0	0	1	2	0	0	2

The percentage of patients who were cured or improved was 97% (67/69) in the norfloxacin group and 99% (66/67) in the TMP-SMX group.

Bacteriological outcome for evaluable patients is given below (number eradicated/number isolated):

Pathogen	Norfloxacin	TMP-SMZ
<u>Staphylococcus aureus</u>	2/2	0/0
<u>Staphylococcus saprophyticus</u>	1/1	0/0
<u>Citrobacter species</u>	0/0	1/1
<u>Citrobacter diversis</u>	1/1	0/0
<u>Enterobacter aerogenes</u>	0/1	2/2
<u>Enterobacter agglomerans</u>	1/1	0/0
<u>Enterobacter cloacae</u>	1/1	0/0
<u>Escherichia coli</u>	53/54	58/58
<u>Klebsiella pneumoniae</u>	2/2	3/3
<u>Proteus mirabilis</u>	3/3	1/1
<u>Pseudomonas aeruginosa</u>	4/5	0/0
<u>Pseudomonas fluorescens</u>	0/0	1/1
Total	67/69 (97%)	66/66 (100%)

Adverse clinical and laboratory experiences for all patients are shown below:

Adverse Reactions	Norfloxacin		TMP-SMZ	
	No.	No. Discon- tinued	No.	No. Discon- tinued
Drug Related				
Dyspepsia	1		0	
Nausea, headache, & insomnia	1	1	0	
Total	2 pts			
Not Drug Related				
Pain and insomnia	1	1	0	
Headache	1		3	1
Dyspepsia	1	1	0	
Nausea and anorexia	0		1	
Nausea	0		1	
Diarrhea	0		1	
Total	3 pts		6 pts	
No. pts with AR	5 pts		6 pts	
Total No. Patients	81		79	

Abnormal Laboratory Effects	Norfloxacin No.	TMP-SMZ No.
Drug Related	0	0
Not Drug Related		
WBC Count	0	1
Segmented neutrophils and elevated lymphocytes	1	0
Alanine transferase	0	1
Total	1	2
No. Patients	81	79

The applicant reports that there were no serious adverse reactions or laboratory abnormalities. No changes were found in ophthalmologic and neurologic examinations.

The applicant concludes that all 148 isolates were susceptible to norfloxacin and it was highly effective in the treatment of uncomplicated urinary tract infections. It was well tolerated and safe. The efficacy, safety and tolerance of norfloxacin and trimethoprim/sulfamethoxazole are similar.

Medical Officer's Comments:

1. Since the presence or absence of crystalluria was not addressed in the applicant's summary, the medical officer reviewed each case report form to observe the presence of crystals in the optional (during therapy (48-72 hour) urine specimen. Nonamorphous crystals were reported for 0/38 specimens in the norfloxacin group and for 3/31 specimens in the TMP/SMZ group. Urine sediment was examined microscopically for an additional six norfloxacin and five TMP/SMZ specimens but no entry was made for the presence or absence of crystals. There was no laboratory sheet for one norfloxacin patient (Case No. 117). There was no during therapy laboratory report for the remaining patients in each group.

2. No conclusion can be drawn regarding adverse reactions since adverse reactions are best analyzed from patient diaries. No diaries were reported for this study.

(b) (1) Protocol No. 002 Domestic Multiclinic Study of Complicated and Uncomplicated Urinary Tract Infections

A randomized, controlled multiclinic trial of norfloxacin and trimethoprim-sulfamethoxazole (TMP-SMZ) in the treatment of uncomplicated and complicated urinary tract infections was conducted at five clinical centers. The following investigators participated in this trial and treated the number of patients shown:

Study No. 11 O. Thomas Bolding, M.D., Medical Director, Bolding Research Foundation, Inc., 2022 Brookwood Medical Ctr. Dr., Birmingham, Alabama. (Qualified for efficacy evaluation: 3/8 norfloxacin patients and 1/4 TMP-SMZ patients)

Study No. 8 R. H. K. Eng, M.D., Medical Service (111), V. A. Medical Center, East Orange, NJ. (Qualified for efficacy evaluation: 10/14 norfloxacin patients and 9/14 TMP-SMZ patients)

Study No. 10 Lloyd H. Harrison, M.D., Assistant Professor Dept of Urology, Bowman Gray School of Medicine, Winston-Salem, NC. (Qualified for efficacy evaluation: 24/29 norfloxacin patients and 21/28 TMP-SMZ patients)

Study No. 12 Ralph R. Landes, M.D., Danville Urology Clinic, Danville, VA. (Qualified for efficacy evaluation: 35/62 norfloxacin patients and 15/30 TMP-SMZ patients)

Study No. 9 J. L. Ryan, M.D., Ass't Professor Department of Internal Medicine, Yale University School of Medicine, New Haven, CT. (Qualified for efficacy evaluation: 7/13 norfloxacin patients and 8/11 TMP-SMZ patients)

Male or female patients 18 years of age or over with symptomatic uncomplicated or complicated urinary tract infections were selected. Women of childbearing potential were excluded at the beginning of the study but were allowed later in the study. Patients were required to have a positive urine culture within 48 hours prior to initiation of therapy. Exclusions were the same as those given in the previous study except that patients with symptoms suggestive of upper tract infections were included. FDA's guidelines for the study of urinary tract infections were followed. This study was similar to the one described above.

Patients received either two 200 mg tablets of norfloxacin two times a day orally or two tablets of trimethoprim-80 mg with sulfamethoxazole-400 mg twice a day orally. Treatment was to be 7 to 30 days. Drugs were dispensed in unit doses to hospitalized patients and, for outpatients, in pre-labeled bottles containing enough for a 14-day course. The investigator dispensed supplemental drug if therapy beyond 14 days was deemed clinically appropriate.

Drs. Bolding and Landes' studies were designed to admit twice as many norfloxacin as TMP-SMZ patients. There were 213 treatment courses for 210 patients, 124 of whom were treated with norfloxacin and 86 of whom were treated with TMP-SMZ. Where more than one course was given, only the first course is included in the efficacy analysis. A total of 133 patients were evaluated for efficacy, 79 in the norfloxacin group and 54 in the TMP-SMZ group.

Reasons for Efficacy Disqualification

	Norfloxacin	TMP-SMZ
Causative pathogen not proven	26	18
Course too short	2	4
Inadequate cultures	17	10
Total Disqualified	45 (34%)	32 (37%)
Qualified	79	54

Characteristics of evaluable patients are shown in the following table:

Age (yrs.)	Norfloxacin			TMP-SMZ		
	Males	Females	Total	Males	Females	Total
No data	1		1			
1-17	1	1	2		1	1
18-21	1	5	6		8	8
22-30	1	25	26		17	17
31-40	3	12	15	4	11	15
41-50	2	8	10	1	8	9
51-60	7	9	16	10	4	14
61-70	10	12	22	8	6	14
71-80	3	8	19	5	1	6
81-90	2	5	7	1	1	2
Total No.	39	85	124	29	57	86
Mean Age	59.8	45.0	49.6	59.2	37.5	44.8
Minimum	13	17	13	34	17	17
Maximum	86	87	87	83	81	83

Most patients in the two treatment groups had urinary tract infections which were uncomplicated, of moderate intensity, and were caused by a single pathogen. Seventy percent of the norfloxacin group and 64% of the TMP-SMZ group had some other disease, about half had had prior drug therapy, and 44% and 30%, respectively, had concomitant procedures. The mean duration of therapy was 12 days for norfloxacin and 10 days for TMP-SMZ.

The two treatment groups were significantly different with respect to several characteristics. There were more Caucasians, patients with complicated UTIs, patients with polymicrobial infections, patients with concomitant procedures, and patients with prior drug therapy in the norfloxacin group than in the TMP-SMZ group. Only one of these parameters, prior drug therapy, was related to the percentage of patients cured or improved, in that, regardless of treatment group, evaluable patients with prior drug therapy had a significantly lower response rate (80%) than those without prior drug therapy (94%).

Clinical outcome for evaluable patients is shown below:

Diagnosis	Cured	Norfloxacin			Cured	TMP-SMZ		
		Impr- ved	Not Impr- ved	# Pts		Impr- ved	Not Impr- ved	# Pts
<u>Applicant</u>								
Upper UTI	13	1	3	17	4	1	2	7
Lower UTI	53	3	6	62	38	2	7	47
<u>Medical Officer</u>								
Upper UTI	13	1	3	17	4	1	2	7
Lower UTI	53	3	5	61	38	2	6	46

Bacteriological outcome for evaluable patients is given below (number eradicated/number isolated):

Pathogen	Applicant		Medical Officer	
	Norfloxacin	TMP-SMZ	Norfloxacin	TMP-SMZ
<u>Corynebacterium</u>	0/1		0/1	
<u>Staphylococcus</u>		1/1		1/1
<u>S. saprophyticus</u>		1/1		1/1
<u>Staphylococcus epidermidis</u>	3/3		3/3	
<u>Streptococci (Grp B)</u>	1/1	1/1	1/1	1/1
<u>Streptococci (Grp D)</u>	6/7	0/1	6/7	0/1
<u>Strep. (Grp D enterococci)</u>	3/3	0/1	3/3	0/1
<u>Strep., alpha hemolytic</u>		1/1		1/1
<u>Citrobacter species</u>	1/1		1/1	
<u>Citrobacter freundii</u>	2/3		2/3	
<u>Enterobacter</u>		1/1		1/1
<u>Enterobacter aerogenes</u>	1/1	1/2	1/1	1/1
<u>Escherichia coli</u>	38/38	27/32	37/37	27/32
<u>Klebsiella pneumoniae</u>	7/10	7/7	7/9	7/7
<u>Morganella morganii</u>	1/1	1/1	1/1	1/1
<u>Proteus vulgaris</u>	1/1		1/1	
<u>Proteus mirabilis</u>	7/7	5/6	7/7	5/6
<u>Providencia rettgeri</u>	2/2		2/2	
<u>Pseudomonas aeruginosa</u>	11/13		11/12	
<u>Lactobacillus</u>	1/1		1/1	
Total strains eradicated	85/93	46/55	84/90	46/54
Percent	(91.3%)	(83.6%)	(93.3%)	(85.1%)
Number Qualified Pts.	79	54	77	53

The differences between the two bacteriological outcome rates and the two clinical outcome rates are not statistically significant.

All 210 patients who received the study drugs were analyzed for safety. The duration of treatment ranged from one to 49 days for norfloxacin and one to 21 days for TMP-SMZ. The percentage of single entry patients with any adverse clinical experience was significantly greater in the TMP-SMZ group (10.5% or 9/86) than in the norfloxacin group (1.6% or 2/124), as was the percentage with any adverse laboratory experience (5.8% or 5/86, vs. 0.8% or 1/124), respectively). Significantly more patients in the TMP-SMZ group (5/86) than in the norfloxacin group (1/124) discontinued due to clinical adverse experiences.

For all characteristics measured in the ophthalmological and neurological examinations, there were no patients in either group who changed from normal at pretreatment to abnormal at post-treatment or from abnormal to normal.

There were no serious or drug related abnormal laboratory reports. In the norfloxacin group, there was one patient with a low WBC count, low segmented neutrophils, and high lymphocyte count. In the TMP-SMZ group, there were two abnormal WBC counts, one abnormal lymphocyte count, one elevated AST, one elevated ALT, and one elevated serum LDH.

Adverse experiences are shown below.

Adverse Reactions	Norfloxacin No.	TMP-SMZ No.
Drug Related		
Rash	0	3
Urticaria	0	2
Nausea	0	1
Insomnia, Depression	0	1
Total	0 pts	7 pts
Not Drug Related		
Nausea	1	0
Diarrhea	0	1
Nervousness	0	1
Dizziness and Dis-orientation	1	0
Total	2 pts	9 pts
Total No. Patients	122	86

Although patients were randomized to either norfloxacin or TMP-SMZ, patients receiving norfloxacin tended to have more complicated infections, more secondary diagnoses, more frequent prior therapies, concurrent procedures, severe infections, and polymicrobial infections. In general, patients who had a prior history of therapy did significantly worse than patients without such prior history. The cure rate for norfloxacin in prior therapy patients is equivalent to TMP-SMZ in patients without prior therapy (89% vs. 90%).

The applicant concludes that (1) norfloxacin showed a greater in vitro and in vivo spectrum of activity than TMP-SMZ, (2) the efficacy of norfloxacin is equivalent or superior to TMP-SMZ in patients with urinary tract infections, (3) no neurological or ophthalmological adverse experiences occurred in either treatment group, and (4) norfloxacin produced fewer adverse experiences than TMP-SMZ.

Medical Officer's Comments:

1. No conclusion can be drawn regarding adverse reactions since adverse reactions are best analyzed from patient diaries. No diaries were reported for this study.
2. No conclusion can be drawn regarding the presence of crystalluria. The applicant did not report the presence or absence of drug crystals.
3. The MO disqualifies three patients because they were under 18 years of age, norfloxacin cases #1498 (13-yr old male treated by Dr. Landes), and #908 (17-yr old female treated by Dr. Ryan), and TMP-SMZ case #916 (17-yr old female treated by Dr. Ryan). Corrected outcome rates are shown above. Case #908 had already be disqualified for another reason. The other two were qualified by the applicant.

(b) (2) Protocols #504-01 and #505-01 International Multiclinic Study of Complicated and Uncomplicated Urinary Tract Infections

Nineteen investigators in eleven countries participated in a randomized, controlled multiclinic trial of norfloxacin and trimethoprim-sulfamethoxazole in the treatment of urinary tract infections. The following investigators participated in this study:

Study No. 514 J. B. J. Boerema, University Hospital St. Radboud, Nijmegen, The Netherlands. (Qualified for efficacy evaluation: 1/15 norfloxacin patients and 1/11 TMP-SMZ patients)

Study No. 505 John Christodoulopoulos, M.D., Diagnostic and Therapeutic Institute of Piraeus, Metaxas Memorial, Piraeus, Greece. (Qualified for efficacy evaluation: 4/6 norfloxacin patients and 3/4 TMP-SMZ patients)

Study No. 543 A. De Greef, M.D., Tygerberg Hospital, Bellville, Cape Town, South Africa. (Qualified for efficacy evaluation: 10/10 norfloxacin patients and 10/10 TMP-SMZ patients)

Study No. 521 Kevin Roy Forward, M.D., St. Clare's Mercy Hospital, St. John's, Newfoundland. (Qualified for efficacy evaluation: 1/5 norfloxacin patients and 2/5 TMP-SMZ patients)

Study No. 515 Ferando B. Gabilondo, M.D., National Institute of Nutrition, Mexico City, Mexico. (Qualified for efficacy evaluation: 7/9 norfloxacin patients and 7/8 TMP-SMZ patients)

Study No. 502 Jorge Guerra, M.D., Infectious Disease Unit, Cayetano Heredia Hospital, Lima, Peru. (Qualified for efficacy evaluation: 20/20 norfloxacin patients and 19/20 TMP-SMZ patients)

Study No. 547 Prof. Dr. med. A. Hofstetter, Head of Dept. of Urology, University of Munich. (Qualified for efficacy evaluation: 7/10 norfloxacin patients and 8/10 TMP-SMZ patients)

Study No. 522 Primarius Dr. Kurt Jurkovic, Head of Urology Department, Hospital of Elisabethinen, Linz, Austria. (Qualified for efficacy evaluation: 7/9 norfloxacin patients and 4/9 TMP-SMZ patients)

Study No. 507 Dr. M. C. Kelsey, Department of Pathology, Barnet Hospital, Hertsford, U.K. (Qualified for efficacy evaluation: 1/5 norfloxacin patients and 1/5 TMP-SMZ patients)

Study No. 508 Dr. M. Levin, M.D., Coronation Hospital, Johannesburg, South Africa. (Qualified for efficacy evaluation: 10/10 norfloxacin patients and 10/10 TMP-SMZ patients)

Study No. 509 S. W. B. Newson, M.D., Consultant Microbiologist, Addenbrooke's Hospital, Cambridge, U.K. (Qualified for efficacy evaluation: 5/16 norfloxacin patients and 5/16 TMP-SMZ patients)

Study No. 506 Giovanni Panichi, Clinical Medical Department, University of Rome, Rome, Italy. (Qualified for efficacy evaluation: 10/20 norfloxacin patients and 20/20 TMP-SMZ patients)

Study No. 523 Allan R. Ronald, M.D., Head of the Department of Microbiology, University of Manitoba, Winnipeg, Manitoba, Canada. (Qualified for efficacy evaluation: 5/10 norfloxacin patients and 4/9 TMP-SMZ patients)

Study No. 517 S. Seiler, M.D., Stephenshorn Hospital, St. Gallen, Switzerland. (Qualified for efficacy evaluation: 2/3 norfloxacin patients and 1/2 TMP-SMZ patients)

Study No. 527 Vincenzo Speranza, M.D., Professor and Head, Surgical Clinic VI, University of Rome Medical School, Rome, Italy. (Qualified for efficacy evaluation: 5/6 norfloxacin patients and 5/5 TMP-SMZ patients)

Study No. 524 Prof. Dino alessandro Subrizi, Department of Obstetrics and Gynecology, University of Rome, Rome, Italy. (Qualified for efficacy evaluation: 8/8 norfloxacin patients and 6/7 TMP-SMZ patients)

Study No. 529 Prof. Alessandro Tizzani, Head of Urology Department, University of Torino, Torino, Italy. (Qualified for efficacy evaluation: 10/10 norfloxacin patients and 10/10 TMP-SMZ patients)

Study No. 525 Enzo Usai, M.D., Head of Urology, University of Cagliari, Cagliari, Italy. (Qualified for efficacy evaluation: 10/10 norfloxacin patients and 10/10 TMP-SMZ patients)

Study No. 540 Brian Watt, M.D., Consultant Microbiologist, Western General Hospital, Edinburgh, Scotland. (Qualified for efficacy evaluation: 7/9 norfloxacin patients and 8/9 TMP-SMZ patients)

Drs. Guerra and Panichi (Study Nos. 502 and 506) followed Protocol No. 504-01 and treated 80 hospitalized patients while all other investigators followed Protocol No. 505-01 and treated 290 outpatients. Hospitalized patients were studied initially until it was determined that there were no safety problems, then, outpatients were selected.

Case reports are available for 370 patients who were treated for cystitis, asymptomatic bacteriuria, and pyelonephritis caused by susceptible uropathogens. Hospitalized patients (#504-01) received either four 100-mg tablets of norfloxacin bid (total 800 mg/day) or two 80/400-mg tablets of TMP-SMZ bid for ten days. Outpatients (#505-01) received either two 200-mg tablets of norfloxacin bid (total 800 mg/day) or two 80/400-mg tablets of TMP-SMZ bid for five days and sufficient drug for a second five-day period at the time of the during therapy evaluation.

FDA's guidelines for protocols for the study of urinary tract infections were followed. Bacteriologic documentation of infection was required in pretreatment cultures. Prior to treatment, urine specimens were obtained for gram stain and for the antibody-coated bacteria immunofluorescence test. Patients were excluded from the study if there was a history of allergy to the

drugs or to related drugs, if patients were pregnant, under 12 or greater than 75 years of age, if they had renal abnormalities, if the infection was caused by a resistant organism, if effective antimicrobial therapy had been given within 72 hours or if there would be concomitant antimicrobial therapy, and if the patient was in coma. Patients receiving cancer chemotherapy, patients with serious systemic infections, and patients with a high probability of death were excluded.

For the bacteriological evaluation of outcome, the applicant divided patients into two groups, evaluable and assessable. Evaluable patients were those with acceptable bacteriological data. Outcome was graded as eradicated, suppressed or persisted (failures), and undetermined. Assessable patients were those in whom either of the two follow-up cultures were not taken within the specified day ranges or those who had only one follow-up post-therapy urine culture. Clinical outcome was based on changes in clinical signs and symptoms and laboratory test results and was graded as cured, improved, not improved or other.

Ninety-four patients were disqualified for the following reasons:

	Norfloxacin	TMP-SMZ
Inadequate bacteriology	34	30
Initial pathogen not proven	15	9
Effective concomitant antimicrobial therapy	0	3
Inadequate length of therapy	1	2
Inadequate dosing	1	0
Second entry into study	1	2
Total	52	46

Characteristics of evaluable patients are shown in the following table:

Age (yrs.)	Norfloxacin			TMP-SMZ		
	Males	Females	Total	Males	Females	Total
5-19		8	8		12	12
20-29	4	19	23	2	22	24
30-39	5	22	27	6	20	26
40-49	3	12	15	4	18	22
50-59	6	18	24	7	13	20
60-69	14	12	26	5	15	20
70-79	5	10	15	4	5	9
80-89					1	1
Total No.	37	101	138	28	106	134
Mean Age	54.8	42.8	46.0	49.9	41.0	42.8
Minimum	21	17	17	21	15	15
Maximum	75	77	77	73	83	83

Symptoms for evaluable patients were

	Norfloxacin	TMP-SMZ
Dysuria	99	100
Frequency of urination	102	93
Malodorous urine	46	33
Suprapubic pain	73	67
Urgency of urination	72	64
Rigor	15	21
Flank pain and fever	21	19

The treatment groups were similar at baseline with respect to age, sex, incidence of secondary diagnoses, incidence of prior therapy, signs and symptoms of UTI and mean values of all laboratory safety variables. Associated diseases or secondary diagnoses at entry were diagnosed for 151 norfloxacin-treated patients (79.5%) and 131 TMP-SMZ-treated patients (72.3%).

Bacteriological outcome for evaluable patients is given below (number eradicated/number isolated):

Pathogen	Norfloxacin	TMP-SMZ
<u>Micrococcus</u>	1/1	1/1
<u>Staphylococcus aureus</u>		1/1
<u>Staphylococcus epidermidis</u>	1/1	2/2
<u>S. saprophyticus</u>	3/3	1/1
<u>Streptococcus faecalis</u>		1/1
<u>Strep. (Grp D enterococci)</u>	1/1	4/4
<u>Alcaligenes faecalis</u>		2/2
<u>Alcaligenes species</u>	1/1	
<u>Citrobacter species</u>	2/2	
<u>Citrobacter freundii</u>	1/1	
<u>Enterobacter</u>	2/2	4/4
<u>Enterobacter aerogenes</u>	0/1	1/1
<u>Enterobacter agglomerans</u>	1/1	
<u>Enterobacter cloacae</u>	5/6	1/1
<u>Escherichia coli</u>	82/82	85/94
<u>Klebsiella species</u>	1/2	1/1
<u>Klebsiella oxytoca</u>	2/2	
<u>Klebsiella pneumoniae</u>	5/9	6/7
<u>Morganella morganii</u>		0/1
<u>Proteus rettgeri</u>	2/2	
<u>Proteus vulgaris</u>	1/1	1/1
<u>Proteus mirabilis</u>	15/15	9/11
<u>Providencia species</u>	1/1	
<u>Pseudomonas aeruginosa</u>	8/8	0/1
<u>Pseudomonas species</u>		1/1
<u>Serratia liquefaciens</u>	1/1	
<u>Serratia marcescens</u>	1/1	1/2
Total strains eradicated	137/144 (95.1%)	122/137 (81.7%)
Eradication by patient	131/138 (95%)	119/134 (89%)

The three most frequently isolated pathogens were E. coli, Proteus mirabilis, and Klebsiella pneumoniae.

Clinical outcome is reported below.

	Norfloxacin	TMP-SMZ
Cured or improved	129 (93%)	126 (94%)
Not improved	9 (7%)	8 (6%)

Seven patients, three in the norfloxacin group and four in the TMP-SMZ group, experienced superinfection. Late post-therapy period cultures were obtained for 145 patient in the norfloxacin group and 132 patients in the TMP-SMZ group. Of these, 15 norfloxacin-treated patients (10%) and ten TMP-SMZ-treated patients (7.5%), experienced relapse. Most were due to E. coli. Seven norfloxacin-treated patients and four TMP-SMZ-treated patients experienced reinfection.

Adverse experiences were reported for 26 norfloxacin-treated patients (13.7%) and for 32 TMP-SMZ-treated patients (17.8%). Only one norfloxacin-group adverse reaction was serious (acute myocardial infarction) and this was not thought to be drug related. It occurred in the follow-up period after termination of the drug.

Adverse reactions are summarized below.

	Norfloxacin	TMP-SMZ
Body as a Whole/Site unspec.	3 (1.6%)	5 (2.8%)
Abdominal pain	1	3
Abdominal swelling	1	
Fever	1	1
Malaise		2
Cardiovascular System	1 (0.5%)	0
Acute myocardial infarction	1	
Digestive System	14 (7.4%)	14 (7.8%)
Anorexia	1	1
Aphthous stomatitis	1	
Constipation	1	1
Dry mouth	1	
Dyspepsia		4
Flatulence	2	
Gastrointestinal cramps	2	
Heartburn	4	2
Mouth ulcer		1
Nausea	6	5
Vomiting		2
Musculoskeletal System	1 (0.5%)	
Back pain	1	

(Continued on next page)

	Norfloxacin	TMP-SMZ
Nervous System & Psychiatry	9 (4.7%)	8 (4.4%)
Depression	1	1
Dizziness	8	2
Headache	3	3
Nervousness		1
Paresthesia		1
Somnolence		1
Tremor		1
Skin & Skin Appendage	0	6 (3.3%)
Allergic dermatitis		1
Pruritus		2
Rash		3
Special Senses	1 (0.5%)	2 (1.1%)
Ear obstruction, NOS		1
Taste perversion	1	1
Visual disturbances		1
Urogenital System	1 (0.5%)	2 (1.1%)
Lactation suppressed		1
Vaginal candidiasis	1	1
No patients with reactions	26 (13.7%)	32 (17.8%)
Number of patients	190	180

One patient in the norfloxacin group and seven patients in the TMP-SMZ group were discontinued from the study because of clinical adverse experiences. The patient in the norfloxacin group had abdominal cramps. Patients in the control group had gastrointestinal experiences and rash.

Adverse laboratory values were reported for 75 patients, 36 in the norfloxacin group and 39 in the TMP-SMZ group. They were not summarized.

Drug crystalluria did not occur.

The applicant concludes that norfloxacin has antimicrobial activity which is superior to that of TMP-SMZ against bacteria encountered in urinary tract infections. It was well tolerated at oral doses of 400 mg bid for ten days. It was effective in the treatment of uncomplicated and complicated urinary tract infections. Norfloxacin is more efficacious than TMP-SMZ for the treatment of urinary tract infections.

Medical Officer's Comments:

1. The statement that norfloxacin is more efficacious than TMP-SMZ should be modified. This study shows that it is only more efficacious than TMP-SMZ for one uropathogen and the sentence should read, "For E. coli, the eradication rate was significantly greater (p = 0.005) in the norfloxacin group than in the TMP-SMZ group."
2. The applicant was requested to summarize adverse laboratory experiences.
3. Patients under 18 years of age should be disqualified.

(c) Bacterial Gastroenteritis

c.1 Protocol No. 005 (Study No. 14) David L. Cohn, M.D. Assistant Director, Disease Control Service, Denver, CO and L. Barth Reller, M.D., University of Colorado Health Science Center, Infectious Disease Section, Denver, CO, conducted a double-blind, randomized three-way comparison of norfloxacin, erythromycin, and placebo in the treatment of patients with bacterial gastroenteritis. The purpose of the study was to measure clinical efficacy, tolerance, and safety of norfloxacin when compared to placebo and erythromycin in the treatment of adults with acute gastroenteritis due to Campylobacter species and other susceptible micro-organisms.

Patients with diarrhea who met the criteria for selection were enrolled.

1. Men and women 18 years of age or older who were diagnosed as having invasive gastroenteritis, on the basis of an appropriate clinical history and the finding of fecal leukocytes in a stool specimen, were eligible for the study.
2. A second group of patients, i.e., those with no fecal leukocytes but with a positive stool culture for a known bacterial pathogen, who had not already been entered into the study, were eligible.

The reason for separating these two groups was to ensure, via two distinct allocation groups, that by chance alone, patients with fecal leukocytes did not receive one therapy more than either of the other two. However, the separation was ignored in the analysis because of the small number of patients in the second stratum.

Exclusions included patients who were pregnant; those who were under 18 years of age; those who had a history of hypersensitivity to the drugs; those who had concomitant disease; those who received other antimicrobial agents within 72 hours of the onset of their gastro-intestinal symptoms; those who had renal abnormalities; those who had a history of visual disturbance, psychiatric or central nervous system disorders; and those who had a condition which in the judgement of the investigator should exclude them. Women of childbearing potential were excluded during the early months of the study.

Patients were randomized to receive either one 400 mg tablet of norfloxacin three times a day, or 337 mg of erythromycin three times a day, or placebo tablets three times a day. Treatment was to be stopped if the patient had a positive stool culture for Shigella species and still had abdominal cramps, fever, and diarrhea after two to three days of treatment. Other standard therapy was to be given.

Stools were collected for culture of enteric pathogens and for susceptibility testing before therapy, and two days and one month after completion of therapy. Patients received a physical examination including a neurological examination, a special ophthalmological examination, and laboratory studies before therapy and on the second day after completion of therapy.

Clinical outcome was graded as cured, improved, or did not improve. Bacteriological outcome was graded as eradication or persistence.

Of the 69 patients who were entered into the study, 43 patients were evaluable: 14/24 in the norfloxacin group, 16/23 in the erythromycin group, and 13/13 in the placebo group.

Reasons for Efficacy Disqualification

	Norfloxacin	Erythromycin	Placebo
Bacteriology not proven	8	6	6
Other effective therapy	0	1	0
Inadequate cultures	2	0	3
Total	10	7	9

The average length of therapy was five days. A secondary diagnosis of some other disease was present in 36% of evaluable patients in the norfloxacin group, 25% in the erythromycin group and 15% in the placebo group.

There were eleven patients who did not complete treatment, three in the norfloxacin group (lost to follow-up), two in the erythromycin group (one resistant organism and one lack of therapeutic response), and six in the placebo group (one protocol deviation, three lacked therapeutic response, and two were uncooperative)

Characteristics of evaluable patients are shown in the following table:

Age (yrs.)	Norfloxacin			Erythromycin			Placebo		
	Males	Females	Total	Males	Females	Total	Males	Females	Total
18-21	3		3	1		2	1	1	2
22-30	3	3	6	8		8	9	1	10
31-40	3	1	4	3	1	4	1		1
41-50		1	1						
51-60				1	1	2			
Total No.	9	5	14	13	3	16	11	2	13
Mean Age	26.3	29.6	27.5	28.3	37.3	30.0	25.8	24.5	25.6
Minimum	20	22	20	21	20	20	21	20	20
Maximum	38	43	43	52	60	60	31	29	31

The bacteriological response is shown below (number of strains eradicated/number of strains susceptible). The difference in rates is not statistically significant.

Pathogen	Norfloxacin	Erythromycin	Placebo	Unknown
<u>Aeromonas hydrophilia</u>	1/1			
<u>Campylobacter jejuni</u>	6/9	12/13	4/12	
<u>Salmonella enteritidis</u>	1/1			
<u>Shigella species</u>				1/1
<u>Shigella flexneri</u>	2/2			
<u>Shigella sonnei</u>	1/1	1/1		
Total	11/14	13/14	4/12	1/1
Percent	78.6%	92.9%	33.3%	

Clinical outcome for evaluable patients is shown below.

	Cured or Improved		Not Improved
	No. pts.	%	No. pts.
Norfloxacin	7/9	(77.8%)	2
Erythromycin	11/12	(100.0%)	0
Placebo	6/11	(54.5%)	5

Cumulative counts of evaluable patients who were free of symptoms of gastroenteritis by day of treatment.

	Number symptom-free by						
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 7	
Norfloxacin	1	1	3	7	10	10	(71.4%)
Erythromycin	0	1	2	7	12	16	(100.0%)
Placebo	0	0	3	4	5	7	(53.8%)

Two patients in each treatment group had had a recurrence of gastroenteritis when contacted one month after withdrawing therapy..

	Norfloxacin	Erythromycin	Placebo
<u>Adverse Reactions</u>			
Serious/Drug Related			
Dizziness and Mydriasis		1	
Not Serious/Not Drug Related			
Diarrhea and Pruritis			1
Dizziness		1	
Dizziness and Nausea			1
Dizziness and Asthenia			1
GI Cramps and Nausea		1	
Nausea		1	
Headache			1
Photosensitivity		1	
Back Pain and Paresthesia		1	
Discontinued because of AR			1
Number Pts. with AR	0	6	4
<u>Abnormal Laboratory Reports</u>			
Not Serious/Drug Related			
Serum bilirubin, AST and alkaline phosphatase	1		
Elevated AST and LDH		1	
Elevated AST		1	
Urine WBC			1
No. Pts. with Adverse Lab.	0	6	4
Number of Patients	24	23	22

All 69 patients were included in the analysis for safety. Adverse reactions and abnormal laboratory reports are summarized by the applicant are shown above. It should be noted that patient diaries were not kept in this study.

The applicant concludes that norfloxacin and erythromycin are more effective at eradicating Campylobacter jejuni from the gastrointestinal tract than placebo is, and that norfloxacin produces fewer adverse experiences than either erythromycin or placebo. Norfloxacin eradicates other pathogens including Shigella, Salmonella, and Aeromonas species.

Medical Officer's Comments:

1. Although six of nine C. jejuni infections were eradicated by norfloxacin, no efficacy conclusion can be drawn from this study because of the small numbers. There is only a suggestion of norfloxacin efficacy. Erythromycin appears to be superior.
2. This study should not be considered in the evaluation of adverse effects due to norfloxacin because the very adverse effects that one would watch for are symptoms of the disease. Symptoms of gastroenteritis, besides diarrhea that were used in the evaluation of outcome, were abdominal cramps, nausea, vomiting, anorexia, etc. Gastrointestinal-type adverse effects that would be anticipated with norfloxacin are gastrointestinal cramps, nausea, vomiting, heartburn, flatulence, anorexia, abdominal pain, dyspepsia, etc.
3. The presence or absence of crystalluria cannot be evaluated because urine sediment was only examined before treatment and again two days after treatment was discontinued. Urine sediment should have been examined for the presence of drug crystals during treatment at the height of the drug excretion period.

There is a discrepancy between the printout and several case report forms regarding the presence of nonamorphous crystals.

Case #302 - Printout shows 50 nonamorphous crystals/HPF on Day 7. The case report shows "Many" nonamorphous crystals two days after treatment.

Case #308 - Printout shows 4/HPF before treatment. The case report shows 4+ before treatment.

Case #113 - Printout shows 1/HPF on Day 8. The case report shows 1+ calcium oxalate two days after treatment.

(c) (2) Protocol #519-01 Seven investigators in seven countries conducted a randomized, controlled, trial of two doses of norfloxacin and trimethoprim-sulfamethoxazole, orally administered, in the treatment of acute bacterial gastroenteritis caused by susceptible pathogens. The following investigators participated in this study:

Study No. 588 Amador Carcelen, M.D., Honorio Delgado High Altitude Institute, Unit of Neumology, San Martin, Lima Peru. (Qualified for efficacy evaluation: 19/36 800-mg norfloxacin patients, 13/38 1200-mg norfloxacin patients, and 14/36 TMP-SMZ patients)

Study No. 591 Cid Vieira Franco de Godoy, M.D., Associate Professor and Head Department of Microbiology and Immunology, University of Sao Paulo, Sao Paulo, Brazil. (Qualified for efficacy evaluation: 6/33 800-mg norfloxacin patients, 10/35 1200-mg norfloxacin patients, and 13/43 TMP-SMZ patients)

Study No. 595 Dr. Pablo Pagliano, Chief of the Pediatrics Department, Luis A. Maspero Hospital, Buenos Aires, Argentina. (Qualified for efficacy evaluation: 2/13 800-mg norfloxacin patients, 0/11 1200-mg norfloxacin patients, and 1/13 TMP-SMZ patients)

Study No. 609 Guillermo G. Rodriguez, M.D., Intensive Care Unit, Hospital Mexico, San Jose, Costa Rica. (Qualified for efficacy evaluation: 7/18 800-mg norfloxacin patients, 5/17 1200-mg norfloxacin patients, and 7/15 TMP-SMZ patients)

Study No. 590 Guillermo Ruiz-Palacios, M.D., Chief of the Department of Infectious Diseases, Instituto Nacional de la Nutricion, Tlalpan, Mexico. (Qualified for efficacy evaluation: 8/21 800-mg norfloxacin patients, 8/22 1200-mg norfloxacin patients, and 11/24 TMP-SMZ patients)

Study No. 589 Augusto S. Salazar, M.D., Chief of the Department of Gastroenterology of the Colombianna Association of Diabetes, Bogota, Colombia. (Qualified for efficacy evaluation: 11/18 800-mg norfloxacin patients, 9/19 1200-mg norfloxacin patients, and 7/19 TMP-SMZ patients)

Study No. 634 Vincenzo Vagni, M.D., Department of Surgery, General Hospital (Ospedale Generale S. Giovanni Decollato Andosilla), Civita Castellana, Italy. (Qualified for efficacy evaluation: 3/3 800-mg norfloxacin patients, 3/3 1200-mg norfloxacin patients, and 2/2 TMP-SMZ patients)

Patients selected for the study were inpatients or outpatients with clinical diagnoses of acute gastroenteritis. Bacteriological documentation of infection in pretreatment cultures (specimens taken within the three-day period before initiation of treatment) was required for evaluation of bacteriological outcome.

Exclusions included those with a history of allergy to nalidixic acid, oxolinic acid, norfloxacin, sulfonamides or trimethoprim; those who were pregnant, less than 12 years of age, or over 75 years of age; renal, visual, psychiatric or CNS abnormalities, other effective antimicrobial therapy; and

concomitant disease contraindicating the use of the study drugs.

Each patient received either one 400-mg tablet of norfloxacin bid, one 400-mg tablet of norfloxacin tid, or two 80/400-mg tablets of TMP-SMZ. The usual length of treatment was five days. Patients who were treated at least three days were considered to be evaluable. Patients were numbered consecutively in the order of acceptance into the study and were assigned to treatment according to a randomized allocation schedule.

Patients were examined before treatment, between the second and fifth post-treatment days, and one month after therapy. The pretreatment examination included a complete history, physical examination, laboratory studies, and evaluation of the characteristics of the diarrheal disease (length of illness, number of stools, presence of blood, fecal leukocytes, or mucus, history of fever and GI symptoms). Stools were cultured for enteric pathogens. *E. coli* was regarded as a pathogen only when enterotoxin production was demonstrated. Three investigators performed these assays. Stool cultures and laboratory studies were repeated at the two follow-up evaluations.

Tolerability to the study drug was monitored throughout the study (well, moderately well, and poorly tolerated). Patients of two investigators, Drs. Carcelen and Ruiz-Palacios, kept diaries on the number of stools per day after the initiation of treatment.

Adverse experiences volunteered by the patient were recorded and evaluated at each post-therapy visit. Adverse laboratory experiences were evaluated by the investigator.

Bacteriological outcome was graded as eradicated, persisted, or reinfection. Clinical outcome was graded as cured, improved, not improved, or other (lost to follow-up).

Characteristics of evaluable patients are shown in the following table:

Age (yrs.)	Norfloxacin 800-mg			Norfloxacin 1200-mg			TMP-SMZ 160/800		
	Males	Females	Total	Males	Females	Total	Males	Females	Total
13-17	1	2	3	1		1	3		3
18-21	8	2	10	1	1	2	5	2	7
22-30	6	9	15	9	10	19	12	4	16
31-40	5	4	9	8	3	11	10	3	13
41-50	2	7	9	2	5	7	4	8	12
51-60	3	2	5	3	2	5	2		2
61-70		5	5	1	2	3	2		2
Total No.	9	31	56	25	23	48	38	17	55
Mean Age	26.3	38.2	34.3	35.8	37.2	36.5	32.8	35.1	33.5
Minimum	20	13	13	16	18	16	15	18	15
Maximum	38	65	65	62	68	68	67	49	67

Of the 439 patients in the study, 159 were evaluable (36%), 56 in the 800 mg group, 48 in the 1200 mg group and 55 in the TMP-SMZ group.

Reasons for Efficacy Disqualification

	800 mg Nor.	1200 mg Nor.	TMP-SMZ
No initial pathogen isolated	80	93	91
Effective concomitant antimicrobial therapy	0	0	1
Inadequate cultures	6	4	5
Total	86	97	97

Common signs and symptoms of gastroenteritis before treatment for evaluable patients are listed below:

	800 mg Nor.	1200 mg Nor.	TMP-SMZ
Abdominal cramps	53	42	49
Nausea	33	23	34
Vomiting	18	12	23
Rash	3	0	1
Fever	32	20	32
Anorexia	27	24	23
Tenesmus	22	17	12
Chills	24	21	24

Bacteriological outcome for evaluable patients is shown in the following table.

Pathogen	Number eradicated/Number Qualified					
	800 mg Nor.		1200 mg Nor.		TMP-SMZ	
	Merck	MO	Merck	MO	Merck	MO
<u>Aeromonas hydrophilia</u>	6/6	6/6			4/4	4/4
<u>Campylobacter species</u>					1/1	1/1
<u>Campylobacter fetus ss. jejuni</u>					1/2	1/2
<u>E. coli (invasive)</u>			1/1	1/1		
<u>E. coli, enterotoxigenic</u>	15/16	14/15	19/19	19/19	9/10	9/10
<u>Plesiomonas shigelloides</u>	2/2	2/2	1/1	1/1	3/3	3/3
<u>Salmonella species</u>	4/4	4/4	2/2	2/2	7/8	6/7
<u>Salmonella enteritidis</u>					2/2	2/2
<u>Shigella species</u>					1/1	1/1
<u>Shigella boydii</u>	1/1	1/1			4/4	3/3
<u>Shigella dysenteriae</u>	1/1	1/1	3/3	3/3	2/2	2/2
<u>Shigella flexneri</u>	19/19	18/18	15/15	15/15	16/16	15/15
<u>Shigella sonnei</u>	5/5	5/5	4/4	4/4		
<u>Vibrio cholerae</u>	1/1	1/1				
<u>Vibrio parahaemolyticus</u>	3/3	2/2	3/3	2/2	2/2	2/2
Total strains	56/57	52/63	49/49	48/48	52/55	49/52
Number patients	52/56	53/54	48/48	47/47	52/55	49/52
	98%	98.1%	100%	100%	95%	94.2%

Two patients had polymicrobial infections, one in each of the norfloxacin groups. Shigella flexneri and enterotoxigenic E. coli were the most commonly isolated organisms. The only one of the failures to develop resistance was

the Campylobacter fetus subspecies jejuni strain and the resistance was to TMP-SMZ.

In the evaluation of clinical outcome, all of the evaluable patients were rated as either cured or improved.

Clinical Outcome for Evaluable Patients			
	800 mg Nor.	1200 mg Nor.	TMP-SMZ
Cured	55 (98%)	47 (98%)	48 (87%)
Improved	1	1	7
Total	56	48	55

Approximately 35% of the patients in each treatment group had diarrhea eliminated after one day of therapy. After two days, the percentages increased to 50%. The three treatment groups were similar regarding the number of days required for the elimination of diarrhea. Information on the usual number of stools per day before the development of gastroenteritis and daily diaries on the number of stools per day after the initiation of treatment was available for 43 evaluable patients.

Time Required for the Elimination of Diarrhea			
Days	800 mg Nor.	1200 mg Nor.	TMP-SMZ
1	5	5	5
2	4	3	3
3	2	3	1
4	1	1	1
5 or more	3	1	5
Total	15	13	15

Late post-therapy stool cultures which were performed for 142 of the 155 patients with a bacteriological outcome of eradication revealed that two patients had reinfections after the post-therapy visit.

Adverse reactions were reported by the applicant for twelve patients. Most of the adverse reactions were related to the nervous system (anxiety, dizziness, drowsiness, headache, insomnia, and nervousness). The second most common body system was hypersensitivity manifested as skin reactions (pruritus, rash, and urticaria).

The study drug was discontinued in one patient in each group because of adverse clinical effects. The norfloxacin patient had pneumonia and the TMP-SMZ patient had pruritus, rash, and edema.

Adverse reactions as reported by the applicant are shown below.

	800 mg Nor.	1200 mg Nor.	TMP-SMZ
Serious/Not drug related			
Pneumonia	1		
Not Serious/Drug Related			
Eyelid edema, two rashes, and pruritus			1
Urticaria		2	
Not Serious Nor Drug Related			
Insomnia	1		
Flatulence		1	
Anxiety disorders and nervousness		1	
Headache		1	
Headache and somnolence			1
Somnolence			1
Dizziness and asthenia	1		
Vomiting & abdominal pain		1	
No. pts with ARs	3 (2%)	6 (4%)	3 (2%)
Number pts.	142	145	152

Adverse laboratory experiences were reported for 41 patients during the study: 16 (19%) in the 800-mg norfloxacin group, 12 (15%) in the 1200-mg norfloxacin group, and 13 (16%) in the TMP-SMZ group. The most common adverse laboratory experiences were elevated aspartate transferase and alanine transferase values. None of the adverse experiences were serious and all recovered without medical action.

	800 mg Nor.	1200 mg Nor.	TMP-SMZ
Low Hemoglobin	2	0	1
Low Hematocrit	3	2	1
Low WBCs	1	5	2
High Lymphocytes	0	0	1
High Eosinophils	1	1	3
High Platelet count	0	1	0
High BUN	1	0	0
High Serum creatinine	1	0	1
High ASAT	7	5	3
High ALAT	6	4	3
High Serum Alk. Phos.	3	2	0
High Serum sodium	0	0	1
Low Serum Potassium	1	0	1
High Serum chloride	0	0	2
High Urine RBCs	1	0	0
High Urine WBCs	1	0	0
Total pts with Adverse values	16	12	13
No. felt to be drug related	2	3	2
No. pts	86	79	79

The applicant concludes that norfloxacin in doses of 400 mg bid or tid is effective in the treatment of acute bacterial gastroenteritis. There were no significant differences between norfloxacin and TMP-SMZ. Norfloxacin is well tolerated and has a good safety profile for oral administration at these doses.

Medical Officer's Comments:

1. This study cannot be used for the evaluation of adverse reactions for two reasons.

a) No patient diaries were submitted and patients were not observed or questioned for the presence of adverse reactions during treatment. The only observation was a post-treatment observation. Diaries to record the number of stools and with check-off boxes are not acceptable as patient diaries with blank lines intended to record the presence of adverse reactions.

b) Symptoms of the infection were so similar to the gastrointestinal-type adverse reactions of norfloxacin that were to be assessed that no side effect information can be drawn from this study.

2. This study cannot be used for the evaluation of the presence of drug crystals. Urine was not examined during treatment. The post-treatment urine specimen was collected after the drug had been fully excreted at a time when crystals would not be expected to be present.

3. The following seven underage applicant-qualified patients should be disqualified from the efficacy evaluation and safety evaluation. The lower age limit for the use of the quinolones in humans has been set at 18 years because of the development of arthropathy in juvenile animals in all species that have been tested. This represents a serious protocol violation.

Carcelen #4022 15-yr old in 800 mg Nor. - V. parahaemolyticus -Eradicated
 Carcelen #4056 15-yr old in 800 mg Nor. - S. flexneri - Eradicated
 Salazar #4122 13-yr old in 800 mg Nor. -E. coli, enterotox. - Eradicated
 Carcelen #4029 16-yr old in 1200 mg Nor. - V. parahaemolyticus -Eradicated
 Carcelen #4109 17-yr old in TMP-SMZ - S. flexneri - Eradicated
 De Godoy #4451 15-yr old in TMP-SMZ - Salmonella - Eradicated
 Rodriguez #4641 17-yr old in TMP-SMZ - Shigella boydii- Eradicated

These disqualifications change the bacteriological cure rates slightly as shown in the table. Differences between group rates are not statistically significant.

d Suppression of Aerobic Bowel Flora in Patients With Granulocytopenia

(1) Study No. 16 Jai Joshi, M.D., Clinical Associate, Medical Oncology Fellow, Baltimore Cancer Research Center, University of Maryland School of Medicine, Baltimore, MD, conducted a randomized, controlled comparison of a regimen of norfloxacin plus amphotericin B with a regimen of TMP-SMZ with amphotericin B in the prevention of infections derived from the gastrointestinal tract during neutropenia.

Patients selected for the study were infection-free men and women 18 years of age or older. Pregnant women were excluded. Other exclusions were patients with a temperature or any manifestation of infection; patients receiving or who had received other antibiotic therapy within the preceding 36 hours; allergic patients; patients who were to be treated with thymidine or methotrexate; comatose patients and those with a high probability of death; patients with renal abnormalities, visual disturbances, psychiatric or CNS disorders; and patients with acute leukemia involving the central nervous system.

Before treatment, patients were examined and complete histories were obtained. Examinations included visual acuity tests, and tests of neurologic function. All patients had surveillance cultures of their nose, throat, perirectal areas and urine. Isolates were tested for susceptibility. Specimens were obtained for hematology, blood chemistry and urinalysis including microscopic examination for the present of drug crystals. These studies were repeated during treatment approximately three times a week, and, again, post-therapy. Subjects were observed for the presence of adverse reactions.

Patients enrolled in this study received either one 400-mg tablet of norfloxacin tid or one tablet containing 160 mg of trimethoprim and 800 mg of sulfamethoxazole (TMP-SMZ) tid. In addition, the protocol provided that all patients were to "swish (preferably for one minute) and swallow the equivalent of 12.5 mg of amphotericin B" tid. Drugs were to be administered while the patient's neutrophil count remained below $1000/\text{mm}^3$. When neutropenia persisted for more than two months, treatment was continued if the benefit outweighed the potential risk of continued therapy. Treatment was stopped if the neutrophil count increased above 1,000 cells per cm^3 , if the patient developed an allergic reaction or a serious side effect, and if the prophylactic drug was incompatible with cancer chemotherapeutic drugs.

Clinical outcome was assessed on the basis of the occurrence of infections and/or febrile episodes. Febrile episodes were classified as either microbiologically documented, clinically documented, equivocal, or noninfectious episodes. A clinical outcome of "effective" prophylaxis was ascribed to patients where no microbiologically and/or clinically documented episodes occurred. Patients with one or more microbiologically or clinically documented infectious episodes were considered prophylactic failures. Bacterial and fungal organisms identified in infectious episodes were further defined as gastrointestinal-related pathogens or not-GI-related pathogens. Organisms monitored from gastrointestinal sites during surveillance cultures which subsequently initiated an infectious process were considered GI related. Oral cavity, perirectal, and perineal surveillance sites were

considered gastrointestinal in origin. Cultures from the nose were not considered gastrointestinal in origin.

There were 72 treatment courses given to 66 patients, 34 received norfloxacin and 32 received TMP-SMZ. Only the first entry of the six patients with multiple entries was included in the analysis. A total of 46 patients were evaluable for efficacy, 21 in the norfloxacin group and 25 in the TMP-SMZ group.

Characteristics of evaluable patients are shown in the following table:

	Norfloxacin & Amphotericin B			TMP-SMZ & Amphotericin B		
	Males	Females	Total	Males	Females	Total
<u>Age (yrs.)</u>						
18-19	1		1			
20-29		1	1	2		2
30-39	2		2	4	3	7
40-49	2	1	3	4	1	5
50-59	4	1	5	2	3	5
60-69	6	2	8	2	3	5
70-79	1		1		1	1
Total No.	16	5	21	14	11	25
Mean Age	53.7	50.8	53.0	44.1	52.5	47.8
Minimum	18	23	18	20	30	20
Maximum	75	67	73	69	75	75
Mean Duration (Days)			49.0	38.5		
<u>Primary Diagnoses (%)</u>						
Leukemia, Acute	47.6%			48%		
Lung Neoplasm, Malignant	23.8%			4%		
Lymphoid leukemia, Acute	14.3%			12%		
Myeloid leukemia, acute	14.3%			16%		
Myeloid Leukemia, chronic	0			12%		
Other	0			8%		

A majority of patients had secondary diagnoses of other diseases. About one-third had prior therapy with other antibiotics within 72 hours prior to the start of the study. However, approximately 88% of the patients had antibiotic therapy for the treatment of possible infections which developed during the course of the study. Most patients entered the study with a granulocyte count greater than 1000 mm^3 . In general, the evaluable patient population was similar to the population of all patients.

Twenty of the 66 patients (30%) were disqualified from the efficacy analysis for the following reasons:

N19384 -03

<u>Reason for Disqualification</u>	<u>Norflox/Amp B</u>	<u>TMP-SMZ/Amp B</u>
Inadequate length of neutropenia	4	5
Infection before prophylaxis	9	2
Total Disqualified	13	7
Total Qualified	21	25

The applicant judged prophylactic response by measuring the percentage of patients who were prophylactic failures, that is, those with at least one microbiologically documented or one clinically documented infectious episode. Prophylactic successes were patients who were free of microbiologically documented or clinically documented episodes. Prophylactic response was reported by the applicant as follows:

	<u>Norflox/Amp B</u>	<u>TMP-SMZ/Amp B</u>
Microbiologically Documented Cases	8 (38.1%)	14 (56%)
Only Clinically Documented Cases	5 (23.8%)	4 (16%)
Non-Infectious or Equivocal Cases	6 (28.6%)	3 (12%)
Cases with No Episodes	2 (9.5%)	4 (16%)
Total Cases	21 (100%)	25 (100%)

Since the proportion of patients receiving norfloxacin for more than 35 days was significantly greater than that proportion for TMP-SMZ, results were analyzed according to length of treatment as follows:

<u>Duration/Outcome</u>	<u>Norflox/Amp B</u>	<u>TMP-SMZ/Amp B</u>
5 Days or less		
Success	2 (50%)	5 (36%)
Failure	2	9
Over 35 Days		
Success	6 (54%)	2 (18%)
Failure	11	9
Total	21	25

The applicant reports that those receiving therapy for 35 days or less had a greater success rate if they were receiving norfloxacin (50%) than if they were receiving TMP-SMZ (36%). Three norfloxacin-treated patients and five TMP-SMZ-treated patients had GI-related septicemias. These data were also analyzed according to granulocyte count, according to the presence of GI-related septicemia, according to the percentage of febrile-free and infection-free days, and for all patients both qualified and disqualified.

A similar proportion of patients in each treatment group had at least one clinical adverse experience, 14/34 (41%) in the norfloxacin group and 14/32 (44%) in the TMP-SMZ group. Treatment was discontinued because of adverse reactions in 2/34 patients in the norfloxacin group and in 5/32 patients in the TMP-SMZ group.

Adverse experiences are listed below.

	Norflox/Amp B	TMP-SMZ/Amp B
Serious and Drug Related	0	0
Serious and Not Drug Related		
Death	7	6
Fever	0	1
Fungemia	0	1
Fungus Infection	0	1
Cardiac Arrest	2	0
Congestive Heart Failure	1	0
Intracranial Hemorrhage	1	0
Diarrhea	1	0
Dysphagia	0	1
Gastrointestinal Cramps	0	0
Gastrointestinal Hemorrhage	2	1
Hepatic Failure	0	1
Vomiting	0	0
Hemolysis	1	0
Thrombocytopenia	0	1
Brain Compression	0	1
Cerebellar Ataxia	1	0
Fungal Pneumonia	1	1
Hemoptysis	1	0
Pulmonary Insufficiency	1	0
Rash	0	1
Nystagmus	1	0
Renal Failure	2	1
Abdominal Pain	0	0
Dehydration	0	0
Not Serious but Drug Related		
Vomiting	1	0
Rash	0	2
Not Serious and Not Drug Related		
Diarrhea	1	0
Gastrointestinal Cramps	1	0
Nausea	1	0
Bone Marrow Depression	0	1
Rash	8	4
Fever	0	0
Number of pts. with one or more AEs	14 (41.2%)	14 (43.8%)
Number of pts. without AEs	20	18
Total No of Single entry pts.	34	32

Laboratory adverse experiences in these 66 patients are shown in the next table.

	Norflo/Amp B	TMP-SMZ/Amp B
Drug Related	0	0
Serious		
Elevated Serum Creatinine	2	1
Not Serious		
Elevated Serum Creatinine	1	3
Elevated Total Serum Bilirubin	20	15
Elevated AST	14	13
Elevated ALT	14	17
Elevated Serum Phosphatase	15	12
Elevated Serum LDH	11	10
Elevated Serum Uric Acid	1	0
Elevated Urine Protein	0	1
No. Pts. with one or more Laboratory AEs	26 (76.5%)	25 (78.1%)
No. Pts. without Laboratory AEs	8	7

Results of ophthalmological examinations were reported for most patients. Eye motility was abnormal post-treatment for 2/27 norfloxacin-treated patients and for 1/22 TMP-SMZ-treated patients. One norfloxacin patient's retina changed from abnormal before treatment to normal after treatment. No data were recorded for visual acuity or for color vision (except for one TMP-SMZ patient). Other ophthalmological parameters that were normal before treatment were normal after treatment.

Results of neurological examinations were reported for most patients. Romberg's sign was positive for 2/10 norfloxacin-treated patients and for 1/16 TMP-SMZ-treated patients. The straight-line walk test was improperly performed by 1/14 norfloxacin-treated patients and by 2/15 TMP-SMZ-treated patients. Deep tendon reflexes were abnormal for 2/26 norfloxacin-treated patients and for 1/20 TMP-SMZ-treated patients.

The applicant concludes that norfloxacin is at least as effective as TMP-SMZ in the following aspects:

1. Decreasing the occurrence of microbiologically documented infections.
2. Preventing the development of infections of any type
3. Preventing gram-negative aerobic bacteremias and fungemias.
4. Preventing septicemias emanating from the GI tract.

The applicant also concludes that Norfloxacin and TMP-SMZ are safe and tolerable when given to neutropenic patients for up to two months or more.

Medical Officer's Comments: The medical officer does not agree with any of the applicant's conclusions.

1. The route of administration of amphotericin B in this study, swishing it in the mouth for one minute then swallowing it, is an investigational route for the use of intravenous vials. Amphotericin B was provided in 50 mg intravenous vials and efficacy and safety by the oral route have not been established. Oral amphotericin B, however, is available as a fixed

combination with tetracycline (Mysteclin-F^R (Squibb): NAS/NRC rated as ineffective). It is labeled as being "extremely well tolerated and is virtually nontoxic in prophylactic doses." Adverse reactions which are reported in this labeling are those due to tetracycline rather than to amphotericin B. This study should be disregarded because two investigational drugs should not be studied at the same time.

No comparison can be made regarding fungemias since amphotericin B was given to all patients in each group.

2. No decision regarding prophylactic efficacy can be made on the basis of this study because of the use of another investigational drug and because of the small size of the treatment groups. The conclusion regarding the superiority of norfloxacin in patients treated 35 days or less is based upon success in two of only four patients. This does not represent substantial evidence and this difference is surely due to chance alone. One cannot even conclude that there is a suggestion of superiority. There are too few qualified patients for which to adjust efficacy rates.

3. Since patients randomized to receive norfloxacin and graded as evaluable were five times more likely to be profoundly neutropenic at the time of randomization as were the patients in the control group, there must have been a randomization bias. There must also have been a duration-of-treatment bias in that the norfloxacin group was treated longer than the control group, 49 days versus 38 days.

4. No decision regarding the safety of norfloxacin can be made from this study.

a) There was no evaluation of adverse reactions during treatment by the investigator.

b) No adverse reaction diaries were kept as requested in order to ascertain the patient's concept of how he felt.

c) No data were recorded for visual acuity or for changes in color perception as requested.

d) The adverse reaction rate for TMP-SMZ (43.8%) is twice as high as would be expected.

e) The rate of abnormal laboratory values of 78.1% for TMP-SMZ is four times higher than would be expected.

f) No report of the presence or absence of crystalluria is included. However, the computerized printout in the appendix revealed that four patient had nonamorphous crystals, one norfloxacin-treated patient and three TMP-SMZ-treated patients.

(2) Study No. 17 D. J. Winston, M.D., Assistant Professor of Medicine, UCLA Center for Health Sciences, Los Angeles, conducted a randomized, controlled comparison of a regimen of norfloxacin plus nystatin with a regimen of polymyxin plus vancomycin, plus nystatin in the prevention of infections derived from the gastrointestinal tract during neutropenia. Except for the different treatment regimens, this study was the same as Study No. 16, described above.

Patients enrolled in this study received either one 400 mg tablet of norfloxacin tid or two 50 mg capsules of polymyxin B plus two 250 mg capsules of vancomycin tid. In addition, all patients received 10 mg of nystatin oral suspension, 100,000 units per ml, tid. The investigator was furnished with norfloxacin and nystatin. Polymyxin B, 50/mg/capsule and vancomycin, 250 mg/capsule were supplied to the investigator by the institution's own pharmacy.

There were 82 treatment courses given to 62 patients, 35 received norfloxacin/nystatin and 32 received polymyxin/vancomycin/nystatin. Only the first entry of the 15 patients with multiple entries was included in the analysis. A total of 40 patients were evaluable for efficacy, 25 in the norfloxacin/nystatin group and 15 in the control group.

Characteristics of evaluable patients are shown in the following table:

	Norfloxacin & Nystatin			Polym./Vanco./Nystatin		
	Males	Females	Total	Males	Females	Total
<u>Age (yrs.)</u>						
18-19		1	1	2		2
20-29	1	5	6	3		3
30-39	3	1	4	1	2	3
40-49	2	2	4	2		2
50-59	3	1	4			
60-69	2	3	5	3	1	4
70-79		1	1	1		1
Total No.	11	14	25	12	3	15
Mean Age	44.3	42.1	43.1	42.0	42.3	42.0
Minimum	21	19	19	18	30	18
Maximum	62	70	70	73	63	73
Mean Duration (Days)			31.3			22.2
Primary Diagnoses (%)						
Myeloid Leukemia, Acute			72.0%			73.3%
Lymphoid Leukemia, Acute			16.0%			20.0%
Myeloid Leukemia, Chronic			12.0%			6.7%
Lymphoid Leukemia, Chronic			0.0			0.0%

Over 86% of patients had secondary diagnoses of other diseases. Sixteen percent of the norfloxacin group and none of the control group had had prior therapy with other antibiotics within 72 hours before the start of the study. However, 96% in the norfloxacin group and 100% of the control had antibiotic therapy for the treatment of possible infections which developed during the course of the study. Most patients entered the study with a granulocyte count greater than 1000 mm³. In general, the evaluable patient population was similar to the population of all patients.

Twenty-two of the 62 patients (35%) were disqualified from the efficacy analysis for the following reasons:

<u>Reason for Disqualification</u>	<u>Norflox/Nyst</u>	<u>Poly/Van/Nyst</u>
Inadequate length of neutropenia	9	6
Infection before prophylaxis	1	4
Effective concomitant prophylaxis	0	2
Total Disqualified	10	12
Total Qualified	25	15

The applicant judged prophylactic response by measuring the percentage of patients who were prophylactic failures, that is, those with at least one microbiologically documented or one clinically documented infectious episode. Prophylactic successes were patients who were free of microbiologically documented or clinically documented episodes. Prophylactic response was reported by the applicant as follows:

	<u>Norflox/Nyst</u>	<u>Polym/Van/Nyst</u>
Microbiologically Documented Cases	11 (44.0%)	12 (80.0%)
Only Clinically Documented Cases	3 (12.0%)	1 (6.7%)
Non-Infectious or Equivocal Cases	10 (40.0%)	2 (13.3%)
Cases with No Episodes	1 (4.0%)	0 (0.0%)
Total Cases	25 (100%)	15 (100%)

Results were analyzed according to length of treatment as follows:

<u>Duration/Outcome</u>	<u>Norflox/Amp B</u>	<u>TMP-SMZ/Amp B</u>
28 Days or less		
Success	8 (57.1%)	1 (8.3%)
Failure	6	11
Over 28 Days		
Success	3 (27%)	1 (33%)
Failure	8	2
Total	25	15

The applicant reports that the percentage of evaluable patients who were prophylactic successes was significantly greater in the norfloxacin group than in the control, 44% vs. 13%, respectively, regardless of duration of therapy,

sex, or granulocyte count range. Seven norfloxacin-treated patients and seven control patients had GI-related septicemias. These data were also analyzed according to granulocyte count, according to the presence of GI-related septicemia, according to the percentage of febrile-free and infection-free days, and for all patients both qualified and disqualified.

The percentage of single entry patients with both a clinical and a laboratory adverse experience in the norfloxacin group (23/35, 66%) was greater than that in the polymyxin/vancomycin group (14/27, 52%). A similar proportion of patients in each treatment group (28/35, 80%, for norfloxacin and 21/27, 78%, for polymyxin/vancomycin) had at least one clinical adverse experience. No serious and drug-related adverse experiences were reported. Two patients in the norfloxacin group (6%) and no patients in the polymyxin/vancomycin group discontinued the study due to a clinical adverse experience. A greater proportion of patients in the norfloxacin group (25/35, 71%) than in the polymyxin/vancomycin group (15/27, 56%) had at least one laboratory value that was considered adverse by the investigator but this difference was not significant.

Adverse Clinical and/or Laboratory Experiences
Regardless of Drug Relationship

	Norfloxacin	Polym/Vanco.
Adverse Clinical Experience Only	5 (14.3%)	7 (25.9%)
Adverse Laboratory Experience Only	2 (5.7%)	1 (3.7%)
Adverse Clin. and Lab. Experiences	23 (65.7%)	14 (51.9%)
Patients with Adverse Experiences	30 (85.7%)	22 (81.5%)
Patients without Adverse Experiences	5 (14.3%)	5 (18.5%)
Total Single Entry Patients	35	27

Adverse experiences are listed below.

	Norflox/Amp B	TMP-SMZ/Amp B
Serious and Drug Related	0	0
Serious and Not Drug Related		
Death	5	7
Fungemia	1	1
Fungus Infection	1	2
Cardiac Arrest	1	0
Heart Failure	1	0
Intracranial Hemorrhage	1	0
Diarrhea	2	0
Gastrointestinal Hemorrhage	1	0
Vomiting	1	0
Leukemia	1	1
Respiratory Failure	1	2
Hematuria	1	0
Renal Failure	2	1
Abdominal Pain	0	1
Bacterial Septicemia	0	1
Septic Shock	0	1
Acute Cerebrovasculae Disease	0	1
Hepatorenal Syndrome	0	1
Acute Myeloid Leukemia	0	2
Rhabdomyolysis	0	1
Oliguria and Anuria	0	1
Dysarthria	0	0
Asthenia	0	0
Not Serious but Drug Related		
Diarrhea	0	3
Vomiting	0	1
Not Serious and Not Drug Related		
Abdominal Pain	3	2
Syncope	1	0
Bowel Sound Abnormalities	1	0
Diarrhea	20	15
Dyspepsia	1	0
Nausea	2	1
Vomiting	14	8
Muscle Cramps	1	0
Headache	2	0
Rash	8	6
Conjunctivitis	3	0
Constipation	0	1
Erythematous Condition	0	0
Arthostatic Effects	0	0
Dysuria	0	0
Tachycardia	0	0
Number of pts. with one or more AEs	28 (80.0%)	21 (77.8%)
Number of pts. without AEs	7	6
Total No of Single entry pts.	35	27

Laboratory adverse experiences in these 66 patients are shown in the next table.

	Norflox/Amp B	TMP-SMZ/Amp B
Drug Related	0	0
Serious and Not Drug Related		
Elevated Serum Creatinine	2	6
Elevated Total Serum Bilirubin	1	4
Elevated ALT	0	1
Elevated Ser. Alk. Phosphatase	0	1
Elevated Serum LDH	0	2
Elevated BUN	1	5
Elevated Urine RBC's	2	1
Not Serious and Not Drug Related		
Elevated Serum Creatinine	7	3
Elevated Total Serum Bilirubin	11	3
Elevated AST	15	8
Elevated ALT	19	9
Elevated Serum Alk. Phosphatase	8	6
Elevated Serum LDH	1	1
Elevated Serum Uric Acid	0	1
Elevated Urine Protein	6	4
Elevated BUN	6	2
Elevated Urine Glucose	1	1
Elevated Urine RBC's	2	1
Elevated Granular Casts	0	0
No. Pts. with one or more Laboratory AEs	25 (71.4%)	15 (55.6%)
No. Pts. without Laboratory AEs	10	12

Results of ophthalmological examinations were reported for most patients. For all but one of the parameters measured, there were no patients who changed from normal at pretreatment to abnormal at post-treatment or from abnormal to normal. One patient's deep tendon reflex (polymyxin/vancomycin group) changed from normal at pretreatment to abnormal at post-treatment.

The applicant concludes that norfloxacin is superior to polymyxin plus vancomycin in preventing infectious complications during neutropenia and may be less likely to produce drug-related adverse clinical experiences.

Medical Officer's Comments: The medical officer does not agree with the applicant's conclusions.

1. The routes of administration of polymyxin and vancomycin in this study are investigational routes for these products.

2. This study must be regarded as an uncontrolled trial because the control was not approved for this indication. Two investigational regimens should not be studied at the same time.

3. No decision regarding the safety of norfloxacin can be made from this study. The adverse reaction rate for norfloxacin is four times higher than would be expected. The rate of abnormal laboratory values is four times higher than would be expected. No report of the presence or absence of crystalluria is included. No adverse reaction diaries were kept in this study.

(e) Gonorrheal Infection

(1) Protocol No. 010 (Study No. 30) Samuel William Berg II, M.D., Head of the Infectious Disease Branch, Naval Regional Medical Center, San Diego, California conducted a controlled study of orally administered norfloxacin and intramuscularly administered spectinomycin in the treatment of symptomatic uncomplicated gonorrheal urethritis in 130 men at Subic Bay Naval Base in the Phillipines. A random design was not followed. Each patient received either 1200 mg of norfloxacin given orally as three 200 mg tablets and followed in four hours by three additional 200 mg tablets, or spectinomycin 2 grams IM in one dose.

Patients were men 18 years of age or older who were "presumptively diagnosed if they had a history of recent sexual exposure and/or signs or symptoms of urethritis or cervicitis, and a urethral or cervical gram stain showing polymorphonuclear neutrophils and intracellular gram-negative diplococci."

✓ Medical Officer's Comment: Obviously, reference to cervicitis and cervical smears in men is an error.

Exclusions were patients unlikely to return for test-of-cure cultures, those requiring concurrent antibacterial therapy, those with hypersensitivities to the two drugs or related compounds, those with conditions which precluded evaluation, those having successful antimicrobial therapy within the three-day period preceding the p-treatment examination, those with syphilis, and those with other varieties of gonococcal infection.

All patients had a pretreatment urethral swab for gram stain, a gonococcal culture (urethral, pharyngeal, or rectal specimens), and a serological test for syphilis. Before treatment, a history was taken and patients received a physical examination. These findings were compared to repeat examinations at the completion of the study. The test-of-cure visit was 3-7 days after treatment. Smears and cultures were repeated 3-7 days after treatment. In addition, laboratory studies which were obtained before and after treatment were hematocrit, hemoglobin, WBC with differential, platelet estimate, BUN & creatinine, ASAT (SGOT), ALAT (SGPT), total bilirubin, LDH, alkaline phosphatase, and urinalysis with observation for non-amorphous crystals.

Clinical outcome was graded as cured, improved, recurrence, no improvement, or unable to evaluate. Bacteriological outcome was graded as eradication or persistence. Patients whose beta-lactamase status changed during the study were presumed to be re-infected and were deleted from analysis.

There were 131 treatment courses given to 130 patients. Seventy-four of the 107 norfloxacin patients and 16 of the 23 spectinomycin patients were evaluable for efficacy.

Characteristics of evaluable patients are shown in the following table:

	Norfloxacin Males	Spectinomycin Males
<u>Age (yrs.)</u>		
18-21	28 (37.8%)	9 (56/3%)
22-39	38 (51.4%)	6 (37.5%)
31-40	6 (8.1%)	1 (6.3%)
41-42	2 (2.7%)	
Total No.	74	16
Mean Age	24.3	22.6
Minimum	18	19
Maximum	42	31
<u>Strain</u>		
<u>N. gonorrhoeae</u>	5 (7.0%)	0
<u>N. gonorrhoeae</u> pcnase +	32 (43.2%)	3 (18.8%)
<u>N. gonorrhoeae</u> pcnase -	37 (50.0%)	13 (81.2%)

The imbalance in distribution of patients occurred because the investigator did not follow the allocation schedule. The medical personnel at Subic Bay Naval Base were notified that they were to be moved from the site in six weeks. They felt that it was imperative to obtain as much information on norfloxacin as possible. Of the 74 evaluable norfloxacin patients, five were diagnosed by gram stain. The remaining 69 patients were diagnosed by gram stain and positive culture. All 16 evaluable spectinomycin patients were diagnosed by gram stain and positive culture.

Forty patients were disqualified from the efficacy evaluation because the diagnosis was not microbiologically confirmed for one norfloxacin patient and because cultures were inadequate for 32 norfloxacin patients and seven spectinomycin patients.

Only 28 of the 90 evaluable patients had in vitro susceptibility tests performed. Of these, 26 were susceptible to both drugs. Two were susceptible to norfloxacin and resistant to spectinomycin.

All evaluable patients regardless of susceptibility or with unknown susceptibility had a bacteriological response of eradicated. All evaluable patients regardless of susceptibility or with unknown susceptibility were graded as clinical cures. In addition, two patients in the norfloxacin group had gonococcal pharyngitis and these were cured.

The applicant reports that all 90 evaluable patients were clinically cured. Yet, three norfloxacin-treated patients had signs and symptoms present at the follow-up evaluation. Case #1851 had nonspecific urethritis on Day 6, case #1899 had dysuria, and case # 2009 had dysuria and a mucoid urethral discharge at the first post-therapy visit.

Two patients treated with norfloxacin and none of the patients treated with spectinomycin reported adverse clinical experiences. None were considered serious or drug related.

Adverse Reactions

	Norfloxacin	Spectinomycin
Nausea and headache	1	0
Insomnia, nervousness and anorexia	1	0
Total with adverse reactions	2	0
Total without adverse reactions	105	23

The applicant concludes that norfloxacin and spectinomycin are effective in the treatment of gonococcal urethritis. Both drugs are safe in this treatment. Norfloxacin in extraurethral gonorrheal infection merits further study. Both drugs are active in vitro against penicillin-resistant N. gonorrhoeae.

Medical Officer's Comments: (1) Failure to randomize lessens the value of this study and removes it from the list of controlled trials. (2) In spite of the 100% cures in each group, the medical officer can only accept 27 of the 90 patients that the applicant found qualified because only these 27 cases had susceptibility testing, 22 in the norfloxacin group and 5 in the spectinomycin group. (One cannot be accounted for.) Cases for which there was no susceptibility testing should be disqualified. (3) Post therapy cultures should have been obtained 4-7 days after therapy instead of 3-7 days after therapy. (4) The presence or absence of drug crystals is not reported. No diaries were used in this study.

(2) Protocol No. 015 Lisa Kaplowitz, M.D., Assistant Professor, Department of Medicine, Medical College of Virginia, Richmond, Virginia (Study No. 49), and Margaret Simpson, M.D., Acting Director, Section of Infectious Disease, Hennepin County Medical Center, Minneapolis, Minnesota (Study No. 48), conducted a randomized, controlled, multiclinic study to compare norfloxacin and a regimen of ampicillin plus probenecid in the treatment of gonorrheal infection in men and women.

Fifty-seven patients 18 years of age or over with symptomatic urethritis or cervicitis were enrolled to receive either 1200 mg of norfloxacin given as three 200-mg tablets orally, then followed in four hours by three additional 200-mg tablets, or 3.5 grams of ampicillin given as seven 500-mg tablets plus two 500-mg tablets of probenecid. Twenty-eight patients received norfloxacin and 29 received the control regimen.

Exclusions were similar to those given above for Study #30. Laboratory observations were similar. Microbiological outcome criteria were the same.

Of the 57 patients treated, there were 48 that were considered by the applicant to be evaluable, 26 in the norfloxacin group and 22 in the ampicillin/probenecid group.

Characteristics of evaluable patients are shown in the following table:

	Norfloxacin			Ampicillin/Probenecid		
	Males	Females	Total	Males	Females	Total
Age (yrs.)						
8-21	6		6	5	3	8
22-30	14	1	15	9	2	11
31-40	3	1	4	2		2
41-50				1		1
51-60						
61-70	1		1			
Total No.	24	2	26	17	5	22
Mean Age	26.2	31.0	26.6	24.9	21.4	24.1
Minimum	19	25	19	18	20	18
Maximum	69	37	69	41	23	41

At enrollment, the two treatment groups were comparable except that twice as many patients in the ampicillin/probenecid group received other anti-infective therapy before the 72-hour prestudy interval than did those in the norfloxacin group (48.3% vs 21.4%, $p =$ less than 0.05). Most of these anti-infective agents had been taken for a previous episode of gonorrheal infection.

Nearly all evaluable patients in each treatment group had a diagnosis of gonococcal urethritis (males) or gonococcal cervicitis (females). Only one patient in the ampicillin/probenecid group was classified with a different diagnosis, gonococcal proctitis. One norfloxacin patient also had herpes, one ampicillin/probenecid patient had gonococcal proctitis and two ampicillin/probenecid patients had gonococcal pharyngitis. No patient had concomitant antimicrobial therapy.

Susceptibilities were determined by the disk method or by measuring MICs. For norfloxacin, 46 of 46 (100%) pathogens were susceptible. For ampicillin/probenecid, 33 of 33 (100%) pathogens were susceptible. For 13 patients, susceptibility was tested for norfloxacin but not for ampicillin. Data were incomplete for 22 patients.

Two norfloxacin patients and four ampicillin/probenecid patients were not evaluable because of inadequate cultures. In addition, three ampicillin/probenecid patients were unevaluable because bacteriology was not proven (2) and because the clinical diagnosis was not clear (1).

Pathogens from all evaluable patients were eradicated. The microbiological outcome is shown in the following table:

N. gonorrhoeae	Norfloxacin		Ampicillin/Probenecid	
	Eradicated	Persisted	Eradicated	Persisted
Norfloxacin susceptible (Pcnase negative)	20 (100%)	0	14 (100%)	0
Susceptibility not tested	6	0	8	0
Total	26 (100%)	0	22 (100%)	0

The symptomatic outcome for evaluable patients is shown below:

	Norfloxacin	Ampicillin/Probenecid
Symptom-Free	22 (88%)	18 (82%)
At Least One Symptom Present	3 (12%)	4 (18%)
Total	25	22

There was no significant difference between rates. One norfloxacin-treated patient who did not have signs or symptoms is excluded.

In the norfloxacin group, one patient continued to have a urethral discharge. One patient had a urethral discharge before therapy but the discharge had changed to mucoid at the post-therapy visit. One patient continued to have a vaginal discharge. In the ampicillin/probenecid group, two patients had a urethral discharge before therapy but the discharge was mucoid after treatment. One patient continued to have dysuria and had a purulent urethral discharge before therapy but the discharge was mucoid after therapy. One patient continued to have a vaginal discharge and developed dysuria at the post-therapy visit.

Adverse experiences and adverse laboratory effects are summarized below:

	Norfloxacin	Ampicillin/Probenecid
<u>Adverse Experiences</u>		
Not Serious but Drug-Related		
Dizziness	1	0
Headache and Nausea	1	0
Nausea alone	0	1
No. Pts. with Adverse Reactions	2 (7.1%)	1 (3.4%)
No. Pts.	28	29
<u>Adverse Laboratory Effects</u>		
Dec. WBC, elevated Lymphocytes, Alk. phos. and LDH		1
Band Neutrophils	1	
Lymphocytes	3	1
Eosinophils	1	
Elevated AST and ALT		1
Urine Glucose	1	
Nonamorphous crystals	1	
No. Pts with Adverse Lab	7 (25%)	3 (10.3%)
No. Pts	28	29

The applicant concludes that norfloxacin is active in vitro against N. gonorrhoeae. It is effective in treating gonococcal urethritis and cervicitis. Norfloxacin is as safe as ampicillin when used to treat

gonorrhoeal infection.

Reviewer's Comments:

1. Although norfloxacin is probably effective, data from this study are inadequate to show that norfloxacin is effective in treating gonococcal urethritis and cervicitis. There were only two evaluable females in the norfloxacin group and only five in the control group. Susceptibility was not tested for one of the two norfloxacin females and for four of the five control female cases. For a common infection like gonorrhoeal infection, at least 75 or 100 cases would be needed. The same is true for males: in this study, there were only 24 evaluable males in the norfloxacin group and only 17 in the control group. These low numbers might be acceptable for a rare infection but they do not represent the substantial data needed for a common infection like gonorrhoeal infection.
2. The applicant's clinical outcome criteria which mistakenly included microbiological outcomes were disregarded. The medical officer graded clinical outcome on the presence or absence of signs and symptoms.
3. The fact that one norfloxacin-treated patient had nonamorphous crystals after only two 600-mg doses four hours apart may be significant.
4. Post-therapy cultures should have been obtained 4-7 days after therapy instead of 3-7 days after therapy.
5. No diaries were used in this study.
6. The applicant has mistakenly classified isolates for which there was no susceptibility testing with evaluable cases. These cases should be disqualified. Strains from only 19 of the 24 males in the norfloxacin group, 13 of 17 males in the control, and for only two females were tested for susceptibility.

3. Uncontrolled Clinical Studies

a) Acute Bacterial Gastroenteritis

Study No. 31 Mark J. Kunkel, M.D., Director of Diagnostic Virology Laboratory and Consultant in Infectious Disease, Danbury Hospital, Danbury, CT, studied norfloxacin in doses of 400 mg tid in the treatment of acute bacterial gastroenteritis. Of 14 patients, nine were evaluable.

Campylobacter jejuni had been eradicated from eight of the nine patients (89%) five days after norfloxacin was stopped. One patient experienced taste perversion, irritability, and euphoria. One patient had paresthesia and headache. One patient had dizziness and headache. One had joint pain.

Medical Officer's Comment: This diarrhea study had been placed "on hold" status pending evaluation of a report of a Phase I tolerance study of norfloxacin in doses as high as 1200 mg/day. This study had already been in progress. The applicant mistakenly classified this report with controlled trials. The reviewer put it with uncontrolled trials.

(b) Urinary Tract Infections - Two multiclinic studies were conducted.

(b) (1) Protocols No. 011 and 017 - Domestic Studies A multiclinic uncontrolled study of norfloxacin in the treatment of complicated and uncomplicated urinary tract infections in men and women over 18 years of age was conducted at eight clinical centers. The following investigators participated in this trial and treated the number of patients shown:

Study No. 37 Ellie J.C. Goldstein, M.D., R. M. Alden Research Laboratory and Associate Clinical Professor of Medicine, U.C.L.A. School of Medicine, Los Angeles, California. (Qualified for efficacy evaluation: 11/14 patients)

Study No. 38 Lloyd Harritage Harrison, M.D., Professor of Surgery, Department of Surgery, Division of Urology, Bowman Gray School of Medicine, Winston-Salem, North Carolina. (Qualified for efficacy evaluation: 14/19)

Study No. 27 Mark J. Kunkel, M.D., Director Virology Laboratory, Consultant in Infectious Disease, Danbury Hospital, Danbury, CT. (Qualified for efficacy evaluation: 14/16)

Study No. 25 Ralph R. Landes, M.D., Danville Urology Clinic, Danville, Virginia. (Qualified for efficacy evaluation: 28/36)

Study No. 36 Anthony Joseph Schaeffer, M.D., Associate Professor, Department of Urology, Northwestern University Medical School. (Qualified for efficacy evaluation: 15/19)

Study No. 40 Rodney M. Snow, M.D., Norwood Clinic, Inc., Birmingham, Alabama. (Qualified for efficacy evaluation: 5/11)

Study No. 35 Frank E. Thomas, M.D., Assistant Professor of Medicine, Meharry Medical College, Nashville, TN. (Qualified for efficacy evaluation: 0/1)

Study No. 28 W. Glen Wells, Jr., M.D., Brookwood Medical Center, Birmingham, Alabama. (Qualified for efficacy evaluation: 11/21)

Male or female patients with symptomatic urinary tract infections were selected to receive one 400-mg tablet of norfloxacin twice daily. The treatment period was at least seven days for lower urinary tract infections and at least ten to fourteen days for upper urinary tract infections. Exclusions were similar to those given above for controlled trials. Urine specimens were obtained for culture within 48 hours of the initiation of treatment, during the first 2-4 days of therapy, 5-9 days after completion of therapy, and 4-6 weeks after completion of therapy. The 4-6 week culture was optional. Appropriate physical examinations and laboratory studies were conducted. Ophthalmological and neurological tests were conducted before treatment and again at the one-week follow-up visit.

In studies of Drs. Goldstein, Harrison, Schaeffer, Snow, and Thomas, patients were to complete diary cards on which they described how they felt each day of

the study. The investigator was to review each diary card and comment on any adverse clinical experiences noted by the patient. In other studies, adverse reactions were to be recorded by the investigator.

There were 137 treatment courses given to 136 patients. Patients were mostly female (72%) and most infections were uncomplicated infections (61%) caused by a single pathogen (79%). Of these, 97 patients (courses) were evaluable for efficacy. The mean duration of therapy was 13 days. The mean duration for evaluable patients was 14.9 days and 90.8% of infections in evaluable patients were due to single pathogens.

Characteristics of evaluable patients are shown in the following table:

Age (yrs.)	Males	Females	Total
18-21	2	2	4
22-30	1	20	21
31-40	3	9	12
41-50	1	7	8
51-60	6	2	8
61-70	5	10	15
71-80	7	13	20
81-90	5	5	10
Total No.	30	68	98
Mean Age	61.3	49.4	53.0
Minimum	20	19	19
Minimum	87	90	90

The microbiological outcome for evaluable patients is given below:

	# Eradicated/# Susceptible	
Gram-positive		
<u>Staphylococcus sp.</u>	1/1	
<u>S. aureus</u>	2/3	
<u>S. epidermidis</u>	3/3	
<u>Staphylococcus, coag.-</u>	1/1	
Streptococci Group D	1/1	
Strep. Grp D enterococci	2/4	
Strep. beta-hemolytic	1/1	
Total Gram-positive	11/14	(79%)
Gram-negative		
<u>Acinetobacter sp.</u>	0/1	(One developed resistance)
<u>Citrobacter freundii</u>	3/3	
<u>E. aerogenes</u>	2/3	
<u>E. agglomerans</u>	1/1	
<u>Escherichia coli</u>	43/44	
<u>K. pneumoniae</u>	8/8	
<u>Proteus species</u>	1/1	
<u>P. vulgaris</u>	1/1	
<u>Pseudomonas aeruginosa</u>	13/15	(One developed resistance)
Total Gram-negative	81/86	(94%)
All	92/100	(92%) 6 persisted 2 acquired resistance

In regard to signs and symptoms, 76 of 89 patients (85%) who were symptomatic before therapy were symptom free at their post-therapy visit. Thirteen patients had at least one symptom at the follow-up.

Adverse reactions were experienced by 14 of 136 patients (10.3%) and adverse laboratory events were reported for 5 of 136 patients (3.7%).-

	<u>No. patients</u>
Adverse Reactions	
Nausea and headache	1
Nausea	2
Dizziness	1
Dizziness, nausea, tinnitus	1
Taste perversion	1
Dream abnormalities	1
Flatulence	1
Musculoskeletal disorders	1
Insomnia	1
Vaginal discharge	1
Headache	1
Dry skin	1
Constipation	1
Total	14 (10.3%)
Adverse Laboratory Reports	
Elevated Alk. Phosphatase	3
Elev. ALT/Dec. Seg. Neutrophils	1
Elevated BUN	1
Total	5 (3.7%)

The applicant concludes that norfloxacin is active in-vitro against uropathogens, that it is effective in treating urinary infections due to both gram positive and negative bacteria, that it is effective in treating complicated and uncomplicated infections whether polymicrobial or monomicrobial in nature, and that norfloxacin is safe in the treatment of these infections.

Medical Officer's Comment:

1. The applicant reports that patient diaries were kept in five of these eight studies, yet, completed diaries cannot be located. At least 100 patient diaries were requested. Patient diaries should be handwritten by the patient and should not be transcribed or altered in any way. Original unaltered diaries should have been filed as part of the case report forms. During the norfloxacin IND period, we talked about patient diaries as follows: Conference with Merck 8-18-82, TC 12-13-82, MOR 8-19-82, Letter to Merck 9-10-82, Letter from Merck 11-10-82, TC 3-11-83, MOR 12-19-83, and End of Phase II Conference 12-8-83.
2. The applicant's clinical outcome criteria which mistakenly included microbiological outcomes were disregarded. Clinical outcome was graded on the presence or absence of signs and symptoms.

b) (2) International Studies (Protocols No. 506-01 and No. 508-01) A multiclinic uncontrolled study of norfloxacin in the treatment of complicated and uncomplicated urinary tract infections in men and women over 18 years of age was conducted at 19 clinical centers in twelve countries. The protocols were essentially the same as the one for the domestic study of urinary tract infections described above (Section 3.b.1.) except for tablet strength. In Protocol No. 506-01, patients received two 200-mg tablets twice daily (five investigators), and in Protocol No. 508-01, patients received one 400-mg tablet twice daily (24 investigators).

The following investigators participated in this trial and treated the number of patients shown:

Study No. 554 Pr. J. L. Albarede, Hospital Purpan, Toulouse, France. (Qualified for efficacy evaluation: 4/8)

Study No. 545 Dr. Carlo P. Baccarani, Primario Divisione Urologica, Ospedale degli Infermi, Rimini, Italy. (Qualified for efficacy evaluation: 11/15)

Study No. 535 Prof. Alberto Baglioni, Primario Chirurgo, Ospedale Generale Provinciale "SS. Trinita", Sora (Fr), Italy (Protocol #506-01). (Qualified for efficacy evaluation: 14/15)

Study No. 539 Ross Raymond Bailey, M.D., Department of Nephrology, Christchurch Hospital, Christchurch, New Zealand. (Qualified for efficacy evaluation: 7/10)

Study No. 549 Dr. Michael John Bendall, Senior Lecturer/Consultant Physician, Department of Health Care of the Elderly, University of Nottingham, Sherwood Hospital, Nottingham, UK. (Qualified for efficacy evaluation: 3/3)

Study No. 538 Prof. Dr. med. P. Bruehl, Department of Urology, University of Bonn, Venusbery, West Germany. (Qualified for efficacy evaluation: 10/15)

Study No. 565 Prof. W. Brumfitt, Head of the Department of Medical Microbiology, Royal Free Hospital, Hampstead, London, UK. (Qualified for efficacy evaluation: 4/5)

Study No. 542 Dr. Franco Clara, Ospedale civico, Lugano, Switzerland. (Qualified for efficacy evaluation: 1/16)

Study No. 564 N. Desplaces, M.D., Hospital St. Joseph, Paris, France. (Qualified for efficacy evaluation: 0/3)

Study No. 530 Prof. C. Dimopoulos, Department of Urology, University of Athens Medical School, Athens, Greece. (Qualified for efficacy evaluation: 12/15)

Study No. 518 Dr. Roberto Esguerra, Hospital Militar Central, Bogota, Colombia, So. America. (Qualified for efficacy evaluation: 11/15)

- Study No. 551 Prof. D. Fries, Hospital Paul Brousse, Villejuif, France. (Qualified for efficacy evaluation: 3/13)
- Study No. 534 Prof. Antonio Furbetta, Direttore della Cattedra di Urologia Ginecologica, University of Rome, Rome, Italy (Protocol #506-01). (Qualified for efficacy evaluation: 9/15)
- Study No. 533 Prof. Carlo Grassi, Clinica Tisiologica e Malattie dell'Apparato Respiratorio, University of Pavia, Pavia, Italy (Protocol #506-01). (Qualified for efficacy evaluation: 9/15)
- Study No. 541 W. D. Heinrich, Urologist, Essen, West Germany. (Qualified for efficacy evaluation: 12/15)
- Study No. 528 PD Dr. K. Hell, Kantonsspital, Liestal, Switzerland. (Qualified for efficacy evaluation: 2/6)
- Study No. 537 Dr. med. J. Jost, Urologist, Furstenfeldbruck, West Germany. (Qualified for efficacy evaluation: 9/15)
- Study No. 532 R. Kloek, Private Practice, Heemskerk, The Netherlands. (Qualified for efficacy evaluation: 4/12)
- Study No. 519 Louis Laplante, M.D., Assistant Professor, School of Medicine, University of Montreal, Hospital Maisonneuve-Rosemont, Montreal, Quebec, Canada. (Qualified for efficacy evaluation: 5/12)
- Study No. 555 Donald Albert Leigh, M.D., Consultant Bacteriologist, Wycombe and Amersham District General Hospitals, High Wycombe, Buckinghamshire, England. (Qualified for efficacy evaluation: 1/6)
- Study No. 548 John Rees Morgan, Senior Lecturer, Department of Medical Microbiology, Welsh National School of Medicine, Cardiff, Wales, United Kingdom. (Qualified for efficacy evaluation: 3/9)
- Study No. 544 Prof. Aldo Pauselli, Clinica Urologica, Ospedale Provinciale "S. Maria," Terni, Italy (Protocol #506-01). (Qualified for efficacy evaluation: 15/15)
- Study No. 531 Dr. J. Pretorium, Sandton Clinic, Peter Place, Lyme Park, Sandton, South Africa. (Qualified for efficacy evaluation: 10/13)
- Study No. 504 Nelson Rodrigues Netto Junior, Faculdade de Ciências Médicas-UNICAMP, Campinas, Brazil. (Qualified for efficacy evaluation: 13/18)
- Study No. 546 J. P. Schepers, Gynecology Department, R. C. Hospital, Sittard, The Netherlands. (Qualified for efficacy evaluation: 9/21)
- Study No. 536 Albrecht Schilling, M.D., University Hospital for Urology, University of Munich, Munich, West Germany. (Qualified for efficacy evaluation: 13/15)

Study No. 516 Prof. Andrea Trenti, "Primario Chirurgo," Gubbio Hospital, Gubbio (Perugia), Italy (Protocol #506-01). (Qualified for evaluation: 14/15)

Study No. 559 Dr. P. Vialatte, Department Head, Visceral Surgery, Hospital St. Michel, Paris, France. (Qualified for efficacy evaluation: 0/1)

Study No. 552 Dr. D. White, Public Health Laboratory, Royal United Hospital, Combe Park, Bath, UK. (Qualified for efficacy evaluation: 1/4)

For analysis, the applicant divided patients into two groups: evaluable and assessable. Evaluable patients were those who contributed bacteriological data. Assessable patients were those in whom follow-up cultures were not taken within the specified day ranges or those who had only one follow-up post-therapy urine culture. However, having met all other criteria for evaluability, a bacteriological outcome could be determined in these patients. The applicant reports that for these patients a single post-therapy urine culture obtained within 20 days after drug discontinuation determined bacteriological outcome.

Another change was that a pretherapy culture obtained within 12 days before initiation of the study was acceptable.

Patients with bacteriological outcomes of "suppressed" (during therapy culture equal to or less than 10^4 but post-therapy culture greater than 10^4) and "persisted" were treatment failures.

The five Italian investigators who gave two 200-mg tablets twice daily treated 75 patients and other investigators treated 265 patients, a total of 340 patients. One investigator, Dr. Rodriguez-Netto, conducted neurological examinations before and after therapy on 18 patients.

Of the 340 patients, the applicant found 209 evaluable patients. The distribution by age and sex is shown below:

Age (yrs.)	Males	Females	Total
No data		1	1
5-19	1	7	8
20-29	4	27	31
30-39	4	21	25
40-49	10	21	31
50-59	14	25	39
60-69	14	17	31
70-79	20	17	37
80-89	1	4	5
90-99		1	1
Total No.	68	141	209
Mean Age	57.5	47.0	50.4
Minimum	13	9	9
Maximum	81	90	90

The applicant reports microbiological outcome (number eradicated/number of patients) for evaluable patients as follows:

	Upper UTI	Lower UTI	Total
Complicated UTI	12/14	50/57	62/71
Uncomplicated UTI	22/29	103/109	125/138
Total	34/43	153/166	187/209

Forty-three clinical adverse experiences were reported in 27 patients. Some of them are listed below.

	No. patients
Serious and definitely drug related	
Anxiety, dry mouth, tachycardia, rash, tongue enlargement, euphoria, accommodation disorder (Day 1)	1 Recovered
Serious and probably not drug related	
Fever, purpura, knee pain (Day 2)	1 Recovered
Serious and not drug related or other	
Severe convulsive disorder (Day 1)	1 Recovered
Congestive heart failure (Day 18)	1 Died
Cerebrovascular accident (Day 41)	1 Died
Shock, hypovolemia (Day 6)	1 Died
Acute myocardial infarction (Day 6)	1 Died
Hypovolemic shock (Day 31)	1 Died
Other	
Cutaneous rash	1
Nausea	3
Nausea and vomiting	1
Heartburn	1

Only 14 of the 43 adverse reactions are summarized. (The above table is the medical officer's combination of two summary tables.)

Forty patients (12%) had laboratory adverse experiences. None were reported to be serious, definitely or probably drug related. None were statistically significant. Drug crystalluria which was reported for one patient during therapy disappeared in the post-therapy urinalysis. There is no summary table of abnormal laboratory values. Summary tables compare pretherapy mean values with post-therapy mean values but do not list the 40 adverse laboratory experiences.

The applicant concludes that norfloxacin has excellent in vitro antimicrobial activity against bacteria encountered in upper and lower UTI. It is effective in women and men in the treatment of upper and lower UTI caused by susceptible bacteria. It is effective in UTIs caused by *P. aeruginosa* in patients without severe structural or functional abnormalities of the urinary tract. It is effective in the treatment of acute pyelonephritis and complicated UTIs caused by susceptible bacteria. Norfloxacin is well tolerated at oral doses of 400 mg twice daily for ten days. Norfloxacin has a good safety profile for oral

administration at these doses.

Medical Officer's Comments: This study has not been analyzed in such a manner that one can come to these conclusions. The applicant should re-analyze this study so that the following deficiencies are corrected:

1. The clinical outcome criteria which contain microbiological assessments should be disregarded. The clinical outcome should be based upon a comparison of the presence or absence of signs and symptoms before and after therapy.
2. "Assessable" patients should be regarded as unevaluable patients.
3. Patients with pretherapy urine cultures obtained earlier than 48 hours before the initiation of treatment should be considered unevaluable. In this study pretherapy cultures were considered if they were obtained within 12 days of the initiation of treatment.
4. Culture timing requirements are not acceptable and should be revised to be in keeping with FDA guidelines for the treatment of urinary tract infections. In this study, they were changed from those specified in FDA's guidelines that were used in other studies to read as follows:

Relative-Day Ranges (page I-6157, Vol 2.17)

Protocol	Actual	Nomenclature Used in Text
Day 3 or 4 during therapy	Days 2 to 5 during therapy	During therapy
5 to 9 days post-therapy	5 to 20 days post-therapy	Post-therapy
4 to 6 weeks post-therapy	25 to 48 days post-therapy	Late post-therapy

5. Patients under 18 years of age should be disqualified. There are approximately eight, the youngest was 9 years old.
6. No effort should be made to separate upper and lower urinary tract infections because of the impreciseness of the diagnostic technique.
7. The report lacks a summary table which gives the microbiological outcome according to uropathogens.
8. Adverse reactions are tallied in the appendix but the report lacks a summary table to show all 43 adverse reactions. Unfortunately, no patient diaries were used in this study.
9. Summary tables compare pretherapy mean values with post-therapy mean values but do not list the 40 adverse laboratory experiences.

c) Compassionate Treatments

(c) (1) Treatment of Salmonellosis

Studies No. 61, 62, 63, 67, and 71 Two investigators used norfloxacin on a compassionate basis to treat six patients for salmonellosis. Investigators were

Robert Lyons, M.D., St. Francis Hospital, Hartford, CT. (Qualified for efficacy evaluation: 4/5)

Howard A Nadworny, M.D., St. Mary's Hospital, Waterbury, CT. (Qualified for efficacy evaluation: 1/1)

Norfloxacin was given in doses of 400 mg twice daily (4 patients) and three times daily (1 patient) for 8-22 days. One patient who was treated twice was treated for 43 days. There were three females and two males. Three patients were 83 years of age, one was 88 and the other was 62. Salmonella species isolated from each patients were susceptible to norfloxacin. The organism was eradicated after norfloxacin treatment in three of the five patients. One patient developed eosinophilia.

The applicant concludes that norfloxacin is effective in the eradication of salmonellosis in patients with active infection or chronic carrier states. The applicant concludes that norfloxacin is safe when given as 400 mg bid for up to 43 days to treat salmonellosis.

Reviewer's Comments: Data from this study are inadequate to draw these conclusions.

(c) (2) Treatment of Multiple Antibiotic Resistant Infections

Studies No. 68, 23, 33, 20, 22, 69, 42, 43, 44, 52, 47 Seven investigators in United States treated thirteen patients compassionately for infections due to organisms resistant to multiple antimicrobial agents. The investigators are listed below.

Study No. 23 Myles Gombert, M.D., SUNY Downstate Medical Center, Brooklyn, NY. (Qualified for efficacy evaluation: 1/1)

Studies No. 20 and 22 Ralph Landes, M.D., Danville Urologic Clinic, Danville, VA. (Qualified for efficacy evaluation: 2/2)

Studies No. 42, 43, 44, and 52 John Ryan, M.D., West Haven V.A. Hospital, West Haven, CT. (Qualified for efficacy evaluation: 4/4)

Study No. 47 James Tan, M.D., Professional Center, Akron, OH. (Qualified for efficacy evaluation: 1/1)

Study No. 33 H. Bradford Hawley, M.D., Good Samaritan Hospital, Dayton, OH. (Qualified for efficacy evaluation: 1/1)

Study No. 68 S. Fikrig, M.D., SUNY Downstate Medical Center, Brooklyn, NY. (Qualified for efficacy evaluation: 1/1)

Study No. 69 Wick Many, M.D., 3439 Prytania, Suite 508, New Orleans, LA. (Qualified for efficacy evaluation: 1/1)

Ten patients were treated for complicated urinary tract infections. One seven-year old boy with chronic granulomatous disease of childhood and who was treated for salmonellosis was a special entry patient. Doses varied from 100 mg tid to 400 mg bid. Repeat courses for two of these patients are not included in the analysis.

Microbiological outcome is summarized as follows

	Eradicated	Persisted/Suppressed
<u>P. aeruginosa</u>	3/8	5/8
<u>E. coli</u>	0/1	1/1
<u>S. epidermidis</u>	0/1	1/1
<u>Salmonella species</u>	0/1	1/1

Eight of eleven treatments were failures, three were successes.

One patient had an adverse experience, insomnia. The seven-year old boy had close neurological and ophthalmological supervision during therapy. A line walk and observation for joint pain and limp were performed. No such adverse experiences occurred.

The applicant does not draw conclusions from these studies.

✓ Medical Officer's Comment: The applicant did not include these data in the total data on efficacy in this NDA. They should have been included.

d) Suppression of Aerobic Bowel Flora in Patients With Granulocytopenia

d) (1) Studies No. 19 and 15 Two investigators participated in a double-blind, randomized controlled trial of norfloxacin plus nystatin and placebo plus nystatin in the prevention of infections in patients with neutropenia. Investigators were

Study No. 19 Robert Harold Rubin, M.D., Associate Professor of Medicine, Massachusetts General Hospital, Boston, MA. (Qualified for efficacy evaluation: 0/4. Qualified for safety evaluation: 4/4.)

Study No. 15 George Harrison Talbot, M.D., Hospital Epidemiologist, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania. (Qualified for efficacy evaluation: 0/19. Qualified for safety evaluation: 19/19.)

Patients enrolled in this study received either one 400-mg tablet of norfloxacin tid or one tablet of placebo tid. In addition, all patients received 1.0 mg of nystatin, 100,000 units per ml. qid.

There were 27 treatment courses given in these two studies to 23 patients. Twelve were treated with norfloxacin/nystatin and eleven with placebo/nystatin. Only the first entry of multiple-entry patients was included in the safety analysis.

Nine patients (75%) treated with norfloxacin and seven patients (64%) treated with placebo reported one or more adverse effects. None was considered by the investigator to be drug related. The applicant reports them as follows:

Clinical Adverse Experiences (Table S1 - Vol. 2.20, p. I-07158)

	Placebo (n=11)		NOROXIN™ (n=12)	
<u>Drug Related</u>	0		0	
<u>Serious</u>	3	(1)	3	
Peripheral Nervous System Disorder	1		0	
Fungus Infection	1		2	
Blood Stream Infection	1		0	
Intra-abdominal Abscess	1		0	
Death	2	(1)	3	
Intra-cerebral hemorrhage	0	(1)	0	
Pneumonia	0		1	
<u>Not Serious</u>	7 ^a	(1)	9 ^a	(1)
Nausea	1		3	
Diarrhea	5	(1)	6	
Visual Disturbances	0		1	
Rash	4		5	(1)
Flatulence	1		0	
Vomiting	3	(1)	0	
Jaundice	0		1	
Anorexia	1		2	
Fever	3		2	
Pharyngeal Pain	0		1	
Melena	0		1	
Headache	0		1	
Epistaxis	0		1	
Abdominal Pain	1		1	
Gingivitis	0		1	
Cough	1		0	
Nasal Congestion	1		0	
Dysphagia	1		0	
Mouth Ulcer	1		0	
Pneumothorax	1		0	
Dysuria	1		0	
Anal and Rectal Pain	1		0	
Total Single Entry Patients with at Least One Adverse Experience	7	(64%)	9	(75%)
Total Single Entry Patients without Adverse Experience	4	(36%)	3	(25%)
Total Single Entry Patients	11		12	

(#) number of multiple entry patients with AE.

(a) Three patients had both serious and not serious adverse experiences.

Five patients treated with norfloxacin and one patient treated with placebo had laboratory values that were considered adverse by the investigator. This difference was not significant.

<u>Adverse Laboratory Experiences</u>	<u>Placebo/N</u>	<u>Norfloxacin/N</u>
Drug Related	0	0
Not Drug Related		
Elevated AST and Urine Glucose	0	1
Elevated Total Serum Bilirubin	0	3
Elevated Alk. Phos. and/or Serum LDH	0 (1)	1
Elevated Urine RBC	0	1
Elevated Urine WBC	1	0
Elevated Urine Protein, WBC, RBC	0	1
Total Number of Patients with Laboratory Adverse Experience	1 (9.1%)	5 (41.7%)
Total Number of Patients without Laboratory Adverse Experience	10 (90.9%)	7 (58.3%)
Total	11	12

() Number of multiple-entry patients with adverse laboratory experience.

The applicant concludes that there appear to be no differences between the number of adverse experiences with norfloxacin and placebo. The types of adverse experiences are similar. Norfloxacin appears to be as safe as placebo when given to patients who are neutropenic.

Medical Officer's Comments:

1. The applicant failed to analyze these data for efficacy or to explain why this was not done. The medical officer's review of the data reveals that cases cannot be evaluated for efficacy because all patients received one or more other highly active antibiotics that interfered with the evaluation of outcome due to the test regimens. One patient received thirteen antibiotics, one received ten, seven received between 7 and 9, and the rest received one or more other antibiotics.
2. Unfortunately, no diaries were kept in this study. Diaries from patients receiving this high dose, 1200 mg/day, would have been important for the evaluation of daily side effects.
3. A norfloxacin adverse reaction rate as high as 75% seems to be unacceptable. At the same time, an adverse reaction rate in the placebo group of 64% is not to be consistent with what might be expected with placebo. (Oral nystatin is considered to be well tolerated. Large oral doses have occasionally produced GI reactions but these were not large doses.) The applicant's summary of adverse reactions is difficult to interpret. Adverse reactions as summarized by the reviewer are shown below.

Case #		Norfloxacin/ Nystatin	Placebo/ Nystatin
#403	Nausea, Diarrhea, Anorexia, Fever	1	
#404	Diarrhea	1	
#406	Nausea, Rash, Visual Disturbances	1 Disc.	
#408	Rash (Re-entry of #402)	1 Disc.	
#411	Fungus Infection, Pharyngeal Pain, Melena, Rash, Death*	1	
#414	Anorexia, Headache, Diarrhea, Jaundice	1	
#418	Diarrhea, Pneumonia, Death*	1	
#419	Diarrhea, Rash	1	
#477	Fungus Infection, Diarrhea, Rash Death*	1	
#480	Epistaxis, Fever, Abdominal Pain, Rash, Gingivitis, Nausea	1 Disc.	
#401	Fever, Diarrhea, Flatulence (See #409 & #416)		1
#402	Fever Cough, Nasal Congestion, Vomiting, Dysphagia, Mouth Ulcer, Diarrhea, Rash (See #408)		1
#405	Anorexia, Nausea, Rash, Diarrhea, Fungus Infection, Death*		1
#407	Peripheral Nervous System Disorder Rash		1 Disc.
#409	Diarrhea, Vomiting (Re-entry #401)		1 Disc.
#410	Vomiting		1 Disc.
#413	Diarrhea, Vomiting, Rash, Blood- stream Infection, Intra-Abdom. Abscess, Death*		1
#416	Death*, Intracerebral Hemorrhage (3rd Entry for #401)		1
#479	Pneumothorax, Dysuria, Abdominal Pain, Diarrhea, Anal & Rectal Pain		1
	No. pts. with one or more adverse reactions	9 (75%)	7 (64%)
	No. pts. without adverse reactions	3	4
	Total	12	11

* Death not drug related.

d) (2) Study No. 24 Jack I. LeFrock, M.D., Chief, Division of Infectious Diseases and Clinical Microbiology, Hahnemann Medical College and Hospital of Philadelphia, initiated a randomized controlled study to compare a regimen of norfloxacin plus nystatin with a regimen of trimethoprim/sulfamethoxazole (TMP-SMZ) with nystatin in the prophylaxis of infections in patients with neutropenia. At the time this application was filed, two TMP-SMZ patients had been treated. Both patients experienced rashes which were considered possibly drug related.

4. Controlled Urinary Tract Infection Studies Filed for the Evaluation of Safety Only

a) Studies No. 507, 508, 512, 509, 510, and 511 Six investigators in two countries followed Protocol No. 503-01 to conduct a randomized, controlled, nonblinded comparison of norfloxacin and trimethoprim/sulfamethoxazole (TMP-SMZ) in the treatment of acute uncomplicated urinary tract infections. The following investigators participated in this study:

Study No. 507 Prof. Alberto Albertazzi, Chief of Urology Department, University of Chieti, Italy. (Qualified for efficacy evaluation: 10/10 norfloxacin patients and 10/10 TMP-SMZ patients)

Study No. 508 Prof. George K. Daikos, Head of the Department of Medicine, Athens University Medical School, Athens, Greece. (Qualified for efficacy evaluation: 8/10 norfloxacin patients and 10/10 TMP-SMZ patients)

Study No. 512 Prof. Rullio Lotti, Director of Urology Department, University of Naples, Italy. (Qualified for efficacy evaluation: 10/10 norfloxacin patients and 10/10 TMP-SMZ patients)

Study No. 509 Prof. Ettore Martini, Head of Urology, S. Salvatore Hospital L'Aquila, Italy. (Qualified for efficacy evaluation: 10/10 norfloxacin patients and 9/10 TMP-SMZ patients)

Study No. 510 Prof. Lucio Miano, Head of Urology Department, University of Rome, Italy. (Qualified for efficacy evaluation: 10/10 norfloxacin patients and 10/10 TMP-SMZ patients)

Study No. 511 Prof. Fabio Prosperi, Head of Urology Department, S. Camillo Hospital, Rome, Italy. (Qualified for efficacy evaluation: 8/10 norfloxacin patients and 6/10 TMP-SMZ patients)

Characteristics of evaluable patients are shown in the following table:

Age (yrs.)	Norfloxacin			TMP-SMZ		
	Males	Females	Total	Males	Females	Total
11-12	1	1	2			
13-17		1	1		1	1
18-21		3	3		2	2
22-30		7	7		11	11
31-40	1	10	11		7	7
41-50	3	8	11	1	6	7
51-60	4	4	8	2	8	10
61-70	5	2	7	7	3	10
71-80	4	2	6	6	1	7
Total No.	18	38	56	16	39	55
Mean Age	56.9	39.3	45.0	66.8	40.2	47.9
Minimum	12	11	11	44	16	16
Maximum	73	73	73	74	74	74

Patients selected for the study were ambulatory outpatients with urinary tract infections caused by bacteria proven susceptible to both norfloxacin and TMP-SMZ. Urine specimens were obtained for gram stain and ACB testing. Patients with positive ACB test results were withdrawn from the study and received appropriate alternate therapy. Exclusions were similar to those given for other UTI studies.

In this study, 115 patients received either 200 mg of norfloxacin bid or 80/400 mg of TMP-SMZ bid. The duration of treatment was ten days.

Although clinical visits were scheduled on Day 3 or 4 during therapy, five to nine days after therapy, and four to six weeks after therapy, some patients did not have their visits exactly at these times. A broader range for the collection of urine specimens for culture similar to the one that was used in the uncontrolled international UTI study, above, was used in this study as follows:.

Visit	Urine Specimen for Culture
Day 3 or 4 during therapy	Days 3 to 7 during therapy
5 to 9 days after therapy	5 to 14 days after therapy
4 to 6 weeks after therapy	20 to 88 days after therapy

Four patients in the norfloxacin group and five in the TMP-SMZ group were considered to be nonevaluable and were excluded from the analysis of efficacy because of inadequate bacteriological data.

Treatment groups differed markedly ($p = \text{less than } 0.0001$) with respect to baseline susceptibility patterns of causative pathogens. Twenty pathogens from 20 patients were susceptible to one study drug and not to the other and all received the drug to which the pathogen was susceptible. Eighteen of these patients were in the norfloxacin group. This strongly suggests that randomization was not strictly followed and is a source of bias.

The applicant reports microbiological outcome and clinical outcome for evaluable patients as follows:

	Norfloxacin	TMP-SMZ
Microbiological Outcome		
Eradicated	51 (94%)	45 (87%)
Suppressed/Persisted	3 (6%)	7 (13%)
Clinical Outcome		
Cured/Improved	52 (96%)	45 (87%)
Not Improved	2 (4%)	7 (13%)

E. coli, Proteus mirabilis, and K. pneumoniae were the most frequently isolated uropathogens. All others were isolated four times or less.

Only one patient reported a clinical adverse experience in this study. She experienced gastric fullness on the eighth day of treatment with TMP-SMZ. Three patients had adverse laboratory experiences and all occurred 5-9 days after treatment. One norfloxacin-treated patient had an increased bilirubin,

and two TMP-SMZ-treated patients experienced increased LDH and increased potassium, respectively.

The applicant concludes that norfloxacin has in vitro antimicrobial activity superior to that of TMP-SMZ against bacteria encountered in UTI, that it is at least as effective in the treatment of UTI, and that it is well tolerated and safe at oral doses of 200 mg twice daily for ten days.

After the cut-off date, five additional case reports were received. Three patients were treated with TMP-SMZ and two were treated with norfloxacin. There were no clinical or laboratory adverse effects.

Medical Officer's Comments: No conclusion can be drawn from this study.

1. This study cannot be used in the evaluation of efficacy for the following reasons:

- a) Removal of patients with positive tests for ACB after randomization and after treatment had begun biased results as does the assignment based upon the susceptibility of the pathogen.
- b) The change in the recommended times for the collection of urine specimens for culture is not acceptable as mentioned above on page 68 in the review of uncontrolled international studies.
- c) The medical officer agrees with the applicant's observation that there may be a randomization allocation bias because treatment groups differed significantly in regard to susceptibility patterns of uropathogens ($p = \text{less than } 0.0001$).
- d) The clinical outcome based upon a change in clinical signs and symptoms plus laboratory test results is not acceptable. Clinical outcome should be based upon signs and symptoms alone.

2. No diaries were reported for this study and there is no evidence that any special effort to observe the presence or adverse reactions was made.

3. There is no report of the presence or absence of drug crystallization in the urine.

4 (b) Studies No. 568, 567, 693, 573, 694, 574, and 692 Seven investigators in the United Kingdom participated in a multiclinic, randomized, controlled trial to compare a three-day course of norfloxacin with a three-day course of nalidixic acid/sodium citrate in patients twelve years of age or older in the treatment of uncomplicated urinary tract infections. Investigators were

Study No. 568 Adrian John Biut, M.B., Ch.B., Consultant Microbiologist, Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom. (Qualified for safety evaluation: norfloxacin 17/17 patients and 17/17 nalidixic acid patients)

Study No. 567 R. W. Lacey, M.D., District General Hospital, Kings Lynn, Norfolk, United Kingdom. (Qualified for safety evaluation: norfloxacin 43/43 patients and 16/16 nalidixic acid patients)

Study No. 693 Meena Manendra, M.B.B.S, Department of Microbiology, West Middlesex Hospital - Isleworth, Middlesex, U.K. (Qualified for safety evaluation: norfloxacin 11/11 patients and 11/11 nalidixic acid patients)

Study No. 573 Dr. R. V. Mummery, Consultant Microbiologist, Enfield District Hospital, Enfield, Middlesex, UK. (Qualified for safety evaluation: norfloxacin 17/17 patients and 21/21 nalidixic acid patients)

Study No. 694 S. W. B. Newson, M.D., Consultant Microbiologist, Addenbrooke's Hospital, Cambridge, U.K. (Qualified for safety evaluation: norfloxacin 5/5 patients and 5/5 nalidixic acid patients)

Study No. 574 David Sims Reeves, M.R.C.Path, Consultant Medical Microbiologist, Southmead Hospital Group, South Western Regional Hospital Board, Bristol, U.K. (Qualified for safety evaluation: norfloxacin 28/28 patients and 28/28 nalidixic acid patients)

Study No. 692 M. O. Unadkat, M.D., St. Johns Health Center, Twickenham, London, U.K. (Qualified for safety evaluation: norfloxacin 5/5 patients and 4/4 nalidixic acid patients)

Nonpregnant females and males 12 years and older with symptoms of uncomplicated urinary tract infections and with positive urine cultures were selected. There were 126 patients in the norfloxacin group and 102 in the nalidixic acid/Na citrate group. Patients received either one 400 mg tablet of norfloxacin twice daily or one sachet containing 0.66 g nalidixic acid and 3.75 g of sodium citrate (MICTRAL) three times daily for three days.

Clinical efficacy was judged by the investigator and specimens were obtained for the microbiological evaluation one week after the initiation of the three-day course. Another culture was obtained 4-6 weeks after therapy. There was no during-therapy culture.

The investigator monitored and recorded adverse experiences volunteered by the patient. There were no serious adverse reactions. No laboratory adverse experiences were reported in these studies. Some patients had more than one adverse experience. Also, some patients had both drug related and non-drug related adverse experiences. Eleven patients had vaginal pruritis, irritation and discharge, and vaginitis monilial: these reactions were not considered adverse experiences.

Adverse reactions are summarized in the following table.

Adverse Reactions	Total		Drug-Related		Not-Related		Relationship Unknown	
	Norflx	Nal/Cit	Norflx	Nal/Cit	Norflx	Nal/Cit	Nor.	Nal/Cit
Abdominal Pain	1	1	0	0	1	0	0	1
Asthenia	1	1	0	1	1	0	0	0
Fatigue	3	3	0	1	3	1	0	1
Constipation	1	1	0	0	1	1	0	0
Diarrhea	3	7	1	0	2	7	0	0
Flatulence	0	1	0	0	0	1	0	0
Dry Mouth	0	1	0	1	0	0	0	0
Dyspepsia	1	1	1	1	0	0	0	0
Tongue Pain	0	1	0	0	0	1	0	0
Heart Burn	1	0	0	0	1	0	0	0
Mouth Ulcer	2	0	0	0	1	0	1	0
Nausea	11	20	4	10	6	10	0	0
Vomiting	0	3	0	1	0	2	0	0
Leg Pain	1	0	0	0	1	0	0	0
Depression	2	3	0	1	2	0	0	0
Weakness, local	1	1	0	0	1	1	0	0
Dizziness	5	7	2	1	3	5	0	1
Hallucinations	1	0	1	0	0	0	0	0
Explosive Personality Disorders	1	0	0	0	1	0	0	0
Headache	12	12	1	2	11	9	0	1
Somnolence	5	2	1	1	4	1	0	0
Rash	3	1	1	0	2	1	0	0
Flashing Lights	0	1	0	1	0	0	0	0
Dysmenorrhea	1	0	0	0	1	0	0	0
Vaginal Swelling	1	0	1	0	0	0	0	0
Breast Pain	0	1	0	0	1	0	0	0
Renal Colic	1	0	0	0	1	0	0	0
No. pts. with one or more ARs	38	44						
Percent (p = less than 0.05)	30.2%	43.1%						
Total Patients	126	102						

The applicant concludes that regardless of drug relationship, fewer clinical adverse experiences occurred with norfloxacin than with nalidixic acid even when nalidixic acid is given at two grams daily, one-half the recommended dose in United States.

Medical Office's Comments: (The reviewer redesigned the applicant's adverse reaction table to put drug-related, not-drug-related, and relationship-unknown adverse reactions side by side together with a total for each type of reaction.)

1. The reviewer agrees with the applicant in considering this study for safety only. A three-day course of nalidixic acid for the treatment of UTIs is not recommended in the labeling. Therefore, what was used as a control regimen is an investigational regimen. Also, FDA guidelines were

Adverse Reactions	Total		Drug-Related		Not-Related		Relationship Unknown	
	Norflx	Nal/Cit	Norflx	Nal/Cit	Norflx	Nal/Cit	Nor.	Nal/Cit
Abdominal Pain	1	1	0	0	1	0	0	1
Asthenia	1	1	0	1	1	0	0	0
Fatigue	3	3	0	1	3	1	0	1
Constipation	1	1	0	0	1	1	0	0
Diarrhea	3	7	1	0	2	7	0	0
Flatulence	0	1	0	0	0	1	0	0
Dry Mouth	0	1	0	1	0	0	0	0
Dyspepsia	1	1	1	1	0	0	0	0
Tongue Pain	0	1	0	0	0	1	0	0
Heart Burn	1	0	0	0	1	0	0	0
Mouth Ulcer	2	0	0	0	1	0	1	0
Nausea	11	20	4	10	6	10	0	0
Vomiting	0	3	0	1	0	2	0	0
Leg Pain	1	0	0	0	1	0	0	0
Depression	2	3	0	1	2	0	0	0
Weakness, local	1	1	0	0	1	1	0	0
Dizziness	5	7	2	1	3	5	0	1
Hallucinations	1	0	1	0	0	0	0	0
Explosive Personality Disorders	1	0	0	0	1	0	0	0
Headache	12	12	1	2	11	9	0	1
Somnolence	5	2	1	1	4	1	0	0
Rash	3	1	1	0	2	1	0	0
Flashing Lights	0	1	0	1	0	0	0	0
Dysmenorrhea	1	0	0	0	1	0	0	0
Vaginal Swelling	1	0	1	0	0	0	0	0
Breast Pain	0	1	0	0	1	0	0	0
Renal Colic	1	0	0	0	1	0	0	0
No. pts. with one or more ARs	38	44						
Percent (p = less than 0.05)	30.2%	43.1%						
Total Patients	126	102						

The applicant concludes that regardless of drug relationship, fewer clinical adverse experiences occurred with norfloxacin than with nalidixic acid even when nalidixic acid is given at two grams daily, one-half the recommended dose in United States.

Medical Officer's Comments: (The reviewer redesigned the applicant's adverse reaction table to put drug-related, not-drug-related, and relationship-unknown adverse reactions side by side together with a total for each type of reaction.)

1. The reviewer agrees with the applicant in considering this study for safety only. A three-day course of nalidixic acid for the treatment of UTIs is not recommended in the labeling. Therefore, what was used as a control regimen is an investigational regimen. Also, FDA guidelines were

not followed in this study.

2. Patients between 12 and 17 years of age should be disqualified from any type of evaluation.

3. Some adverse reactions which the investigator labeled not-drug-related reactions are very likely drug related and are typical of the type of adverse reactions that occur with the quinolones.

4 (c) Study No. 53 Allan Ross Ronald, M.D., Head, Section of Infectious Diseases, Department of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada, is conducting a randomized controlled study to compare norfloxacin and nalidixic acid in the treatment of patients with urinary tract infections. The study is ongoing. At the time the application was filed, 25 patients had been selected for the study, 12 in the norfloxacin group and 13 in the nalidixic acid group. Patients received either one 400-mg tablet of norfloxacin twice daily or one one-gram tablet of nalidixic acid qid for 7 to 14 days. All patients are completing diaries.

In these 25 reports, there were six patients with adverse reactions, three in each group as follows:

Norfloxacin	
#2113 Dry mouth, suprapubic pain, vaginal pain	Drug discontinued
#2132 Scratchy eyes	Drug discontinued
#2135 Headache, abdominal pain	Drug discontinued
Nalidixic Acid	
#2106 Nausea	Not discontinued
#2128 Emotional lability	Discontinued
#2131 Nausea	Not discontinued

Efficacy is not summarized or discussed. The applicant makes no attempt to draw conclusions from this study.

Medical Officer's Comments: There is clearly a difference between the way the applicant summarizes adverse reactions and the way the medical officer summarizes the same adverse reactions.

The medical officer reviewed the diaries in this study and found thirteen patients instead of six with adverse reactions to the two quinolones. Most of these reactions are typical of those which have been found with other quinolones. Diary entries which appear to be symptoms of the urinary tract infections were not included. Adverse reactions according to the MO's review of the diaries are listed as follows:

Norfloxacin

- #2101 Diarrhea, headache (8-day course)
 #2108 Slept poorly (6-day course)
 #2111 Very tired, no energy, bloated, chills (8-day course)
 #2113 Tired, thirsty, sweaty, uncomfortable, don't feel like walking, nausea, dry mouth, sick feeling in stomach
 #2132 Right hand tingles, eyes sore and sandy, burning eyes, eyes tired, sore and irritable, hands swollen, chills, nausea
 #2134 Nausea, backache (14-day course)
 #2135 Headache, wavy lights in right eye

Disc. Day 3Disc. Day 13Disc. Day 2Nalidixic Acid

- #2105 Aching legs, arms, and back (8-day course)
 #2106 Upset stomach (7-day course)
 #2114 Dizziness, cramps (5-day course)
 #2128 Tired, tense, edgy, bad nerves, real sick
 #2129 Tired, dizzy, weak (14-day course)
 #2131 Hard time getting to sleep, headache, sore stomach, dizzy

Disc. Day 7Disc. Day 4, Refused to return.AMENDMENTS:

April 2, 1985 In response to my request, the applicant files the interim summary of the dose-escalation, placebo-controlled study conducted by Dr. Roger Ferguson, Study No. 1. The report had been filed in the companion IND, instead of the NDA. As stated on pages 9 and 10 of this MOR, the report of this study in the NDA was incomplete. It lacked a report of the presence or absence of drug crystals. Urine was to be examined for crystals in the fractions collected 0-1, 1-2, 2-3, 3-4, and 4-6 hours after administration of norfloxacin. Urine volume and pH were to be measured, an aliquot was to be maintained in a 37° bath before being spun, and the sediment examined for the presence of crystals. There were 14 subjects in six treatment groups and 13 subjects in the highest dose treatment group.

The applicant reports that the review of the microscopic findings in the urine

regarding the presence of crystals shows that no morphological specificity was present since the type of crystals found in the urine after norfloxacin treatments were also present after treatment with placebo. Three types of crystals were identified, amorphous granular material, irregular spheres with multiplane and spiky edges, and spicule or needlelike crystals found individually or in small aggregations. The amorphous type material was extensively present following both placebo and norfloxacin treatments. No particular significance can be ascribed to it. Both the incidence and frequency of spherical and needle-like material do not support a drug-related increased potential for significant crystalluria. It should be noted that urinalysis did not show findings of mechanical irritation or other noxious effects on the urinary tract, i.e. increased urine content of red blood cells, white blood cells, renal tract epithelial cells, or protein in the norfloxacin-treated subjects. The number of urine samples with microscopic findings is shown below:

Treatment	No. Urine Samples Examined	Amorphous Granular Material	Spheres	Needle-like
Placebo	68	15	0	1
Placebo	67	24	2	1
Norfloxacin				
200 mg	69	9	1	0
400 mg	68	13	5	0
800 mg	70	27	3	0
1200 mg	69	34	5	3
1600 mg	64	19	3	6

The applicant concludes that, qualitatively, the crystals present in the urine could not be identified as being morphologically characteristic of the drug and their frequency did not suggest a potential for crystalluria, at least in the proposed therapeutic dose range of the drug.

Medical Officer's Comment: Unfortunately, crystals have not been identified. It is not known if these are crystals of norfloxacin or the metabolites of norfloxacin or crystals of something else. Similar data should be provided following multiple dosing and the crystals should be identified. Item #3 in FDA's letter to the applicant on June 17, 1981 about the IND reads, "Urine sediment should be examined for the presence of drug crystals in subsequent pharmacokinetic studies until it is established that drug crystallization is not a problem." The request following multiple dosing was specifically requested again in FDA's letter to Merck Sept. 10, 1982.

July 23, 1985 At the Swedish Microbiology Society Meeting, Professor Arne Forsgren reported his observation that stimulated T and B lymphocytes exhibited an increase in DNA synthesis (30-40%) as measured by incorporation of tritiated thymidine when ciprofloxacin, norfloxacin, and ofloxacin were added to the culture. He also found doubling of DNA synthesis when these quinolones are added to cultures of stimulated lymphocytes with hydroxyurea added to block S phase DNA synthesis. These were interpreted as induced repair synthesis. The number of DNA strand breaks studied in Epstein-Barr transformed lymphoblasts were also found to be increased when exposed to quinolones. The applicant gives six reasons why these observations of an apparent increase in induced DNA repair synthesis is of little significance as to human risk.

August 1, 1985 The applicant responds to a request from Dr. K-Y Lo of the Division of Biopharmaceutics for additional information.

September 13, 1985 In response to a telephone conversation with Mr. John Davitt, pharmacologist, the applicant files a copy of a published article by Dr. David Levin which provides the results of an Ames test using the Salmonella strain TA102.

Medical Officer's Comment: The applicant filed a 42-page computer printout instead of a simple half-page summary table. Adverse laboratory experiences are tallied from this printout by the MO as follows:

	Norfloxacin TMP-SMZ		Norfloxacin TMP-SMZ	
Hemoglobin dec.	4/184	9/174	ALT inc.	8/168 9/154
Hematocrit dec.	2/163	8/152	Alk. Phos inc.	4/166 10/156
WBC dec.	4/184	7/173	Serum LDH inc.	2/128 3/120
inc.	1/184	0/173	Ser. Na inc.	1/178 1/169
Neutrophil dec.	2/171	2/159	Ser. K dec.	2/178 2/169
Lymphocytes inc.	1/171	0/159	inc.	1/169
Eosinophils inc.	12/170	7/158	Ser. Cl inc.	3/132 5/126
Platelets inc.	2/176	4/153	dec.	4/132 1/126
dec.	1/176	1/153	Urine	
Blood urea inc.	1/34	1/36	Protein inc.	2/176 0/166
BUN inc.	3/149	3/132	Glucose inc.	2/176 0/164
Ser. creat. inc.	1/182	4/171	WBCs inc.	1/185 2/171
Tot S. Bilir. inc.	3/179	0/167	RBCs inc	2/175 1/166
AST	10/182	11/168	Hyaline casts	0/2 1/4

October 10, 1985 In response to my request, the applicant files copies of curricula vitae for clinical investigators.

October 18, 1985 In response to my request, the applicant indicates that 94 (83 norfloxacin and 11 nalidixic acid) patient diaries had been filed in the original application from four studies, #45, #59, #66, and #53.

Medical Officer's Comments:

1. The MO's reviews of these diaries will be found on pages 12-13, 17, and 79-80.

2. Diaries from Dr. Zinny's study #59 cannot be included as part of the minimum 100 diaries that FDA required because this study was a single-dose study. We asked for as many diaries as possible but we required a minimum of 100 patient diaries, diaries which were prepared by patients who were receiving full doses for the longest recommended treatment period.

In my telephone conversation with the director of regulatory affairs, I reminded him that patient diaries have been specifically requested with all of the quinolones to address drug safety. Therefore, the MO disqualifies diaries from Dr. Zinny's Study #59 in this regard. That leaves 63 norfloxacin diaries instead of 83 in the original submission. Dr. Zinny's single-dose study diaries show that 18% and 32% of subjects report adverse reactions after a single 400-mg tablet.

Under the norfloxacin IND, we talked about patient diaries as follows:

Conference with Merck 8-18-82	Telephone Call 3-11-83 (Design of
Telephone Call 12-13-82	the diary card)
MOR 8-19-82	MOR 12-19-83
Letter to Merck 9-10-82	End of Phase II Conference 12-8-83
Letter from Merck 11-10-82	

The failure to submit diaries is a major deficiency of the application. I would not consider the application completely filed until all patient diaries have been filed.

Undated Amendment Received October 30, 1985 In response to my request, the applicant rechecked its patient diaries and learned that diaries from 50 norfloxacin patients and 17 TMP-SMZ patients (total 67) from five other studies were available from investigators. These have never been submitted and are submitted now. The applicant, however, failed to summarize these diaries.

Medical Officer's Comment: These new diaries have been reviewed by the MO. Positive symptoms that are not related to the urinary tract infection are summarized by the medical officer as follows:

1. From the Phase III uncontrolled domestic urinary tract infection study (See 3 b (1), above.)

Study No. 40 Dr. Snow Five of six diaries are acceptable. Four of five patients had one or more effects.

- #2003 Slight headache all afternoon - Days 1-2. Slight headache all day - Day 8.
- #2006 Nauseated - Day 2.
- #2007 Felt bad - Day 2. Weak - Day 3.
- #2012 "First tablet vomited up" - Day 1. No vomiting - Day 2. Backache - Day 3.
- #2014 - Very weak all day and nervous - Day 1. Took two Urised tablets - Days 3, 4, 8, 13, and 17. Should be disqualified because of concomitant therapy.

Study No. 38 Dr. Harrison Nine of eleven patients reported one or more effects.

- #1804 Felt fine but did not sleep well - Day 1.
- #1812 A little tired and sleepy during the day - Day 5. Sleepless night - Day 6.
- #1807 Very drowsy and not very responsive - Day 3. Alert and very good - Day 4.
- #1805 Seemed quite tired but usually have this feeling when taking Septra also - Days 2, 3, and 4. Still extremely tired - Days 5 and 6. Some vision problem and experiencing tiredness - Days 7, 8 and 9. Back pains and extremely tired - Days 10-15.
- #1804 Recovering from previous stomach upset - Days 1-3. Washed out feeling - Day 4. Better but do not feel up to par - Day 5. Nervousness, sore tongue - Day 12.
- #1803 Stomach hurts - Day 4. Headache - Days 5-12. Hospitalized Day 8. "I never have headaches and I am still having them."
- #1802 Constipation - Day 5.
- #1806 Legs ached and went to bed after supper - Day 1. Dizzy - Day 2.
- #1815 Nausea and tense - Day 1. Not steady on feet, tired, vertigo-type sensation - Day 2. Dizzy, could not stand at first, tired, unsteady, headache in frontal area - Day 3. Tense, loss of equilibrium, very tired and wobbly - Day 4. Impossible to stand on first arising this AM for an hour, all day some rocky feeling - Day 5. Headache especially if I bend head downward, unsteady, very tired - Day 6. Pain top of head, face and upper body, wet with sweat, nausea, very tired - Day 7. Pain top of head, very tired, nausea - Day 8. Headache, nausea, balance unsteady, very tired - Day 9. Tired, nausea, "embalance," eyes hurt - Day 10. Slept 9 hours, unusual to sleep so long, awake with severe ache in forehead and eyes, lack of balance upon arising briefly, unsteady (No pills today) - Day 10. Resumed pills, dizziness - Day 12. Headache, very tense, eyes hurt, head swimming, nausea - Day 13. Eyes hurt - Day 14. Dizzy when held head up, unsteady - Day 16. (Some symptoms continued after treatment.)

Study No. 37 Dr. Goldstein Four of seven patients reported one or more effects.

- #1702 Headache and nausea - Day 1. Get very nauseous about 1 hour after taking pills - Day 2. Headache and nausea - Days 3-10.
- #1704 Headache approximately 1 hour after taking pill - Day 1.
- #1706 Tired and headachy, probably not related of medicine - Day 12.

#1707 Difficult to fall asleep - Day 1. Tired probably due to overwork - Day 4. Very tired but did double shift yesterday - Day 8. Itching of left eye - Day 9.

2. From the controlled domestic trial of norfloxacin and TMP-SMZ in UTI. (See section 2 a, above.)

Study No. 7 Dr. Ellie J. C. Goldstein Sixteen norfloxacin sheets and 17 TMP-SMZ sheets are filed.

None of the 33 check-off sheets are acceptable because they are not designed according to our agreement with the applicant about the design of patient diaries. It was agreed that there would be one question, "How do you feel?," with a blank space or blank lines for the patients to fill in his response to the question each day. Dr. Goldstein's diaries have five symptoms printed on the sheet for each treatment day with a check of block for a yes or no answer. This format does not give the patient the freedom to answer the question in his own words.

3. From the uncontrolled study of bacterial gastroenteritis (See section 3 a, above.)

Study No. 31 Dr. Mark J. Kunkel Ten norfloxacin sheets are filed.

None of these ten check-off sheets are acceptable, first, because of the same reason given for Dr. Goldstein's study, No. 7, above. One of the main purposes of these sheets was to determine the number of stools/day. Sheets also have four printed symptoms each with a yes or no to be circled daily in response to the question "Did you feel well today?"

They are also not acceptable because concomitant medications which were taken interfere with the evaluation of adverse effects. Concomitant medications taken by six of the ten patients were Bufferin, Aspirin, Aldactazide, Tylenol, and Ascriptin.

In summary,

1. Diaries reported to have been kept by the patients in the following studies are still missing:

Study No. 36 Dr. Anthony Joseph Schaeffer - The applicant reported in a telephone conversation 10-25-85 that Dr. Schaeffer threw his diaries away. Nineteen patients were treated.

Study No. 35 Dr. Frank E. Thomas - Only one patient was treated.

2. This October 30 amendment adds 23 acceptable norfloxacin diaries (27 are not acceptable). If these 23 are included with the 63 acceptable diaries filed in the original submission, a total of 86 acceptable norfloxacin diaries have been filed. This number falls short of the 100 norfloxacin diaries that were originally requested for the characterization of drug-induced adverse reactions.

3. The applicant failed to summarize diary information.

Also filed in the October 30 amendment is a table showing the microbiological outcome for evaluable patients in the 19-investigator, multiclinic, uncontrolled international urinary tract infection study (See section 3 b (2), above for Protocols No. 506-01 and 508-01).

<u>Gram Negative</u>	<u>Eradicated/ Total Isolated</u>	<u>Gram Positive</u>	<u>Eradicated/ Total Isolated</u>
<u>Citrobacter diversis</u>	2/2	<u>S. aureus</u>	5/5
<u>Citrobacter freundii</u>	3/4	<u>S. epidermidis</u>	3/3
<u>Enterobacter species</u>	1/1	<u>S. saprophiticus</u>	3/3
<u>Enterobacter cloacae</u>	1/2	<u>Enterococcus</u>	4/5
<u>E. agglomerans</u>	2/4	<u>S. faecalis</u>	4/4
<u>E. coli</u>	109/118	<u>Streptococcus</u>	1/1
<u>Klebsiella species</u>	1/1	<u>nonhemolytic</u>	
<u>Klebsiella oxytoca</u>	2/2		
<u>Klebsiella pneumoniae</u>	11/14		
<u>Morganella morganii</u>	1/1		
<u>Proteus species</u>	2/2		
(non-mirabilis)			
<u>Proteus indole positive</u>	3/3		
<u>Proteus mirabilis</u>	26/27		
<u>Proteus vulgaris</u>	3/3		
<u>Pseudomonas aeruginosa</u>	11/13		
<u>Pseudomonas cepacia</u>	1/1		
<u>Providencia stuartii</u>	1/1		
<u>Subtotals</u>	<u>180/199</u>		<u>20/22</u>
<u>Total eradicated</u>		<u>200/221 (90.5%)</u>	

Applicant's Efficacy Summary: The applicant summarized efficacy data for the four indications for evaluable patients in this application as follows. (Favorable Responses.* Protocol numbers are in parentheses.)

Indication & Claim No.	Organism	Controlled Trials		Protocol #	Uncontrolled Trials - Proto-	
		Norfloxac- acin	Control		#E/#I	col #
Urinary Tract Infections						
1.1	<u>E. coli</u>	53/54	58/59	(#001)	15/15	(#011)
		37/38	28/33	(#002)	29/30	(#017)
		78/82	84/94	(#504/505)	107/117	(#506/508)
	Total	168/174 (96.5%)	170/186 (91.4%)		151/162 (93.2%)	
1.2	<u>Klebsiella sp. including K. pneumoniae</u>	2/2	3/3	(#001)	4/6	(#011)
		7/11	7/7	(#002)	3/3	(#017)
		8/13	6/8	(#504/505)	13/17	(#506/508)
	Total	17/26 (65%)	16/18 (88.9%)		20/26 (76.9%)	
1.3	<u>Enterobacter sp. including E. aerogenes, cloacae, glomerans</u>	2/2	2/2	(#001)	3/4	(#011)
		1/1	2/3	(#002)	4/7	(#506/508)
		7/10	6/6	(#504/506)		
	Total	10/13 (76.9)	10/11 (90.9%)		7/11 (63.6%)	
1.4	<u>Proteus mirabilis</u>	3/3	1/1	(#001)	5/5	(#011)
		7/7	5/6	(#002)	5/5	(#017)
		15/15	9/11	(#504/505)	25/26	(#506/508)
	Total	25/25 (100%)	15/18 (83%)		36/36 (100%)	
1.5	<u>Proteus, indole positive</u>	0/0	0/0	(#001)	1/1	(#011)
		2/2	0/1	(#002)	7/7	(#506/508)
		3/3	1/2	(#504/505)		
	Total	5/5	1/3		8/8 (100%)	
1.6	<u>Pseudomonas sp. including P. aeruginosa</u>	4/5	1/1	(#001)	11/14	(#011)
		8/14	2/2	(#002)	2/3	(#017)
		7/8	1/2	(#504/505)	13/15	(#506/508)
	Total	19/27 (70.4%)	4/5 (80%)		26/32 (81%)	
1.7	<u>Serratia sp. including S. marcescens</u>	2/2	1/2	(#504/505)		
1.8	<u>Providencia sp.</u>	2/2	0/0	(#002)		
		2/2	0/0	(#504/505)		

Indication & Claim No.	Organism	Controlled Trials			Uncontrolled Trials - Proto-	
		Norfloxac- acin	Control	Protocol #	#E/#I	col #
UTI - Con't						
1.9	<u>Citrobacter</u> sp.	1/1	1/1	(#001)	1/1	(#011)
		3/4	0/0	(#002)	2/2	(#017)
		3/3	0/0	(#504/505)	5/7	(#506/508)
	Total	7/8 (87.5%)	1/1		8/10 (80%)	
1.10	<u>Staphylococcus</u> sp. including <u>S.</u> <u>saprophyticus</u> , <u>aureus</u> , <u>epidermidis</u>	2/2	0/0	(#001)	4/5	(#011)
		3/3	2/2	(#002)	3/3	(#017)
		3/4	4/4	(#504/505)	9/11	(#506/508)
	Total	8/9 (88.9%)	6/6 (100%)		16/19 (84.2%)	
1.11	Enterococcus in- cluding <u>S. faecalis</u>	3/3	1/2	(#002)	1/2	(#011)
		1/1	4/4	(#504/505)	1/2	(#017)
	Total	4/4	5/6		8/9 10/13 (76.9%)	(#506/508)
1.12	Other Grp D Streptococci	7/8	0/1	(#002)	4/4	(#011)
		0/0	1/1	(#504/505)		
	Total	7/8 (87.5%)	1/2		4/4	
1.13	Other Streptococci including Grp B	3/3	1/1	(#002)	1/1 1/1	(#001) (#506/508)
Gonococcal Urethritis Uncomplicated						
2.1	<u>Neisseria gonor-</u> <u>rhoeae</u> , PCNase positive & neg.	74/74	16/16	(#010)		
		26/26	21/21	(#015)		
	Total	100/100 (100%)	37/37 (100%)			
Gastroenteritis						
3.1	<u>Enterotoxigenic</u> <u>E. coli</u>	34/35	8/10	(#519)		
		Total	(97.1%)	(80%)		
3.2	<u>Shigella</u> species	3/3	1/1	(#005)		
		47/48	23/23	(#519)		
	Total	50/51 (98%)	24/24 (100%)			

Indication & Claim No.	Organism	Controlled Trials			Uncontrolled Trials - Proto-	
		Norfloxac- acin	Control	Protocol #	#E/#I	col #
Gastroenter- itis Con't						
3.3	<u>Salmonella</u> sp.	1/1	0/2	(#005)	3/5	(#009)
		6/6	9/10	(#519)		
	Total	7/7 (100%)	9/12 (75%)			
3.4	<u>Aeromonas</u> sp.	1/1	0/0	(#005)		
		6/6	4/4	(#519)		
	Total	7/7 (100%)	4/4			
3.5	<u>Vibrio</u> species	7/7 (100%)	2/2	(#519)		
3.6	<u>Campylobacter</u> sp.	6/9	12/13	(#005)	8/9	(#012)
		0/0	2/3	(#519)		
	Total	6/9 (66.6%)	14/16 (87.5%)		(88.9%)	

*Favorable response = Cured or improved with bacteriological eradication.

Medical Officer's Comments

1. Percents were added by the medical officer.
2. This summary table is inaccurate as a summary table of microbiological outcome for evaluable patients and will be revised. The denominators do not include those cases which developed superinfections and it contains symptomatic outcome as well as microbiological outcome. The applicant is preparing a table summarizing microbiological outcome for evaluable patients.
3. The applicant's summary table, above, has been revised by the medical officer as follows in order to take the medical officer's disqualifications and comments into consideration. This is a preliminary summary only.

MEDICAL OFFICER'S PRELIMINARY SUMMARY OF EFFICACY

Indication & Claim No.	Organism	Controlled Trials			Uncontrolled Trials - Proto-	
		Norfloxac- acin	Control	Protocol #	#E/#I	col #
Urinary Tract Infections						
1.1	<u>E. coli</u>	53/54	58/59	(#001)	15/15	(#011)
		37/38	28/33	(#002)	29/30	(#017)
		78/82	84/94	(#504/505)		
	Total	168/174 (96.5%)	170/186 (91.4%)		44/45 (97.8%)	
1.2	<u>Klebsiella</u> sp. including <u>K.</u> <u>pneumoniae</u>	2/2	3/3	(#001)	4/6	(#011)
		7/11	7/7	(#002)	3/3	(#017)
		8/13	6/8	(#504/505)		
	Total	17/26 (65%)	16/18 (88.9%)		7/9 (77.8%)	
1.3	<u>Enterobacter</u> sp. including <u>E.</u> <u>aerogenes</u> , <u>cloacae</u> , <u>glomerans</u>	2/2	2/2	(#001)	3/4	(#011)
		1/1	2/3	(#002)		
		7/10	6/6	(#504/506)		
	Total	10/13 (76.9)	10/11 (90.9%)		3/4 (75%)	
1.4	<u>Proteus mirabilis</u>	3/3	1/1	(#001)	5/5	(#011)
		7/7	5/6	(#002)	5/5	(#017)
		15/15	9/11	(#504/505)		
	Total	25/25 (100%)	15/18 (83%)		10/10 (100%)	
1.5	<u>Pseudomonas</u> sp. including <u>P.</u> <u>aeruginosa</u>	4/5	1/1	(#001)	11/14	(#011)
		8/14	2/2	(#002)	2/3	(#017)
		7/8	1/2	(#504/505)		
	Total	19/27 (70.4%)	4/5 (80%)		13/17 (76.5)	
1.6	<u>Citrobacter</u> sp.	1/1	1/1	(#001)	1/1	(#011)
		3/4	0/0	(#002)	2/2	(#017)
		3/3	0/0	(#504/505)		
	Total	7/8 (87.5%)	1/1		3/3	
1.7	<u>Staphylococcus</u> sp. including <u>S.</u> <u>saprophyticus</u> , <u>aureus</u> , <u>epidermidis</u>	2/2	0/0	(#001)	4/5	(#011)
		3/3	2/2	(#002)	3/3	(#017)
		3/4	4/4	(#504/505)		
	Total	8/9 (88.9%)	6/6 (100%)		7/9 (77.8%)	

Indication & Claim No.	Organism	Controlled Trials			Uncontrolled Trials - Proto-	
		Norfloxac- acin	Control	Protocol #	#E/#I	col #
UTI - Con't						
1.8	Other Grp D	7/8	0/1	(#002)	4/4	(#011)
	Streptococci	0/0	1/1	(#504/505)		
	Total	7/8 (87.5%)	1/2		4/4	
Gastroenteritis						
2.1	Enterotoxigenic <u>E. coli</u>	34/35	8/10	(#519)		
	Total	(97.1%)	(80%)			
2.2	<u>Shigella</u> species	3/3	1/1	(#005)		
		47/48	23/23	(#519)		
	Total	50/51 (98%)	24/24 (100%)			
2.3	<u>Salmonella</u> sp.	1/1	0/2	(#005)	3/5	(#009)
		6/6	9/10	(#519)		
	Total	7/7 (100%)	9/12 (75%)			
2.4	<u>Campylobacter</u> sp.	6/9	12/13	(#005)	8/9	(#012)
		0/0	2/3	(#519)		
	Total	6/9 (66.6%)	14/16 (87.5%)		(88.9%)	

*Favorable response = Cured or improved with bacteriological eradication.

The medical officer's preliminary summary table will be further revised. Disqualified underage patients must be deleted. There will be other deletions.

4. The following organisms should be re-tallied to give a count for each individual species:

Klebsiella species
Pseudomonas species

Enterobacter species
Staphylococcus species

One species in each will probably account for practically all of the isolates reported.

Applicant's Safety Summary: The applicant's summary of adverse reactions and their frequencies by dosage and body system is shown below:

Adverse Experiences Body Site	Non-Neutropenics			Neutropenics	
	400 mg bid	200 mg bid	600 mg q 4 h x 2	400 mg tid	400 mg tid
Number of patients	1159	60	135	138	81
No. of adverse reactions	172	0	5	16	129
No. drug related	57		3	5	2
<u>Body as a whole/ site unspecified</u>					
Abdominal swelling	1				
Asthenia	2				
Death (not drug related)					15
Fatigue	3				
Fever	2				2
Pain	1				
Syncope					1
Total	9				
<u>Vascular System</u>					
Cardiac arrest					3
Cerebrovascular disease	1				
Congestive heart failure	1				2
Hemorrhagic shock	1				
Intracerebral hemorrhage					2
Myocardial infarction	2				
Shock	1				
Tachycardia	1 (1)				
Total	7				
<u>Digestive System</u>					
Abdominal pain	4 (2)			1	
Bowel sound abnormality					1
Anorexia	1 (1)		1		2
Aphthous stomatitis	1				
Constipation	4				
Diarrhea	3 (1)				30
Digestive System Disorder	1 (1)				
Dry mouth	3 (2)				
Dyspepsia	5 (4)				1
Dysphagia	1 (1)				
Flatulence	3			1	
Gastrointestinal cramps	2 (1)				
GI Hemorrhage/Melena					4
Gastrointestinal pain	1				
Gingivitis					1
Heartburn	4				
Jaundice					1

Adverse Reactions Body Site	Non-Neutropenics			Neutropenics
	400 mg bid	200 mg bid	600 mg q 4 h x 2	400 mg tid
Mouth ulcer	2			
Nausea	28 (13)		2 (1)	6
Tongue enlargement	1 (1)			
Vomiting	2			16 (1)
Total	66 (27)			
<u>Hemic and Lymphatic</u>				
Purpura	1			
Hypovolemia	1			
Hemolysis				1
Epistaxis				1
<u>Musculoskeletal</u>				
Back pain	1			
Knee or leg pain	1			
Joint pain				1
Musculoskeletal disorders	1			
Muscle cramp				1
Weakness, local	1			
Total	5			
<u>Nervous and Psychiatric</u>				
Anxiety	1 (1)			1
Cerebellar ataxia				1
Convulsive disorder	1			
Depression	4 (1)			
Disorientation	1			
Dizziness	17 (6)		1 (1)	1
Dream abnormalities	1			
Euphoria	1 (1)			1 (1)
Explosive personality	1			
Hallucinations	1 (1)			
Headache	22 (4)		2 (1)	3
Insomnia	5 (2)		1	
Irritability				1 (1)
Nervousness			1	
Paresthesia				1
Somnolence	5 (1)			
Total	60 (17)			
<u>Respiratory System</u>				
Hemoptysis				1
Pharyngeal pain				1
Respiratory Insufficiency				1
Respiratory Failure				1

Adverse Experiences Body Site	Non-Neutropenics			Neutropenics 400 mg tid
	400 mg bid	200 mg bid	600 mg q 4 h x 2	
<u>Skin and Appendages</u>				
Dry skin	1			
Erythema	3 (2)			
Pruritis	2 (2)			
Pruritis ani	1			
Rash	6 (3)			21
Urticaria				2 (2)
Total	13 (7)			
<u>Special Senses</u>				
Conjunctivitis				3
Epiphora	1 (1)			
Nystagmus				1
Taste perversion	2 (2)			1 (1)
Tinnitus	1 (1)			
"Scratchy eyes"	1			
Visual disturbances				1
Total	5 (4)			
<u>Urogenital</u>				
Dysmenorrhea	1			
Hematuria				1
Renal colic	1			
Renal failure				4
Vaginal swelling	1 (1)			
Vaginal pain	1			
Suprapubic pain	1			
Total	5 (1)			

Numbers in parentheses are the number of drug-related adverse effects.

Adverse Laboratory Events Body Site	Non-Neutropenics			Neutropenics 400 mg tid
	400 mg bid	200 mg bid	600 mg q 4 h x 2	
<u>Hematology</u>				
Hemoglobin increase	6			
decrease	1			
Hematocrit decrease	5			2
WBC Count increase	3			
decrease	7 (3)			5 (3)
Neutrophil decrease	7 (3)			
increase			1	
Lymphocytes rel. increase	3 (1)		3	
Monocyte increase	2			

Adverse Laboratory Events Body Site	Non-Neutropenics			Neutropenics	
	400 mg bid	200 mg bid	600 mg q 4 h x 2	400 mg tid	400 mg tid
Eosinophil increase (5 not drug related)	21 (2)		1	1	
Platelet Count increase	4			2	
decrease				1	
ESR (increase)	1				
Total	60 (9)				
<u>Renal Function (Blood Chem.)</u>					
BUN increase	12				7
Serum creatinine increase	6				12
Total	18				
<u>Liver Function (Blood Chem.)</u>					
Tot. Sr. Bilirubin increase	3	1		1	35
AST, ALT increase	27 (1)			13 (2)	63
Alk. Phosphatase increase (1/19 with no drug relation)	19 (1)			3	24
LDH increase	7				13
Total	56 (2)				
<u>Metabolic (Blood Chem.)</u>					
Ser. Uric Acid increase					1
<u>Electrolytes (Blood Chem.)</u>					
Serum sodium increase	2				
Serum potassium decrease	3				
increase	1				
Serum chloride decrease	4				
increase	3				
Total	13				
<u>Urinalysis</u>					
Urine protein increase	3				7
Urine glucose increase	2		1		2
Urine WBC increase (1/3 with no drug relation)	3				1
Urine RBC increase (2/4 with no drug relation)	4				6
Urine crystals	1				
Non-amorphous crystals				1	
Total	13				
Overall Total	160 (11)		7	28	171

Many patients had multiple adverse experiences so that the number of patients with adverse experiences was always fewer than the number of adverse experiences. The same was true for adverse laboratory events. Most adverse experiences at the 400 mg bid dose were in the digestive tract (38%) or the nervous/psychiatric systems (35%). Forty-seven percent of all drug-related adverse experiences were gastrointestinal compared to 30% for neuropsychiatric. The single most commonly described drug-related adverse experience was nausea. The next most commonly described were dizziness, dyspepsia, and headache. No single adverse laboratory experience approached a frequency of 1%. No single drug related adverse experience except nausea (2.0%), dizziness (1.2%), and headache (1.6%) occurred with a frequency of 1% or more.

The overall adverse reaction rate for 1528 non-neutropenic patients was 8.4% (129/1528)

The applicant's table comparing the frequency of adverse experiences of norfloxacin with those of the six control products is reproduced on the next four pages exactly as filed.

Overall Safety Analysis

The following tables compare the adverse experiences by drug (NOROXIN and all comparative regimens). The table is divided by drug and includes the total number of patients treated for each drug.

Clinical Adverse Experience

Nonneutropenic Studies: #All adverse experiences/drug related adverse experiences

<u>Adverse Experiences</u>	<u>NFX</u> N=1540*	<u>SXT</u> N=554	<u>Nal. Acid</u> N=102	<u>Spec.</u> N=23	<u>Amp</u> N=29	<u>Ery</u> N=23	<u>Plac</u> N=22
<u>Body as Whole/Mscl.</u>							
Abdominal Swelling	1/-	—	—	—	—	—	—
Fever	1/-	1/1	—	—	—	—	—
Malaise	—	2/1	—	—	—	—	—
Pain	1/-	—	—	—	—	—	—
Asthenia	2/-	—	1/-	—	—	—	1/-
Fatigue	3/-	—	3/1	—	—	—	—
TOTALS	8/-	3/2	4/1	—	—	—	—
<u>Cardiovascular</u>							
Myocardial infarction	2/-	—	—	—	—	—	—
Cerebrovascular accident	1/-	—	—	—	—	—	—
Congestive heart failure	1/-	—	—	—	—	—	—
Hemorrhagic shock	1/-	—	—	—	—	—	—
Shock, unspec.	1/-	—	—	—	—	—	—
Tachycardia	1/-	—	—	—	—	—	—
TOTALS	7/-	—	—	—	—	—	—

N = Number of patients receiving that therapy
 NFX = Norfloxacin
 Nal. Acid = nalidixic acid
 SXT = Sulfamethoxazole/trimethoprim

Spec. = spectinomycin
 Amp = Ampicillin
 Ery = Erythromycin
 Plac = Placebo

Clinical Adverse Experience
(Cont'd)

Nonneutropenic Studies: #All adverse experiences/drug related adverse experiences

<u>Adverse Experiences</u>	<u>NFX</u> <u>N=1540*</u>	<u>SXT</u> <u>N=554</u>	<u>Nal. Acid</u> <u>N=102</u>	<u>Spec.</u> <u>N=23</u>	<u>Asp</u> <u>N=29</u>	<u>Ery</u> <u>N=23</u>	<u>Plac</u> <u>N=22</u>
<u>Digestive system</u>							
Abdominal Pain	4/2	3/2	1/-	-	-	-	-
Anorexia	2/1	2/-	-	-	-	-	-
Apthous stomatitis	1/-	-	-	-	-	-	-
Constipation	4/-	1/-	1/-	-	-	-	-
Diarrhea	3/1	2/-	7/-	-	-	-	1/-
Dry mouth	2/2	-	1/1	-	-	-	-
Dyspepsia	5/4	4/1	1/1	-	-	-	-
Flatulence	4/-	1/-	1/-	-	-	-	-
Gastrointestinal Cramps	2/1	-	-	-	-	1/-	-
Heartburn	4/-	2/1	-	-	-	-	-
Nausea	30/14	8/3	20/10	-	1/1	2/1	1/-
Digestive system disease	1/1	-	-	-	-	-	-
Dysphagia	1/1	-	-	-	-	-	-
Gastrointestinal pain	1/-	-	-	-	-	-	-
Vomiting	3/-	2/2	3/1	-	-	-	-
Mouth ulcer	2/-	1/-	-	-	-	-	-
Glossodynia	-	-	1/-	-	-	-	-
TOTALS	70/27	26/9	36/13	-	1/1	3/-	2/-
<u>Hemic</u>							
Purpura	1/-	-	-	-	-	-	-
<u>Metabolic</u>							
Hypovolemia	1/-	-	-	-	-	-	-

N = Number of patients receiving that therapy
 NFX = Norfloxacin
 Nal. Acid = nalidixic acid
 SXT = Sulfamethoxazole/trimethoprim

Spec. = spectinomycin
 Asp = Ampicillin
 Ery = Erythromycin
 Plac = Placebo

Nonneutropenic Studies: #All adverse experiences/drug related adverse experiences

<u>Adverse Experiences</u>	<u>NFX</u> <u>N=1540*</u>	<u>SXT</u> <u>N=54</u>	<u>NaI. Acid</u> <u>N=102</u>	<u>Spec.</u> <u>N=23</u>	<u>Asp</u> <u>N=29</u>	<u>Ery</u> <u>N=23</u>	<u>Plac</u> <u>N=22</u>
<u>Musculoskeletal</u>							
Back pain	1/-	—	—	—	—	1/-	—
Joint pain	1/-	—	—	—	—	—	—
Knee pain	1/-	—	—	—	—	—	—
Musculoskeletal disease	1/-	—	—	—	—	—	—
Leg pain	1/-	—	—	—	—	—	—
Weakness, local	1/-	—	1/-	—	—	—	—
TOTALS	6/-	—	1/-	—	—	1/-	—
<u>Neuro/psychiatric</u>							
Depression	4/1	2/1	1/1	—	—	—	—
Disorientation	1/-	—	—	—	—	—	—
Dizziness	19/7	2/-	7/1	—	—	2/1	2/-
Headache	26/5	8/-	12/2	—	—	—	1/-
Insomnia	4/1	1/1	—	—	—	—	—
Anxiety	2/-	—	—	—	—	—	—
Convulsive disorder	1/-	—	—	—	—	—	—
Dream abnormalities	1/-	—	—	—	—	—	—
Euphoria	2/2	—	—	—	—	—	—
Irritability	1/1	—	—	—	—	—	—
Insomnia	2/1	2/-	—	—	—	—	—
Nervousness	1/-	2/-	—	—	—	—	—
Explosive personality disorder	1/-	—	—	—	—	—	—
Hallucinations	1/1	—	—	—	—	—	—
Somnolence	5/1	2/-	2/1	—	—	—	—
Paresthesia	1/-	1/-	—	—	—	—	—
Tremor	—	1/-	—	—	—	1/-	—
TOTALS	73/20	19/2	22/5	—	—	3/1	2/-

N = Number of patients receiving that therapy
 NFX = Norfloxacin
 NaI. Acid = nalidixic acid
 SXT = Sulfamethoxazole/trimethoprim

Spec. = spectinomycin
 Asp = Ampicillin
 Ery = Erythromycin
 Plac = Placebo

**Clinical Adverse Experience
(Cont'd)**

Nonneutropenic Studies: #All adverse experiences/drug related adverse experiences

<u>Adverse Experiences</u>	<u>NFX</u> <u>N=1540*</u>	<u>SXT</u> <u>N=554</u>	<u>Nal. Acid</u> <u>N=102</u>	<u>Spec.</u> <u>N=23</u>	<u>Amp</u> <u>N=29</u>	<u>Ery</u> <u>N=29</u>	<u>Plac</u> <u>N=22</u>
<u>Skin & Allergies</u>							
Tongue enlargement	1/1	—	—	—	—	—	—
Drug skin	1/-	—	—	—	—	—	—
Erythema	3/2	—	—	—	—	—	—
Pruritis	2/2	3/1	—	—	—	—	—
Pruritis ani	1/-	—	—	—	—	—	—
Rash	6/3	7/7	1/-	—	—	—	1/-
Urticaria	2/2	2/2	—	—	—	—	—
Allergic dermatitis	—	1/1	—	—	—	—	—
Photosensitivity	—	—	—	—	—	1/-	—
TOTALS	16/10	13/11	1/-	—	—	1/-	1/-
<u>Special senses</u>							
Taste perversion (bitter taste)	3/3	—	—	—	—	—	—
Epiphora	1/1	—	—	—	—	—	—
Tinnitus	1/1	—	—	—	—	—	—
Ear obstruction	—	1/-	—	—	—	—	—
Photopsia (flashing lights)	—	—	1/1	—	—	—	—
Hydrasis	—	—	—	—	—	1/1	—
Eyelid edema	—	1/1	—	—	—	—	—
Visual disturbances	—	1/1	—	—	—	—	—
TOTALS	5/5	3/2	1/1	—	—	1/1	—
<u>Urogenital</u>							
Dysmenorrhea	1/-	—	—	—	—	—	—
Renal colic	1/-	—	—	—	—	—	—
Vaginal swelling	1/1	—	—	—	—	—	—
Lactation suppressed	—	1/-	—	—	—	—	—
Metodynia	—	—	1/-	—	—	—	—

N = Number of patients receiving that therapy
 NFX = Norfloxacin
 Nal. Acid = nalidixic acid
 SXT = Sulfamethoxazole/trimethoprim

Spec. = spectinomycin
 Amp = Ampicillin
 Ery = Erythromycin
 Plac = Placebo

Summary of Medical Officer's Comments:

1. Animal Data:

- a) Hemoglobinuria occurred in all monkeys from which urine could be obtained at the 50 mg/kg/day dose and the 200 mg/kg/day dose. The 50 mg/kg/day dose is 2-3 times the expected human dose. The "no-effect" dose for hemoglobinuria in monkeys is not known and should be reported.
- b) The presence of drug crystals in the urine of these monkeys cannot be evaluated because urine was not examined microscopically. Crystals may have been present and may have been the cause of the hemoglobinuria. The "no-effect" crystalluria dose in monkeys is not known and should be reported.
- c) Crystalluria occurred in dogs at 50 mg/kg/day, a dose which will be 2-3 times the recommended human dose. Three dogs, one in the 150 mg/kg/day group and two in the 300 mg/kg/day group were found dead or were sacrificed due to urinary obstruction from drug crystals. The "no-effect" crystalluria dose is not known and should be reported. There may be a possibility that crystalluria could occur at the recommended doses in some patients. Labeling should advise about this possibility.

2. Adverse effects and abnormal laboratory reports in the 949 cases which were studied by Kyorin in Japan are not summarized. If this information is available, it should be summarized in a report. The report should describe how these patients were monitored for the presence of adverse reactions.

3. The question as to whether norfloxacin precipitates in the human urine and whether drug crystals can cause renal obstruction in humans, as happened in dogs, has not been answered. (The reader is referred to the MO's comments on pages 9 and 82 of this MOR.) Crystals which were present in Dr. Ferguson's study No. 1, in Dr. Zinney's study No. 13, and in other studies have not been identified. It is not known if these are crystals of norfloxacin or the metabolites of norfloxacin or crystals of something else.

Most of the time in efficacy studies the presence or absence of crystals during treatment is not reported. In Dr. Zinney's bioavailability study, up to 40% of subjects had non-amorphous crystals after dosing. The presence or absence of crystalluria in Dr. Cohn's gastroenteritis study, Study No. 14, cannot be evaluated because urine sediment was only examined before treatment and again two days after treatment was discontinued. Urine sediment should have been examined for the presence of drug crystals during treatment at the height of the drug excretion period.

There is a discrepancy between the printout and several case report forms regarding the presence of nonamorphous crystals.

Case #302 - Printout shows 50 nonamorphous crystals/EPF on Day 7. The case report shows "Many" nonamorphous crystals two days after treatment.

Case #308 - Printout shows 4/HPF before treatment. The case report

shows 4+ before treatment.

Case #113 - Printout shows 1/HPF on Day 8. The case report shows 1+ calcium oxalate two days after treatment.

The applicant should be requested to summarize all information in this NDA regarding crystalluria. A summary addressing crystalluria cannot be located in what has already been filed.

4. Underage patients:

a) Three patients that were under 18 years of age in the domestic urinary tract infection study which compared norfloxacin with TMP-SMZ (Protocol No. 002) should be disqualified. They were norfloxacin cases #1498 (13-yr old male treated by Dr. Landes), and #908 (17-yr old female treated by Dr. Ryan), and TMP-SMZ case #916 (17-yr old female treated by Dr. Ryan).

b) The following seven underage applicant-qualified patients should be disqualified from the efficacy evaluation and safety evaluation. The lower age limit for the use of the quinolones in humans has been set at 18 years because of the development of arthropathy in juvenile animals in all species that have been tested. This represents a serious protocol violation.

Carcelen #4022 15-yr old in 800 mg Nor. - V. parahaemolyticus -Eradicated
 Carcelen #4056 15-yr old in 800 mg Nor. - S. flexneri - Eradicated
 Salazar #4122 13-yr old in 800 mg Nor. - E. coli, enterotox. - Eradicated
 Carcelen #4029 16-yr old in 1200 mg Nor. - V. parahaemolyticus -Eradicated
 Carcelen #4109 17-yr old in TMP-SMZ - S. flexneri - Eradicated
 De Godoy #4451 15-yr old in TMP-SMZ - Salmonella - Eradicated
 Rodriguez #4641 17-yr old in TMP-SMZ - Shigella boydii - Eradicated

c) Patients under 18 years of age in the international, multiclinic, controlled urinary tract infection study (Protocols No. 504 and 505) and in other studies should be disqualified.

d) Outcome rates should be corrected accordingly.

5. Approval of the prophylactic use of norfloxacin in the suppression of bowel flora in granulocytopenic patients is not recommended. Data are inadequate to support this indication.

a) In regard to Dr. Joshi's study, No. 16:

(1) The route of administration of amphotericin B in this study, swishing it in the mouth for one minute then swallowing it, is an investigational route for the use of intravenous vials. Amphotericin B was provided in 50 mg intravenous vials for oral use. Efficacy and safety of amphotericin B by the oral route have not been established. (Oral amphotericin B, however, is available as a fixed combination with tetracycline (Mysteclin-FR (Squibb): NAS/NRC rated as ineffective). It is labeled as being "extremely well tolerated and is virtually nontoxic in prophylactic doses." Adverse

reactions which are reported in this labeling are those due to tetracycline rather than to amphotericin B.) This study should be disregarded because two investigational drugs cannot be evaluated at the same time.

The applicant's conclusion regarding fungemias is not valid since amphotericin B was given to all patients in each group.

(2) No decision regarding prophylactic efficacy can be made on the basis of this study not only because of the use of another investigational drug, but also because of the small size of the treatment groups. The conclusion regarding the superiority of norfloxacin in patients treated 35 days or less is based upon success in two of only four patients. This does not represent substantial evidence.

(3) Since patients randomized to receive norfloxacin and graded as evaluable were five times more likely to be profoundly neutropenic at the time of randomization as were the patients in the control group, there must have been a randomization bias. There must also have been a duration-of-treatment bias in that the norfloxacin group was treated longer than the control group, 49 days versus 38 days.

b) Regarding Dr. Winston's study, No. 17:

(1) Polymyxin B capsules and vancomycin capsules must be regarded as investigational drugs. The routes of administration of polymyxin and vancomycin in this study are investigational routes for these products.

(2) This study must be regarded as an uncontrolled trial because the control was not approved for this indication. Two investigational regimens cannot be evaluated at the same time.

(3) No decision regarding prophylactic efficacy can be made on the basis of this study not only because of the use of investigational drugs, but also because of the small size of the treatment groups. (Refer to page 52.)

6. Approval of the use of norfloxacin in the treatment of gonorrheal infection is not recommended. Data are inadequate to support this indication.

a) In regard to Dr. Berg's Subic Bay study in males, No. 30:

(1) Failure to randomize lessens the value of this study and removes it from the list of controlled trials.

(2) In spite of the 100% cures in each group, the medical officer can only accept 27 of the 90 male patients that the applicant found qualified because only these 27 cases had susceptibility testing, 22 in the norfloxacin group and 5 in the spectinomycin group. (One cannot be accounted for.) Cases for which there was no susceptibility testing should be disqualified.

(3) Post therapy cultures should have been obtained 4-7 days after therapy instead of 3-7 days after therapy.

(4) The presence or absence of drug crystals is not reported.

b) In regard to the study by Drs. Simpson and Kaplowitz, Nos. 48/49:

(1) Although norfloxacin is probably effective, data from this study are inadequate to show that norfloxacin is effective in treating gonococcal urethritis and cervicitis. There were only two evaluable females in the norfloxacin group and only five in the control group. Susceptibility was not tested for one of the two norfloxacin females and for four of the five control female cases. For a common infection like gonorrheal infection, at least 75 or 100 cases would be needed. The same is true for males: in this study, there were only 24 evaluable males in the norfloxacin group and only 17 in the control group. These low numbers might be acceptable for a rare infection but they do not represent the substantial data needed for a common infection like gonorrheal infection.

2. The applicant's clinical outcome criteria which mistakenly included microbiological outcomes were disregarded. The medical officer graded clinical outcome on the presence or absence of signs and symptoms.

3. The fact that one norfloxacin-treated patient had nonamorphous crystals after only two 600-mg doses four hours apart may be significant.

4. Post-therapy cultures should have been obtained 4-7 days after therapy instead of 3-7 days after therapy.

5. The applicant has mistakenly classified isolates for which there was no susceptibility testing with evaluable cases. These cases should be disqualified. Strains from only 19 of the 24 males in the norfloxacin group, 13 of 17 males in the control, and for only two females were tested for susceptibility.

7. The uncontrolled, international, multiclinic urinary tract infection study (Protocols No. 506/508) has not been analyzed in such a manner that the applicant's conclusions are supported. The applicant should re-analyze this study so that the following deficiencies are corrected:

a) The clinical outcome criteria which contain microbiological assessments should be disregarded. The clinical outcome should be based upon a comparison of the presence or absence of signs and symptoms before and after therapy.

b) "Assessable" patients should be regarded as unevaluable patients.

c) Patients with pretherapy urine cultures obtained earlier than 48 hours before the initiation of treatment should be considered unevaluable. In this study pretherapy cultures were considered if they were obtained

N19384 -4

within 12 days of the initiation of treatment.

d) Culture timing requirements are not acceptable and should be revised to be in keeping with FDA guidelines for the treatment of urinary tract infections. In this study, they were changed from those specified in FDA's guidelines that were used in other studies to read as follows:

Relative-Day Ranges (page I-6157, Vol 2.17)

Protocol	Actual	Nomenclature Used in Text
Day 3 or 4 during therapy	Days 2 to 5 during therapy	During therapy
5 to 9 days post-therapy	5 to 20 days post-therapy	Post-therapy
4 to 6 weeks post-therapy	25 to 48 days post-therapy	Late post-therapy

e) Patients under 18 years of age should be disqualified. There are approximately eight, the youngest was 9 years old.

f) No effort should be made to separate upper and lower urinary tract infections because of the impreciseness of the diagnostic technique.

g) The report lacks a summary table which gives the microbiological outcome according to uropathogens.

h) Adverse reactions are tallied in the appendix but the report lacks a summary table to show all 43 adverse reactions. Unfortunately, no patient diaries were used in this study.

i) Summary tables compare pretherapy mean values with post-therapy mean values but do not list the 40 adverse laboratory experiences.

7. The applicant did not include the eleven isolates from ten compassionate patients in the total data of efficacy in this NDA. They should have been included. These cases were multiple antibiotic resistant infections (Section 3 c (2), above).

8. The applicant should be requested again to submit a report of tests of brain function during treatment with norfloxacin. This was discussed in a conference with the applicant August 18, 1982 following a detailed consideration of a quinolone product by FDA's Anti-Infective Drugs Advisory Committee. This request was included in our letter to the applicant dated September 10, 1982. The applicant agreed to perform brain function tests and addressed this point in the response letter to FDA dated Nov. 10, 1982, response to item #2 h.

Although not labeled as a test of brain function, it is noted that 1/14 norfloxacin patients and 2/15 TMP-SMZ patients in Dr. Joshi's suppression of the bowel flora study improperly performed the straight-line walk test.

9. The applicant should be requested to conduct a study of the enteral absorption of norfloxacin in the presence of antacids. A report by Hoffken and coworkers (European Journal of Clinical Microbiology, Vol. 4: 1985, p. 345) indicates that antacids reduce the enteral absorption of ciprofloxacin, another new fluoroquinolone, in the presence of antacids. The pronounced effect of antacids on the bioavailability of ciprofloxacin should be considered if both these drugs are administered to a patient. This could be an effect with all members of the drug class and norfloxacin should be tested for this interaction.

10. The applicant's microbiological outcome summary table should be revised. The denominators do not include those cases which developed superinfections and symptomatic outcome information should be deleted.

11 Patient Diaries:

a) Only 86 acceptable patient diaries have been filed. A minimum of 100 were requested. Only 63 of the 83 diaries in the original application were acceptable. Diaries from Dr. Zinney's study #59 were not accepted because this was a single dose study. Diaries from courses with the recommended dose for the recommended length of treatment were requested. Only 23 of the 50 diaries in the amendment were acceptable. Those with check-off sheets are disqualified. At least 14 more acceptable patient diaries should be filed.

b) Diaries reported to have been kept by the patients in the following studies are still missing:

Study No. 36 Dr. Anthony Joseph Schaeffer - The applicant reported in a telephone conversation 10-25-85 that Dr. Schaeffer threw his diaries away. Nineteen patients were treated.

Study No. 35 Dr. Frank E. Thomas - Only one patient was treated.

Patient diaries were to be handwritten by the patient and were not to be transcribed or altered in any way. Original unaltered diaries were to have been filed as part of the case report forms. During the norfloxacin IND period, we talked about patient diaries as follows: Conference with Merck 8-18-82, TC 12-13-82, MOR 8-19-82, Letter to Merck 9-10-82, Letter from Merck 11-10-82, TC 3-11-83, MOR 12-19-83, and End of Phase II Conference 12-8-83.

c) The applicant failed to provide an overall summary of patient diaries in this application and should be requested to analyze and summarize them. Patient diaries, a minimum of 100, were specifically requested for norfloxacin studies so that adverse reactions could be characterized and their frequencies observed. There is a high incidence of adverse reactions with most members of this drug class. Virtually all of them are reversible when the drug is discontinued or they subside during the course of treatment. The investigator misses most of them, especially when he has outpatients and does not see the patient until the follow-up visit after treatment has been discontinued.

d) The medical officer summarizes the most frequently occurring entries in the patient diaries as follows:

<u>Diary Entry</u>	<u>Frequency</u>
Tired, lack of energy	35
Headache	28
Sleepy or drowsy	24
Nausea, Sick to stomach, Upset stomach, Vomiting	18
Dizziness, Head swirling Not steady on feet	10
Impaired vision, Burning eyes, Eyes tired, Eyes sore, Eyes itch, Wavy lights in eyes	8
Lightheaded	6
Weakness or sluggish, Washed out feeling	6
Dry mouth or lips	4
Slept poorly	4
Stomachache, Belly pain	4
Nervous, Tense	4
Lump in throat	3
Backache	3

e) The applicant's report of adverse reactions when compared to the information on patient diaries shows that there is underreporting of the frequency of adverse reactions. Both the investigator's and the applicant's adverse reaction rates are too low. (See pages 16 and 80 of this MOR.)

12. Cases being treated for gastroenteritis should not be considered in the evaluation of adverse effects due to norfloxacin because the very adverse effects that one would monitor are symptoms of the disease and are not reported as adverse reactions when they occur. Symptoms of gastroenteritis, besides diarrhea that were used in the evaluation of outcome, were abdominal cramps, nausea, vomiting, anorexia, etc. Gastrointestinal-type adverse effects that would be anticipated with norfloxacin are gastrointestinal cramps, nausea, vomiting, heartburn, flatulence, anorexia, abdominal pain, dyspepsia, etc. One cannot distinguish between disease symptoms and adverse drug effects.

13. Cases receiving norfloxacin in the neutropenia prophylaxis studies should not be included in the evaluation of adverse reactions because they were all receiving multiple drugs. The 80% adverse reaction rate and 71% abnormal laboratory report rate should be disregarded. These patients are not good subjects for drug safety evaluation.

14. Adverse reaction rates for the labeling should be recalculated so that only those patients who received a dose schedule of 400 mg twice daily, the dose to be recommended in the labeling, are included. Adverse reaction rates associated with other dosing schedules can be determined separately.

15. Some adverse reactions which the investigator has labeled not-drug-related reactions are very likely drug related and are typical of the type of adverse reactions that occur with the quinolones.

16. The following organisms should be re-tallied to give a count for each individual species:

Klebsiella species
Pseudomonas species

Enterobacter species
Staphylococcus species

One species in each will probably account for practically all of the isolates reported.

17. The applicant should be requested to report EEG findings in humans. At least one quinolone has epileptogenic potential. At least one norfloxacin-treated patient had a convulsion.

Biopharmaceutics Consultation: Requested April 2, 1985.

Labeling Review: Proposed labeling is unsatisfactory. A separate MOR will be provided for labeling.

Foreign Clinical Data: This application contains foreign clinical data. See pages 19, 29, 39, 64, 75, 77, and 80 in this MOR.

✓ Conclusion: If the deficiencies and comments in this MOR can be resolved, the efficacy data in this application may support the use of norfloxacin in the treatment of the following two indications:

Urinary tract infections caused by E. coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Pseudomonas aeruginosa, Citrobacter species, and Staphylococcus species to be specifically named.

Gastroenteritis caused by enterotoxigenic E. coli, Shigella species, Salmonella species, and Campylobacter species.

Ⓢ Recommendation: Before this application can be considered to be approvable, a meeting should be held with the applicant to consider the deficiencies and comments listed above.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc
Orig NDA
HFN-815
HFN-815/Reed
HFN-815/CSO
HFN-340

4432b pages 1-87
4593b pages 88-109

ET 1/21/86 See Division Director's Memorandum
WRD 2/1/85 - see appended supervisor's comments dated 2/1/85

November 21, 1985

Supervisor's Comments on Dr. Reed's MOR #1 dated November 14, 1985

Drug Name: generic: norfloxacin
 trade: Noroxin

As pointed out in Dr. Reed's review, there are several areas of concern (Does norfloxacin precipitate in human urine in vivo? What is the exact incidence of patient reported side effects caused by norfloxacin?) that are not completely answered by the data submitted by MS&D.

There are some additional areas (underage patients, gonorrhea, clinical outcome criteria including microbiological assessment, ("assessable patients") that deserve comments.

1. Does norfloxacin precipitate in human urine in vivo? Since all of the quinolones are excreted in very high concentration in the urine, and in some studies quinolone crystals have been noted in voided urine, it has been a theoretical concern that this might occur in humans.

It has not been a practical clinical concern for either nalidixic acid or cinoxacin and no mention is made of such an occurrence or concern in the labeling for either product.

In the studies submitted, the sponsor has made a reasonable attempt to elucidate the problem, but a definitive conclusion can not be reached. In urines, kept at body temperature, amorphous crystals were seen per high powered field as commonly in the control groups as in the norfloxacin treated groups, and there appears to be no significant difference in the incidence of patients with crystals before and after therapy. The occasional non-amorphous crystal has not been identified. Since there are six metabolites of norfloxacin, it is a daunting problem to try to identify crystals found only on the high powered field of a microscope.

More convincing that crystalization is not of clinical concern is the absence of reports of renal or ureteral colic or pain, urinary abnormalities such as RBC's, or abnormal urinary function tests that could be attributed to the drug.

Conclusion: Although the question of norfloxacin precipitation in human urine in vivo is not definitively answered, all available data point towards this not having occurred in any clinically meaningful sense. I do not see this as a reason for holding up approval of the NDA.

2. What is the exact incidence of patient reported side effects caused by norfloxacin?

Since all of the quinolones studied to date have caused a variable incidence of vague neurological complaints, ie. sleepy, sluggish, tired, lassitude, light headed, weak, drowsy, coupled with other CNS side effects such as restlessness, tinnitus, insomnia, tingling, photophobia, difficulty in focusing, etc., and the fact that these side effects are more common while on therapy than when off therapy, Dr. Reed has insisted on patient diaries, filled out by the patients themselves with no prompting. She has insisted that 100 patients fill out diaries in which they listed any side effects they had experienced.

The sponsor has been able to submit approximately 68 acceptable diaries (some investigators have thrown the diaries away, and I suspicion that the sponsor has been less than enthusiastic about the diaries).

From these studies, and from previous studies of similar drugs, the type of side effects to be expected are well characterized and are not of sufficient severity or frequency to keep norfloxacin off the market. Despite the limits of the studies submitted, the side effects seen with norfloxacin appears to be less frequent than with nalidixic acid or cinoxacin - certainly not worse.

In Dr. Reed's review of that data, from patients who kept diaries, such complaints as sleepy, sluggish, headache, diarrhea, nausea, tired, lassitude, light headed, weak, and drowsy were reported in approximately 40 to 50% of patients taking norfloxacin, and in about 30% of patients on placebo. This is certainly not a striking difference from placebo.

MS&D's report of the study results (physician reported side effects) contains the following data.

The most common adverse events reported were digestive. In 1,500 treated patients, the following drug related events occurred.

	<u>drug related/reported</u>
Nausea	14/30
Dyspepsia	4/5
Abdominal pain	2/4
Diarrhea	1/3

Neuro-psychiatric experiences for 1,540 treated patients were:

	<u>drug related/reported</u>
depression	1/4
dizziness	7/19
headache	5/26
insomnia	1/4
somnolence	1/5
other	5/15

Conclusion:

From the data presented from approximately 68 evaluable patient diaries, norfloxacin does not appear to cause neurological side effects at an incidence much different than that seen in placebo patients.

From physician reported adverse events, nausea occurred in 0.9% of patients, and dizziness in 0.45% of patients. All neuro-psychiatric experiences combined occurred in only 1.3% of the total patients studied.

No unexpected adverse events were found, and the incidence of adverse events (either patient or physician reported) was low.

I do not agree with keeping the drug off the market because the sponsor has submitted only 68 patient diaries of adverse events, rather than 100, because I do not see what is to be learned from more patient diaries.

3. Underage Patients

I agree with Dr. Reed that patients under age 18 should not have been entered into the studies. This was specified in the protocols because of the occurrence of arthropathy in juvenile animals treated with quinolones.

Dr. Reed has found eight patients under age 18 in the comparative studies. Though they should not have been entered, I can't believe that eliminating eight patients will alter the outcome of the comparative studies in any significant way.

Because of this problem, Dr. Reed requests that the sponsor delete all patients 18 years and younger from the open studies and reanalyze the data.

Conclusion

Before the sponsor undertakes a massive reanalysis of data, I feel that it should be ascertained how many patients 18 years and under are included in the analysis of the open studies. If it is a small number, similar to those in the comparative studies, it seems useless to request reanalysis of the data, unless exclusion of this small number of patients is genuinely thought to significantly alter the analysis of the studies.

4. Prophylactic Use

I concur with Dr. Reed that in one study the sponsor has used amphotericin as the comparative drug when it does not have an approved indication, and in the other study polymyxin B and vancomycin in an unapproved dosage form (capsules). These are both investigational and can not be used as approved comparative drugs for norfloxacin.

5. Gonorrhea

Dr. Reed refuses to accept as evaluable or even supportive any patients without susceptibility testing, despite the fact that norfloxacin is effective against PPNG + and - gonorrhea, and that 100% of cases treated were cured.

Since our 1977 guidelines state that follow-up should be at 4-7 days, she has excluded all patients with follow-up at 3 days. The protocols for the study specified 3-7 days. Automatic exclusion, without good reason, is treating guidelines as "carved in stone" dictum. Since this drug is rapidly excreted in the urine (T 1/2 approx 2.2 hrs), it is unlikely that there is any residual drug effect at 72 hours. The patients should at least be supportive, and probably fully evaluable.

6. Outcome Criteria for Efficacy

Dr. Reed requests that the entire submission be reanalyzed because the company has used a clinical outcome criteria that also includes microbiological assessment, ie. clinical cure with microbiological cure, etc.

She requests that they be analyzed only as (1) clinical cure and (2) microbiological cure with no cross reference.

I personally feel that a clinical cure that is also a bacteriological cure is far more clinically informative than a clinical cure with no reference to bacteriological outcome.

7. "Assessable patients" are unevaluable

This again represents the tendency to use guidelines as absolute hurdles. Any of us that have done studies recognize that it is impossible to get all patients back for follow-up on the exact days specified. If a patient is due for follow-up on Friday, but they come back on Monday because their child was sick on Friday, does that make them truly unevaluable if follow-up was specified between 5 to 9 days and Monday was day 10?

NDA 19-384

- 5 -

I feel that they are least definitely supportive, and if including them makes good clinical sense, evaluable. If they are analyzed separately, and the results are comparable to the results for fully evaluable patients, why should they not be considered evaluable?



George R. Stanley, M.D.
Group Leader, HFN-815

cc:

Orig NDA

HFN-340

HFN-815

HFN-815/CSO

HFN-815/TReed

HFN-815/GRStanley/11m/12/4/85

0507m

ET 1/2/86 See Division Director's memorandum

January 2, 1986

Division Director's Memorandum

The claim for Norfloxacin for the treatment of gastroenteritis should not be granted. Three studies were submitted in support of the claim.

1. Study 005 (p. 35 of M.O.R.), conducted in Denver, Colorado. The medical officer felt that too few patients were evaluable to prove efficacy (p. 38). Although Norfloxacin cured 6/9 patients with Campylobacter jejuni, this was fewer than erythromycin cured (12/13). Norfloxacin cured 3/3 patients with Shigella spp. No other organism was present in more than one patient. No E. coli infections were present. The overall efficacy was 79% compared to 93% for Erythromycin.
2. Study 519-01 (p. 39 of M.O.R.), conducted in seven countries in Mexico, Costa Rica, South American countries, and Italy. Norfloxacin was effective against E. coli, Shigella spp., Salmonella spp., but was not tested against Campylobacter spp. (p. 41). In addition, this is a foreign study without an adequate U.S. study to support it.
3. Study 31 (p. 61 of M.O.R.), conducted in Danbury, CT. Norfloxacin eradicated Campylobacter jejuni in 8/9 patients in an uncontrolled study. No other organisms were studied in evaluable patients. The medical officer should add an addendum to the review stating whether the clinical outcome was also favorable in these patients.

Thus, two adequate well-controlled studies have not been provided for this indication.

I have the following additional comments:

1. Shouldn't the UTI claim be for "Klebsiella spp. including K. pneumoniae?" Similarly for Enterobacter spp.?
2. Asterisks will be needed for UTI for Citrobacter spp. and Staphylococcus spp.
3. The gonorrhea claim should not be denied solely on the failure to provide susceptibility testing, in view of the 100% efficacy against both PPNG and non-PPNG strains.



Edward Tabor, M.D.

cc:
Orig NDA
HFN-815
HFN-815/CSO
HFN-815/TGReed
HFN-815/ETabor:mas-1/3/85-0144d
HFN-815/GRStanley

NDA 19-384

January 28 and 31, 1986

MEMORANDUM OF TELEPHONE CONVERSATIONS

Between: David W. Blois, Ph.D.
Senior Director Regulatory Affairs
Merck Sharp and Dohme Research Laboratories
(215-834-2304)

and

Theresa Greene Reed, M.D.
Medical Officer, HFN-815

Subject: Recommendation regarding norfloxacin

January 28, 1985 Dr. Blois called to ask why I had excluded enterococci from the micro-organisms that I recommend for the urinary tract infection claim. He said that there were 29 evaluable cases and 20 of these were graded by Merck as completely eradicated. He felt that this was an acceptable number. Others which had fewer isolates than that were recommended.

I told him I would have to call him back after I had a chance to look at my file.

January 31, 1986 I called Dr. Blois to tell him that I could not accept most of those cases because they had come from Study No. 506/508, the uncontrolled, multiclinic, international study of norfloxacin in the treatment of complicated and uncomplicated urinary tract infections. This study had 340 patients and had been conducted at 19 clinical centers in 12 countries.

I reminded him about my comments on this study at our meeting on January 10. There were nine deficiencies and the study had not been analyzed in such a manner that any conclusions could be drawn. I asked them to re-analyze this study. Outcome criteria were not acceptable and had to be disregarded. "Assessable" patients should be unevaluable patients. Cases were disqualified when pretherapy urine cultures were obtained earlier than 48 hours before treatment. Culture timing was not acceptable. Patients under 18 years of age should have been disqualified. Upper and lower infections should not be separated. There was no microbiological outcome summary table. Adverse reactions were not properly tallied. Adverse laboratory values were not properly summarized.

Dr. Blois remembered these comments and understood why these cases were not included. He said that they are in the midst of re-analyzing this study. He asked if I would accept the enterococci cases if the re-analyzed study was an acceptable summary. I replied that I would if I agreed that they were qualified cases. Dr. Blois said they will send a package next week to respond to one-half of the questions raised at the meeting.

Theresa Greene Reed

cc

Orig NDA 19-384

HFN-815/CSO

HFN-815

HFN-815/Reed

MRD 3/1/86

February 24, 1986

MEDICAL OFFICER'S REVIEW OF NDA 19-384
and MEMORANDUM OF TELEPHONE CONVERSATION

Amendment Dated February 14, 1986

Applicant: Merck Sharp & Dohme Research Laboratories

MOR #2

Name of Drug: Generic: Norfloxacin

Trade: NOROXINTM

Pharmacological Category: Fluoroquinolone antibacterial agent

Background: The reader is referred to my MOR #1 dated November 14, 1985. In this submission, the applicant responds to requests that the review team gave at the meeting. I called Dr. Girard Picot at Merck (in Dr. Blois' absence) to give him my comments on this amendment.

1. The original report of Dr. Zinney's Phase I study, No. 45, said that, "There were no norfloxacin crystals found in the urine at 1 to 2 hours post norfloxacin and placebo dosing." My MO's comment was that, "The report does not say whether drug crystals or crystals of the metabolites were found in other specimens of urine sediment anytime during the study." Specimens were not only collected 1 to 2 hours after dosing, but also at 0-1, 2-4, 4-6, 6-8, and 8-12 hours on days 1, 2, 7, 14, 22, 23, 28, and 35.

The applicant has not answered this question about Study No. 45 in this amendment. Instead, the applicant reports for Dr. Zinney's Study No. 66, another Phase I tolerance study, that no crystals of norfloxacin were found in the urinalysis samples. There was a difference between these studies. In Study No. 45, volunteers received 400 mg twice daily or placebo for fourteen days in crossover design. In Study No. 66 volunteers received 400 mg or placebo three times daily for five days.

Dr. Picot said he will try to answer the question about the presence of crystals in the other specimens.

2. Although not requested, the applicant provides results of the neurological examinations of subjects in Dr. Zinney's studies Nos. 45 and 66.

3. At the meeting, the medical officer called attention to discrepancies between information in four case report forms and the information in the computer printout regarding the presence of crystals in urine sediment. The applicant now explains these discrepancies by saying that the differences were consistent with coding conventions for this project. The laboratory value "Many" on the case report form was coded as a numerical "50." The 1+ calcium oxalate crystals on the case report form was coded as "1.0" with units equal to "qual no." ("Qual no" was not defined.) The non-amorphous crystals value of 4+ on the case report form was coded as 4/hpf by mistake and should have been coded as "4.0 qual no."

Reviewer's Comment: These are striking examples of how raw data in the

case report forms can be changed when they are transferred to or coded for the applicant's summary tables and how they might have an entirely different meaning. Such changes should be not be permitted and case report forms should always be filed for verification of the data.

Dr. Picot will try to define "qual no."

4. At the meeting, the applicant was asked to add data from the eleven compassionate cases to the summary tables. Eight of these eleven cases were treatment failures and these cases had been omitted.

The applicant did not comply with this request. Instead, an abstract of each case report is filed.

Dr. Picot was specifically requested to revise the summary table of overall results and conclusions on pages I-08282 through I-08286 in Volume 2.23 to include these cases where qualified.

5. At the meeting, the applicant was requested to retabulate adverse reactions in order to separate data from neutropenia, gastroenteritis, and gonorrhoea case report forms from other data. This has been done, in part, in several different tables.

Dr. Picot was asked to provide one large summary table arranged sideways on the page and with the following column headings:

	Phase I		UTI	Total (%)	Gastroenteritis	Ph I	Gonorrhoea		
Body Site/	400 mg bid	400 mg tid	400 mg bid	200 mg bid	(First four columns)	400 mg bid	400 mg tid	All Single Dose	600 mg x 2
Adverse Effect	x subj.	x subj.	1015 pts.	60 pts.		146 pts.	184 pts.		135 pts.

Adverse reactions in neutropenic cases should be reported on a separate page.

6. In response to our request, patient diaries have been summarized. They were summarized by individual studies. Dr. Picot was asked to provide one summary table for all the diaries to show the complaints in patient/days.

Dr. Picot will discuss all of these comments with the staff and will reply.

This is the first part of a two-part response to our comments at the meeting.

Recommendation: Deferred until all responses have been received.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc
Orig NDA 19-384
HFN-815 ET 3/11/76 HFN-815/CSO 4683b
HFN-815/Reed

YRD 25 Feb 86

March 3, 1986

MEDICAL OFFICER'S REVIEW OF NDA 19-384
and MEMORANDA OF TELEPHONE CONVERSATIONS

Amendment (

Applicant: Merck Sharp and Dohme Research Laboratories

MOR

Name of Drug: Trade: NOROXIN™

Generic: Norfloxacin

Pharmacological Category: Fluoroquinolone antibacterial agent

Amendment Dated February 14, 1986: The applicant responds to comments raised by Drs. Mason and Hunt regarding the biopharmaceutical aspects of the application as follows:

"Following oral administration of norfloxacin, 25-30% of that dose is recovered in urine unchanged within 48 hr. Additionally, in the same period of time, another 6-10% of the dose is recovered as norfloxacin metabolites. It is known that norfloxacin and its metabolites are also excreted in bile. In other studies, feces were collected following oral norfloxacin doses and assayed microbiologically. Assuming that all antimicrobial activity was attributable to norfloxacin, fecal recovery would account for another 30% of the dose. Hence, approximately 70% of an oral norfloxacin dose may be accounted for in this manner. The remaining 30% of the dose could very likely be attributed to the following.

"The deficit does not result from improper urine collection procedures or shortcomings in the analytical procedure for urine. Since the solubility of norfloxacin in urine is dependent on pH and temperature, every precaution is taken to obtain a representative urine sample for analysis. Urine aliquots are taken after each urination rather than at the end of a collection interval to avoid the urine being stored and/or chilled. At the analytical lab, urine samples are warmed to 38°C and agitated until all materials have redissolved. Since standards for the HPLC analytical procedure are prepared in freshly-voided human urine, representative estimates of norfloxacin urinary excretion would be anticipated.

"Known norfloxacin metabolites are excreted in bile and are probably present in feces. The bacterial species used in the microbiological assay of fecal specimens cited earlier, E. coli (ATCC 25922), is variably less sensitive to norfloxacin metabolites than to norfloxacin itself. Furthermore, unknown metabolites of norfloxacin which could be formed in the G. I. tract and to which the organism is insensitive would not be detected. Both of these events would have an additive effect on estimates of norfloxacin-related species eliminated via fecal excretion.

"Finally, it has been demonstrated by van Saene, et al [Scand. J. Infect. Dis. 17: 295, 1985] that the inherent antimicrobial activity of antibiotics in feces is significantly decreased. This would cause underestimation of the amount of drug actually there if microbiological assay techniques were used.

"Hence, efforts to delineate excretion patterns in man following oral

administration of norfloxacin using microbiological assays, and specific, sensitive, and quantitative HPLC techniques rather than radiometric procedures, can conservatively account for 70% of the dose as norfloxacin and its metabolites in urine and feces. Shortcomings with microbiological procedures for analysis of fecal specimens and the possibility of unknown metabolites or degradates of norfloxacin being present in feces would conceivably account for much of the remainder."

Two publications are included.

Amendment (): The applicant responds to comments from Dr. Taylor regarding the chemical aspects of the application and files the following information:

1. Additional stability data for the reformulated product,
2. Impurity specification by thin layer chromatography of the bulk drug,
3. Dissolution specification,
4. The pH solubility profile of norfloxacin at 25°C and 37°C,
5. Thin layer chromatography identity test for the finished product as stated in their July 11, 1985 letter to FDA, and
6. A more specific description of the aluminum foil strip that was briefly described in the NDA.

Amendment (): As agreed in a telephone conversation between Dr. Mason of the Division of Biopharmaceutics, the applicant submits published articles concerning the lack of interaction between norfloxacin and probenecid, and about the excretion of norfloxacin in mother's milk. These articles were referenced in the NDA but were not included.

1. "Basic and Clinical Studies on AM-715 in the Field of Obstetrics and Gynecology." by Zenjiro Takase et al, Kawasaki Medical School (Chemotherapy, Dec. 1981).

The peak level in umbilical cord blood was 0.37-0.38 mcg/ml at 6-10 hours after an oral administration of 200 mg of AM-715, and that in amniotic fluid was 0.92 mcg/ml at 10 hrs after, but the levels in neonate blood and excretion in milk were less than the assay limit.

2. "Clinical Studies on AM-715 in the Field of Obstetrics and Gynecology" a 12-line abstract by Seiji Matsuda et al at Juntendo University School of Medicine (Chemotherapy, Dec. 1981).

In a few cases, transference of AM-715 into umbilical cord blood was observed and its concentration was about 50% of the maternal serum concentration. The transference of the drug into umbilical cord blood and amniotic fluid varied.

3. "Mechanism of Renal Excretion of AM-715, a New Quinolonecarboxylic Acid Derivative, in Rabbits, Dogs, and Humans" by Jingoro Shimada et al at the Jikei University School of Medicine in Tokyo and the Central Research Laboratories, Kyorin Pharmaceutical Co. Ltd., Tochigi, Japan (Antimicrobial Agents and Chemotherapy. 1983 (Jan); 23 (1): 1-7).

The mechanisms of the renal excretion of AM-715 were studied in

rabbits, dogs, and humans. In both rabbits and humans, AM-715 clearance was greater than creatinine clearance and was profoundly decreased by the administration of probenecid. Thus, in these subjects, AM-715 was cleared by both tubular secretion and glomerular filtration. In dogs, however, the excretion ratio (close to unity), biological half-life, and stop-flow patterns of AM-715 were not affected by probenecid, indicating that the renal excretion of AM-715 took place mostly through glomerular filtration. These results suggest that renal excretion of AM-715 differs with animal species.

Amendment (#3 Dated February 24, 1986): The applicant responds to four of the comments on the list of comments from the medical officer.

1. The applicant files a set of new tables to provide a retabulation of all UTI studies to show bacterial outcome by bacterial pathogen for 474 evaluable patients. This time FDA guidelines for urine-specimen collection were used. Also, patients under 18 years of age have been disqualified.

✓ Medical Officer's Comment: This is a partial response to the original request. The MO's original request was to revise the overall summary table to delete underage patients that should have been disqualified and to delete cases which should have been disqualified where FDA guidelines for urinary tract infections were not followed. Specifically, the firm was asked to revise the final overall summary table on pages I-08282 through I-08286 in Volume 2.23 to delete all of these disqualified cases. This table, when properly revised, will show what micro-organisms will qualify for the Indications section in the labeling. Micro-organisms for the labeling can be identified when this table is corrected. (Generating new tables at this point is not helpful.)

2. The applicant files similarly revised information for the gastroenteritis study, No. 519.

✓ Medical Officer's Comment: Same as above. The final summary table in Volume 2.23 is the one that should be revised.

3. The uncontrolled multiclinic international urinary tract infection study, described on page 65 of my MOR dated November 14, 1985, had not been analyzed satisfactorily. In response to the MO's request at the meeting with the applicant, it is re-analyzed in this submission to correct a long list of deficiencies. Clinical outcome criteria were incorrect. "Assessable" patients should be unevaluable patients. Patients were to be disqualified if pretherapy cultures were obtained earlier than 48 hours before treatment. Culture timing should comply with FDA guidelines. Patients under 18-yrs. old should be disqualified. UTI's should not be subdivided into upper and lower infections. There should have been a microbiological outcome summary table and an adverse reaction summary table. The 40 adverse laboratory values should have been listed.

With this re-analysis of these 340 cases, there were 232 disqualified cases instead of 131. Ninety-six more cases were disqualified for inadequate culture timing and five were disqualified because they were underage. There were 108 evaluable cases instead of 209.

Bacteriological outcome is summarized as follows:

<u>Pathogen</u>	<u>Eradicated/No. Isolated</u>
<u>Citrobacter diversus</u>	1/1
<u>Citrobacter freundii</u>	2/2
<u>Enterobacter cloacae</u>	1/2
<u>Enterococcus</u>	3/3
<u>Escherichia coli</u>	62/64
<u>Gram-negative rods</u>	1/1
<u>Klebsiella pneumoniae</u>	6/6
<u>Klebsiella oxytoca</u>	2/2
<u>Proteus indole positive</u>	2/2
<u>Proteus mirabilis</u>	16/16
<u>Proteus vulgaris</u>	2/2
<u>Proteus species</u>	1/1
<u>Providencia stuartii</u>	1/1
<u>Pseudomonas aeruginosa</u>	8/9
<u>Pseudomonas cepacia</u>	1/1
<u>Staphylococcus aureus</u>	3/3
<u>Staphylococcus epidermidis</u>	2/2
<u>Staphylococcus saprophyticus</u>	1/1
Total	115/119

Strains were isolated in 108 patients; 10 patients had polymicrobial infections. The eradication rate for the 108 patients was 96.2%.

A clinical outcome of cured was reported for 106 of the 108 qualified patients or 98%. This includes 10 evaluable patients with polymicrobial infections.

There were 43 adverse clinical experiences in 27 patients. The applicant lists them by body system without naming individual reactions. One 65-year old patient had convulsions due to hypoxemia caused by respiratory insufficiency. This was not considered to be drug-related. Five patients who were over 70 years of age died, none of these was considered to be drug-related but were related to the underlying diseases.

ADVERSE EXPERIENCES

	Serious/ Drug Related	Serious/ Not Drug Related	Not Serious/ Drug Related	Not Serious/ Not Drug Related
Anxiety disorders	1			
Dry mouth	1			
Tachycardia	1			
Rash	1			1
Tongue enlargement	1			
Euphoria	1			
Overflow of tears	1			
Fever		1		
Purpura		1		
Knee pain		1		
Convulsive disorder		1		
Cerebrovascular accident		1		
Shock		1		
Hypovolemia		1		
Myocard. infarct., acute		1		
Hypovolemic shock		1		
Congestive heart failure			1	
Pruritus			2	
Erythematous condition			2	1
Depression			1	
Nausea			2	4
Headache			1	
Digestive system disorders			1	
Abdominal or GI pain			1	1
Dyspepsia			2	
Dysphagia			1	
Constipation				1
Vomiting				3
Pruritus ani				1
Pneumonia				1
Total	*7	9	14	13

*All seven serious/drug-related reactions occurred in the same patient.

Fourteen patients discontinued therapy due to clinical adverse reactions.

Forty patients had laboratory adverse experiences. None was serious, definitely or probably drug related. Drug crystalluria which was reported in one patient disappeared in the post-therapy urinalysis.

ADVERSE LABORATORY EXPERIENCES

	Not Serious/ Drug Related	Not Serious/ Not Drug Related	Not Serious/ Relationship Not Stated
WBC count	1	1	-
Elevated ASAT		9	
Elevated ALAT		11	
Elevated monocytes		2	
Urine crystals (circled)		1	
Elevated hemoglobin		1	
Elevated eosinophils		6	2
Elevated alkaline phos.		7	1
Elevated serum LDH		6	
Elevated serum sodium		1	
Elevated serum creatinine		4	
Elevated urine proteun		1	
Elevated serum potassium		1	
Abnormal neutrophils		1	
Elevated blood urea		1	
Elevated BUN		3	
Elevated platelet count		2	
Elevated ESR		1	
Elevated urine WBCs			1

The applicant concludes that norfloxacin is effective in women and men in the treatment of complicated and uncomplicated UTI caused by susceptible bacteria. It is effective in the treatment of UTI caused by P. aeruginosa in patients without severe structural or functional abnormalities of the urinary tract. It was well tolerated at oral doses of 400 mg twice daily for ten days and has a good safety profile when given in this dosage schedule.

Reviewer's Comment: With the re-analysis of this study, the applicant's conclusions can be accepted.

Memoranda of Telephone Conversations March 4 and 5, 1986: In Dr. David Blois' absence, I called Dr. Berger and Dr. Picot to discuss my comments on the clinical data in the amendment. Dr. Berger will see that the overall summary table in Volume 2.23 (pages I-08282-I08286) is revised to delete disqualified patients as described above. This revised table will be available within the next few days. Controls should be included in the revised table.

I asked Dr. Berger to tell me where the bioequivalence study was located. He replied that it is Dr. Zinney's study, Study No. 59, and is located in Volume 2.4, page I-01006.

Status of this NDA: This application will probably be approvable but a statement of this fact is deferred.

1. The pharmacology review is being completed. There are so many safety issues with the quinolones that consideration of the recommendations of the

pharmacologist is a requirement before a recommendation of approval can be made.

2. The biopharmaceutics review is being completed and is being discussed in the Biopharmaceutics Division. It is not available yet but an in-house discussion of these recommendations will be needed. There is a question about the need for a bioequivalence study.

3. Labeling is unsatisfactory. The medical officer and the applicant have agreed to discuss labeling within the next four days. The overall summary table will be revised and ready for these discussions. Mr. Norton, the microbiologist for this application (who replaced Mrs. Eckert when she was given other assignments), is ready to discuss the microbiology section of the labeling at the same time.

4. The question about the potential of norfloxacin to induce crystalluria has been answered in discussions with the biopharmaceuticists. The saturation point of norfloxacin in human urine at body temperature is way above the highest urine concentrations which might be expected with the doses that shall be recommended.

5. There are two remaining unresolved comments, the report of tests of brain function in humans and a report of EEG findings in humans. The applicant suggested that these might be considered Phase IV studies.

Theresa Greene Reed
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cc
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HFN-815/Reed
HFN-815/CSO
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NDA - 19384

March 14, 1986

MEDICAL OFFICER'S REVIEW OF LABELING
and
MEMORANDUM OF CONFERENCE TELEPHONE CONVERSATION

Applicant: Merck Sharp & Dohme Research Laboratories
West Point, PA

Name of Drug: Generic: Norfloxacin

Trade: NOROXIN[®]

Review of Labeling: Labeling dated December 11, 1984 filed on January 14, 1985 in the original application (page I-09306 ff in Volume 2.25) was reviewed. Comments on the labeling were discussed with David W. Blois, Ph.D., Senior Director of Regulatory Affairs, and his staff (215-834-2304). (Underlining, below, means new additions. Editorial changes are not mentioned.)

Description: (Page 1, Line 3) Insert the class name "fluoroquinolone" on the third line.

(Page 2) At the end, add "Examples of other antibacterial drugs that are quinolones are nalidixic acid, cinoxacin, and oxolinic acid."

Clinical Pharmacology:

1. (Page 3, Lines 1-12) Revise the first paragraph to read

"In healthy volunteers, at least 30-40% of an oral dose of NOROXIN is absorbed. Absorption is rapid following single doses of 200 and 400 mg. The presence of food may affect absorption. Mean peak serum and plasma concentrations of 0.8 and 1.5 mcg/mL, respectively, are attained approximately one hour after dosing. Levels in bile exceed serum levels. 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 on either regimen."

2. (Page 4, Line 7) Add "Alteration of dosage is necessary." in regard to patients with impaired renal function.

3. (Page 4, Line 18) "Within 24 hours of drug administration, approximately 28-30%," instead of 30%, "of the dose is recovered in the urine as norfloxacin with an additional 5-8% being recovered as six active metabolites of lesser antimicrobial potency."

4. (Page 5) On the first line, insert "Fecal recovery accounts for another 30% of the dose."

5. (Page 5 Lines 6-8) "The antibacterial efficacy of norfloxacin is not affected by the pH of the urine but its solubility is."

6. The Clinical Pharmacology section should end with a new paragraph to say that following oral administration, norfloxacin has been detected in bile,

NDA - 19384

March 14, 1986

MEDICAL OFFICER'S REVIEW OF LABELING
and
MEMORANDUM OF CONFERENCE TELEPHONE CONVERSATION

Applicant: Merck Sharp & Dohme Research Laboratories
West Point, PA

Name of Drug: Generic: Norfloxacin

Trade: NOROXIN^R

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4. (Page 5) On the first line, insert "Fecal recovery accounts for another 30% of the dose."

5. (Page 5 Lines 6-8) "The antibacterial efficacy of norfloxacin is not affected by the pH of the urine but its solubility is."

6. The Clinical Pharmacology section should end with a new paragraph to say that following oral administration, norfloxacin has been detected in bile,

prostatic fluid, umbilical cord blood, and amniotic fluid, and to give these concentrations. However, this information should only be added if these concentrations are clinically significant. Dr. Blois will check these concentrations.

Microbiology: The Microbiology section is being prepared by our microbiologist. This section will be discussed with the applicant later.

(Page 6, lines 7-8) The statement that "There is generally no cross-resistance between norfloxacin and other antibacterial agents presently marketed." is not true. Cross resistance with nalidixic acid has been reported. (See page 37 or the paper by Duckworth and Williams in the Jo. of Antimicrob. Chemother. (1984; Volume 13: Suppl. B.).

Indications and Usage:

1. (Page 10) Begin this section with the sentence, "NOROXIN is indicated for the treatment of complicated and uncomplicated urinary tract infections in adults that are caused by susceptible strains of"(give names of micro-organisms). Micro-organisms cannot be named until the summary table in Volume 2.23 (Pages I-08282-08286) has been corrected. The Medical Officer's preliminary review shows that we might have Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Pseudomonas aeruginosa, Citrobacter species, and Staphylococcus species to complete this sentence.

Delete everything else on pages 10 and 11.

Insert, at the end of the Indications section, "Uropathogens should be tested in vitro for their susceptibility to norfloxacin prior to administration of the drug and when clinically indicated." This is a class labeling sentence for the quinolones.

Contraindications: (Page 12) Revise this section to read, "NOROXIN is contraindicated in patients with a history of hypersensitivity to norfloxacin or other members of the quinolone group of antibacterial agents (e.g., nalidixic acid, oxolinic acid, cinoxacin).

Warnings: In keeping with the Anti-Infective Drug Advisory Committee recommendations, a Warnings section should be added. The first sentence should be in heavy print or bold type. The section should read as follows:

WARNINGS: "THE USE OF NORFLOXACIN IN PREPUBERTAL CHILDREN AND DURING PREGNANCY IS NOT RECOMMENDED. The oral administration of single doses of norfloxacin, four times the recommended human dose, caused lameness in immature dogs. Histologic examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs (e.g., nalidixic acid, cinoxacin, and oxolinic acid) also produced erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species.

"Crystalluria has been reported in patients receiving doses that are 1/2 and 2 times the recommended daily dosage. Although crystalluria is not expected to occur under normal conditions with a dosage regimen of 400 mg

b.i.d., as a precaution, preventive measures to be taken include keeping the dose as low as possible, maintaining an adequate rate of urine flow, maintaining a urine pH below 7.0, and keeping the patient well hydrated."

Precautions:

1. (Page 12, line 7) Insert the following new paragraphs at the beginning of the section.

"Alteration in dosage regimens is necessary for patients with impaired renal function (See Dosage and Administration)."

"Norfloxacin should be used with caution in patients with a history of hepatic disease or in patients with impaired hepatic function."

The effects of norfloxacin on brain function or on the electrical activity of the brain have not been tested. Central nervous system-type adverse experiences, such as headache, dizziness, lightheadedness, hyperactivity, visual changes, and insomnia, have been reported with some antibacterial agents in the quinolone drug class. Seizures which were not thought to be drug related occurred in two norfloxacin-treated patients that had existing CNS disorders that predispose to seizures and that fully accounted for the events. Until more information becomes available, quinolones should be used with caution in patients with known factors that predispose to seizures."

2. (Page 12, Lines 7-9) Revise the sentence to read, "Diminished urinary excretion of norfloxacin has been reported following the concomitant administration of probenecid and norfloxacin. Serum concentrations, however, are not affected."

3. (Page 12, Line 10) Revise this sentence to read, "The concomitant use of nitrofurantoin is not recommended since nitrofurantoin may antagonize the antibacterial effect of NOROXIN in the urinary tract."

4. (Page 12, Line 12) Add the following new paragraphs:

"The concomitant administration of norfloxacin with antacids is not recommended."

"Information for the Patient:

"Patients should be advised to drink fluids liberally and that antacids should not be given concomitantly or within two hours after dosing."

"Patients should know how they react to norfloxacin before they operate automobiles and machinery or engage in other tasks requiring mental alertness and coordination."

5. (Page 13, Line 16) The Pregnancy Category letter should be "C" instead of "B".

Dr. Blois agreed with the Category C letter.

We shall postpone further consideration of the pregnancy paragraph temporarily because the review team is waiting for the report of a monkey study. Norfloxacin is an known abortifacient in monkeys.

Dr. Blois will file the report of this monkey study next week.

The Medical Officer added that in keeping with our advisory committee recommendations, class labeling for the quinolones calls for this section to end with the sentence, "Since norfloxacin, like other drugs in this class, causes arthropathy in immature animals, its use during pregnancy is not recommended (See Warnings)."

6. (Page 14, line 11) Revise the Nursing Mothers paragraph to read as follows:

"It is not known whether norfloxacin is excreted in human milk. When a 200 mg dose of NOROXIN was administered to nursing mothers, norfloxacin was not detected in human milk. However, because the dose studied was low, because other drugs in this class are excreted 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."

7. (Page 14, Line 21) Delete the first sentence of the Pediatric Use paragraph. The full section shall read, "NOROXIN is not recommended for use in prepubertal children (See Warnings)."

Adverse Reactions: Recommendations for this section are deferred until the applicant files a revised adverse reaction table with corrected rates and a revised adverse laboratory experiences table.

Dosage and Administration:

1. (Page 17, Line 10) Revise the first section to read, "In patients with normal renal function and in patients with creatinine clearance rates greater than 30 ml/min/1.73 m²." Delete the word "apparently" and the phrase "including elderly patients."
2. (Page 17, Lines 15-17) Revise the recommendation to read, "Uncomplicated urinary tract infections: The recommended dosage is 400 mg with a glass of water twice daily one hour before or two hours after meals for 7 to 10 days."
3. (Page 17, Lines 18-20) Revise the recommendation to read, "Complicated urinary tract infections: The recommended dosage is 400 mg with a glass of water twice daily one hour before or two hours after meals for 10 to 30 days."

We discussed the mealtime relationship that the MO added. This will be adjusted for the appropriate time of the day. We also discussed the

possibility of taking the tablet with fruit juice as an innocuous way of acidifying the urine. The original 60-day maximum treatment period was changed to 30 days. The 60-day period did not appear to be supported by clinical studies.

4. (Page 17, end) Insert the following two paragraphs.

"Patients receiving norfloxacin should be well hydrated to prevent crystallization of norfloxacin in the urinary tract."

"Doses higher than 800 mg/day are not recommended."

The medical officer explained that the Division of Biopharmaceutics recommended a ceiling dose. She arbitrarily selected a 1000 mg/day ceiling because drug crystals have been reported at 1200 mg/day. However, the applicant stated that they are not recommending a dose higher than 800 mg/day.

5. (Page 18, Lines 1-9 are deleted.) (Page 18, Line 10) Revise the renal impairment paragraph to read as follows:

"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/1.73 m² or less, the recommended dosage is one 400-mg tablet with a glass of water once daily one hour before or two hours after meals. At this dosage, the urinary concentration exceeds the MICs for most urinary pathogens susceptible to norfloxacin, even when the creatinine clearance rate is less than 10 mL/min/1.73 m². The serum creatinine should represent a steady state of renal function and..."

(Continue on page 19.)

Animal Pharmacology: In keeping with the advisory committee recommendations, there should be an animal pharmacology section after the How Supplied section. The wording of this section is being prepared by our pharmacologist. Examples are the Animal Pharmacology sections in cinoxacin, nalidixic acid, and oxolinic acid package inserts.

Dr. Blois will review these comments and recommendations with his staff and will prepare a revised draft of proposed labeling for additional revision and comment. We have gone as far as we can go without the unfinished sections. He may change the recommended wording in these suggestions to be in keeping with Merck's labeling policy and the firm's views on these subjects.

Conclusion and Recommendation: Labeling is unsatisfactory but labeling discussions with the applicant are progressing very well.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc

Orig NDA 19-384 HFN-815/CSO
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April 19, 1986

MEDICAL OFFICER'S REVIEW OF NDA 19-384
and MEMORANDUM OF TELEPHONE CONVERSATIONS

Amendments

Applicant: Merck Sharp and Dohme Research Laboratories
West Point, PA

Name of Drug: Generic: Norfloxacin

Trade: NOROXIN^R

Pharmacological Category: Fluoroquinolone antibacterial agent for oral use

Amendment In response to our requests, the applicant
files the following two items:

1. An overall summary for the patient diary data previously submitted on Feb. 14, 1986. Additional diaries had been filed but no diaries were summarized.

These data characterize and compare the number of patients with, and days of, each complaint. The percentage of complaints per person was obtained by dividing the number of persons voicing a complaint by the total number of persons receiving each drug. The percentage of days for each complaint was determined by dividing the total number of days of each complaint by the total number of treatment days. Corrected frequencies were obtained by subtracting the percents for placebo-treated subjects from the percents for norfloxacin-treated patients. A negative percent denotes a higher frequency in the placebo group.

ANALYSIS OF PATIENT DIARIES

Complaints	<u>Placebo Cases</u> (N=51)		<u>Norfloxacin Cases</u> (N=100)		<u>Norfl. vs Placebo</u>	
	Total 468 days of RX		Total 995 days of Rx		% of total	
	# Cases	Days of Complaint	# Cases	Days of Complaint	# Cases	days of Complaint
Tired, etc	12 (24%)	21 (4%)	22 (22%)	61 (6%)	-2%	2%
Headache	13 (25%)	31 (7%)	22 (22%)	58 (6%)	-3%	-1%
Sleepy, etc	5 (10%)	6 (1%)	12 (12%)	25 (2.5%)	2%	1.5%
Nausea, etc.	2 (4%)	2	18 (18%)	49 (5%)	14%	5%
Dizzy, etc.	1 (2%)	3 (0.6%)	3 (3%)	5 (0.5%)	1%	-0.1%
Lightheaded			2 (2%)	6 (0.6%)	2%	0.6%
Eye Complaints	2 (4%)	6 (1%)	4 (4%)	14 (1.4%)	0%	0.4%
Stomachache	2 (4%)	2	8 (8%)	11 (1%)	4%	1%
Rotten, sick, etc.			5 (5%)	5 (0.5%)	5%	0.5%
Hyperactive	1 (2%)	1	1 (1%)	1	-1%	0
Numbness, etc.			2 (2%)	3	2%	0.2%
Flank pain			1 (1%)	1	1%	0.1%
Lump in throat			1 (1%)	3	1%	0.3%
Diarrhea			2 (2%)	2	2%	0.2%
Depressed	1 (2%)	1			-2%	-0.2%
Metallic taste	1 (2%)	1			-2%	-0.2%
Poor sleep			8 (8%)	13 (1.3%)	8%	1.3%
Backache			3 (3%)	10 (1%)	3%	1%
Nervous, etc.			2 (2%)	3	2%	0.2%
Constipated			1 (1%)	1	1%	0.1%
Anorexia	1 (2%)	1	1 (1%)	2	-1%	0
Itching, rash			2 (2%)	5 (0.5%)	2%	0.5%
Swollen hands, etc.			2 (2%)	7 (0.7%)	2%	0.7%
Vaginal itching			4 (4%)	7 (0.7%)	4%	0.7%
Dry mouth			1 (1%)	1	1%	0.1%
Tinnitus			1 (1%)	2	1%	0.2%
Joint complaints			1 (1%)	1	1%	0.1%
No comments	28 (55%)	412 (88%)	37 (37%)	768 (77%)		

About 400 placebo treatment days are compared to about 1000 days norfloxacin treatment days. The rates were greater for norfloxacin than placebo, particularly for two complaints, nausea (14% greater), and poor sleep (8% greater). Others that were greater for norfloxacin were stomachache, feeling rotten or sick, and vaginal itching. Rates were greater for placebo than for norfloxacin for several complaints but none were as high as those given above.

2. Two issues that this medical officer asked to be clarified are explained. "Qual no" means qualitative numbers. Computer coding used a scale of 0-4+ for some reports. This scale was used to report urine protein and urine glucose concentrations and appeared on the computer printout as "Qual no." In like manner, words on the case report forms were converted to numerical figures for platelets and other laboratory reports. Therefore, "Many" epithelial cells and nonamorphous crystals on Dr. Cohn's case report #302 was converted to 50 per high power field in the computer printout.

Amendment In response to the medical officer's request, the bacterial efficacy tables for urinary tract infection studies have been revised to exclude underage patients, to include micro-organisms which were not evaluable for the microbiological evaluation for a number of reasons, and to provide separate counts for individual species in five genera. Compassionate cases that had been excluded are included.

These revised bacterial outcome tables should be disregarded because the applicant failed to include data from the control groups. This revision is superseded by the Amendment () which includes data from the controls.

Amendment The applicant files final reports of the three following studies which were requested by the FDA pharmacologist at the January 14, 1986 meeting with the firm:

1. Teratology study of norfloxacin in cynomolgus monkeys,
2. Metabolism study of norfloxacin in pregnant and nonpregnant cynomolgus monkeys, and
3. Embryotoxicity study of norfloxacin in cynomolgus monkeys.

The reader is referred to the review by the pharmacologist.

The results of the teratology study indicate that the oral administration of norfloxacin during organogenesis in the cynomolgus monkey at doses of 75 mg/kg/bid and greater induced dose-related embryotoxicity. The no-effect dose was 50 mg/kg/bid. Doses sufficient to cause embryonic loss are not tolerated in some monkeys. The mechanism of norfloxacin-induced embryotoxicity is most likely hormonal (some aspect of placental progesterone synthesis) and not a direct effect on the embryo. Norfloxacin was not teratogenic in any species.

The applicant concludes that in view of the embryoletality in monkeys, although the relevance of this to humans is not known, norfloxacin should be used in pregnancy only if the benefits justify the potential risk to the fetus.

Reviewer's Comment: Like other quinolones, norfloxacin already is not to be recommended for use in pregnancy because of the development of arthropathy in juvenile animals of all species tested. Embryotoxicity is a second reason.

Amendment ()

1. In response to the medical officer's request the bacterial efficacy tables for urinary tract infection studies have been revised to exclude underage patients, to include micro-organisms which were not evaluable for the microbiological evaluation for a number of reasons, and to provide separate counts for individual species in five genera. Data from control groups have been added. Compassionate cases that had been excluded are included.

The applicant's revised summary of efficacy data for urinary tract infections for evaluable patients in this application is shown below. (Number eradicated/No. Isolated. Protocol numbers are in parentheses.)

Indication & Claim No.	Organism	Controlled Trials			Uncontrolled Trials - Proto-	
		Norfloxac- acin	Control	Protocol #	#E/#I	col #
1.1	<u>E. coli</u>	46/46	44/44	(#001)	13/13	(#011)
		27/27	17/22	(#002)	28/29	(#017)
					0/1	(#019)
	Total	53/53 126/126 (100.0%)	52/55 113/121 (93.4%)	(#504/505)	61/63 102/106 (96.2%)	(#506/508)
1.2	<u>Klebsiella pneumoniae</u>	1/1	2/2	(#001)	5/5	(#011)
		6/8	5/5	(#002)	3/3	(#017)
		1/5	3/4	(#504/505)	6/6	(#506/508)
	Total	8/14 (57.1%)	10/11 (90.9%)		14/14 (100.0%)	
	<u>K. oxytoca</u> <u>Klebsiella sp.</u>	0	1/1	(#504/505)	2/2	(#506/508)
1.3	<u>Enterobacter aerogenes</u>	1/1	1/1	(#002)	2/3	(#011)
		0/1	1/1	(#504/506)		
		Total	1/2	2/2		2/3
		<u>E. cloacae</u> <u>E. agglomerans</u> <u>Enterobacter sp.</u>	4/4 1/1 0	1/1 0 2/2	(#504/505) (#504/505) (#504/505)	1/2 1/1
1.4	<u>Proteus mirabilis</u>	3/3	1/1	(#001)	4/4	(#011)
		5/5	3/4	(#002)	4/4	(#017)
		9/9	8/9	(#504/505)	15/15	(#506/508)
	Total	17/17 (100%)	12/14 (85.7%)		23/23 (100%)	
1.5	<u>Proteus, indole positive group</u> (3 species) Total	1/1	1/1	(#002)	4/4	(#506/508)
		2/2	1/1	(#504/505)		
		3/3	2/2		4/4 (100%)	
1.6	<u>Pseudomonas aeruginosa</u>	4/4	0	(#001)	11/13	(#011)
		4/8	0	(#002)	2/3	(#017)
					2/6	(#019)
	Total	5/5 13/17 (76.5%)	0/1 0/1	(#504/505)	8/9 23/31 (74.2%)	(#506/508)
	<u>Pseudomonas cepacia</u> <u>P. fluorescens</u>	0	1/1	(#002)	1/1	(#506/508)

Indication & Claim No.	Organism	Controlled Trials			Uncontrolled Trials - Proto-	
		Norfloxac- acin	Control	Protocol #	#E/#I	col #
1.7	<u>Serratia marcescens</u>	0	1/1	(#504/505)		
1.8	<u>Providencia stuartii</u> and <u>Providencia sp.</u>	2/2	0/0	(#504/505)		
1.9	<u>Citrobacter freundii</u>	1/2	0/0	(#002)	2/2	(#017)
	Total	1/2	0/0		2/2	(#506/508)
	<u>Citrobacter diversus</u>	0/0	0/0		1/1	(#506/508)
	<u>Citrobacter sp.</u>	0/0	1/1	(#001)		
		1/1	0/0	(#002)		
1.10	<u>Staphylococcus aureus</u>	1/1	0/0	(#001)	2/3	(#011)
		3/3	2/2	(#002)	3/3	(#017)
	Total	4/4	2/2		3/3	(#506/508)
					8/9	(88.9%)
	<u>Staphylococcus epidermidis</u>	3/3	0/0	(#002)	1/1	(#011)
		0/0	1/1	(#504/505)	2/2	(#017)
	Total	3/3	1/1		2/2	(#506/508)
					5/5	
	<u>Staphylococcus saprophyticus</u>	1/1	0/0	(#001)		
		0/0	1/1	(#002)		
	1/1	0/0	(#504/505)	1/1	(#506/508)	
	<u>Staphylococcus coag. neg</u>				1/1	(#011)
					1/1	(#017)
1.11	Group D streptococci	7/8	0/1	(#002)	5/6	(#011)
	cluding <u>S. faecalis</u>	1/1	5/5	(#504/505)	1/2	(#017)
	Total	8/9	5/6		3/3	(#506/508)
		(88.9%)	(83.3%)		9/11	(81.8%)
1.12	Group B streptococci Beta-hemolytic strep.	1/1	1/1	(#002)	1/1	(#011)

Medical Officer's Comments: (Percents were added by the medical officer.)

a) This revised table responds to the medical officer's requests and is satisfactory. It is the final bacteriological outcome table and takes the place of the applicant's table shown on pages 88-89 and the medical officer's preliminary outcome table shown on pages 91-91 of the original

MOR of this application.

b) Therefore, satisfactory efficacy data have been filed to recommend norfloxacin in the treatment of urinary tract infections caused by Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus aureus, and Group D streptococci. Staphylococcus epidermidis, Citrobacter freundii, and Enterobacter cloacae should also be added to this list but with an asterisk to show that there were less than ten cases.

Tallying individual species separately in this revised table deletes Enterobacter aerogenes (only 1/2 eradications in controlled trials and 2/3 eradications in uncontrolled trials).

c) Treatment of gastroenteritis will not be recommended.

2. In response to the medical officer's request, adverse reaction data and laboratory data have been retabulated to provide counts in separate categories by the size and frequency of the dose.

Distribution of Adverse Experiences by Dose
(Only rates greater than 0.15% are shown)

	200 mg bid 60 pts.	400 mg bid 1015 pts	400 mg bid 27 Vol.	400 mg tid 25 Vol.	Total N=1127	% hav- ing AE	% of Drug- Related AEs
Abdominal Swelling		1	1		2	0.17	0
Fatigue		3	3		6	0.53	0
Fever		2		1	3	0.27	0
Myocardial Infarct.		2			2	0.17	0
Abdominal Pain		4 (2)	1		5 (2)	0.44	3.5
Constipation		4			4	0.35	-
Diarrhea		3 (1)			3 (1)	0.27	1.8
Dry Mouth		3 (2)			3 (2)	0.27	3.5
Dyspepsia		5 (4)			5 (4)	0.44	7
Flatulence		3	1		4	0.35	-
G.I. Cramps		2 (1)			2 (1)	0.17	1.8
Heart Burn		4			4	0.35	-
Mouth Ulcer		2			2	0.17	-
Nausea		28 (13)	2	1	31 (13)	2.75	23
Vomiting		2	1		3	0.27	-
Depression		4 (1)			4 (1)	0.35	1.8
Dizziness		16 (6)	4		20 (6)	1.77	10.5
Headache		21 (4)		9	30 (4)	2.66	7
Insomnia		4 (2)			4 (2)	0.35	3.5
Somnolence		5 (1)			5 (1)	0.44	1.8
Pruritis		2 (2)			2	0.17	3.5
Rash		6 (3)			6 (3)	0.53	5.3
Taste Perversion		2 (2)			2 (2)	0.17	3.5
Other (Under 1%)		40 (13)	2	2	44 (15)		
Total		105 (57)	15	13	196 (57)		

The most frequently occurring adverse reactions for 1127 subjects in multiple-dose, non-neutropenic studies that were predominantly urinary tract infection studies with the recommended 400 mg bid dose schedule were nausea - 2.75%, headache - 2.66%, dizziness - 1.77%, rash - 0.53%, and fatigue - 0.53%.

Distribution of Adverse Laboratory Experiences by Dose
(Only rates greater than are shown)

	200 mg bid 60 pts.	400 mg bid 1015 pts	400 mg bid 27 Vol.	400 mg tid 25 Vol.	Total N=1127	% hav- ing AEs	% of Drug- Related AEs
Hemoglobin Dec.		4			4	0.35	0
Hematocrit Dec		2	3		5	0.44	0
WBC Count Dec.*		6 (3)	8		14 (3)	1.2	30
WBC Count Inc.		3	1		4	0.35	0
Neutrophils Dec.*		7 (3)			7 (3)	0.62	30
Lymphocytes Rel Inc.		3 (1)			3 (1)	0.17	10
Eosinophilia		19 (1)	1		20 (1)	1.8	10
Thrombocytopenia		4			4	0.35	0
BUN Elevated		11			11	0.98	0
Ser. Creat. Elev.		5			5	0.44	0
Tot. Biliru. Elev.	1	3			4	0.35	0
AST, ALT Inc.		20 (1)			20 (1)	1.8	10
Alk. Phos. Inc.		16 (1)			16 (1)	1.4	10
Ser. LDH inc.		7			7	0.62	0
Ser. Chloride Dec.		4			4	0.35	0
Ser. Chloride Inc.		3			3	0.27	0
Urine Protein Inc.		3	1		4	0.35	0
Urine RBCs Inc.		3			3	0.27	0
Other (Under 2%)	0	14	1		15		0
Total	1	137 (10)	15	0	153 (10)		

*In most instances, WBC decreases and neutrophil decreases came from the same patients.

In both tables, numbers in parentheses are the number of reactions thought to be drug-related.

The most frequently occurring laboratory adverse experiences were eosinophilia - 1.8%, AST or ALT increase - 1.8%, increased alkaline phosphatase - 1.4%, decreased WBC count - 1.2%, and elevated BUN - 0.98%. No single adverse laboratory experience in urinary tract infection studies was as high as 2%.

Amendment The applicant responds to the request from FDA's Division of Biopharmaceutics for in vitro dissolution data on various lots and formulations of norfloxacin tablets. Dissolution data as agreed upon in a telephone conversation with Dr. Gene Mason of this Division are filed.

The final market image 400-mg formulation, the Kyorin 400 mg-tablet, the Merck Sharp & Dohme Research Laboratories direct compression 400 mg-tablet, and

production scale tablets are compared. The final market image formulation dissolves faster and peaks faster than any of the previous products and has less coating. Eighty percent of the tablet dissolved in 30 minutes. The reader is referred to the chemist's review and to the review by Dr. Gene Mason of the Division of Biopharmaceutics. That Division has accepted this report.

Amendment () Revised proposed labeling is filed. Many of the comments listed in my MOR dated March 14, 1986 have been included. Some were not included. Comments on the new version are listed below.

Clinical Pharmacology:

1. (Page 6, line 7) Insert "Alteration of dosage is necessary (See DOSAGE AND ADMINISTRATION)." in regard to patients with impaired renal function.
2. (Page 6, line 19) Insert "in the urine" in the sentence, "Within 24 hours of drug administration, 26 to 32% of the dose is recovered in the urine as norfloxacin ..."

Microbiology:

1. (Page 9, lines 4-6) Revise this sentence to read, "Nalidixic acid resistant organisms are generally susceptible to norfloxacin in vitro; however, these organisms (particularly P. aeruginosa, K. pneumoniae, Acinetobacter, and enterococci) may have higher MICs to norfloxacin than nalidixic acid-susceptible strains. For this reason, cultures and susceptibility testing may have to be repeated.

Indications and Usage:

(Page 15) Revise the first paragraph to read as follows:

"NOROXIN is indicated for the treatment of adults with complicated and uncomplicated urinary tract infections that are caused by susceptible strains of the designated micro-organisms listed below:

Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus aureus, Staphylococcus epidermidis,* Citrobacter freundii,* Enterobacter cloacae,* and group D streptococci.

*Efficacy for these micro-organisms in urinary tract infections was studied in fewer than ten infections."

Warnings:

1. (Page 16, lines 14-15) Revise the sentence to read, "The oral administration of single doses of norfloxacin, 4 times the recommended human clinical dose, caused lameness in immature dogs."
2. (Page 16, lines 7-12) Switch phrases and revise the first sentence so

that it will read "Needle-shaped crystals in the urine were found in some volunteers who received either 800 mg norfloxacin, 1600 mg norfloxacin (at or twice the recommended dose), or placebo while participating in a single double-blind, crossover study comparing single doses of norfloxacin with placebo." Delete the next sentence "These crystals were not identified."

3. (Page 16, line 17) Add "and an adequate rate of urine flow" to the end of the last sentence.

Precautions:

1. (Page 18, line 3) Insert two paragraphs that were recommended in the last labeling discussion.

↳ "Norfloxacin should be used with caution in patients with a history of hepatic disease or in patients with impaired hepatic function."

"The effects of norfloxacin on brain function or on the electrical activity of the brain have not been tested. Central nervous system-type adverse experiences such as headache, dizziness, lightheadedness, hyperactivity, visual changes, and insomnia have been reported with some antibacterial agents in the quinolone drug class. Seizures which were not thought to be drug related occurred in two norfloxacin-treated patients that had existing CNS disorders that predispose to seizures and that fully accounted for the events. Until more information becomes available, quinolones should be used with caution in patients with known factors that predispose to seizures."

2. (Page 19, lines 2-7) Revise the Information for Patients section to read as follows:

"Patients should be advised to drink fluids liberally and that antacids should not be taken concomitantly or within two hours after dosing.

"NOROXIN may cause dizziness or lightheadedness; therefore, patients should know how they react to norfloxacin before they operate automobiles and machinery or engage in activities requiring mental alertness and coordination."

3. (Page 20, lines 12-19) Switch the first two sentences in the Pregnancy Category C section.

(Page 21, lines 1-3) The last sentence in the pregnancy section should be revised to read, "Since norfloxacin, like other drugs in this class, causes arthropathy in immature animals, its use during pregnancy is not recommended (See Warnings)."

Adverse Reactions: (Pages 22-23) Revise this whole section to read as follows:

"NOROXIN generally is well tolerated. The overall incidence of drug-related side effects in clinical trials involving 1127 subjects was approximately _____%" (Percent figure will be inserted.)

"The most common side effects (less than 3%) observed during clinical trials were either gastrointestinal or neurological and include nausea-2.8%, headache-2.7%, and dizziness-1.8%. Additional reactions with frequencies greater than 0.3% were fatigue, rash, abdominal pain, dyspepsia, somnolence, depression, insomnia, flatulence, and heart burn. Less frequent reactions were dry mouth, diarrhea, fever, vomiting, and erythema. Although not reported with norfloxacin, visual disturbances have been reported with other drugs in this class."

"Abnormal laboratory values observed in clinical trials were eosinophilia-1.8%, elevation of ALAT (SGPT) and ASAT (SGOT)-1.8%, increased alkaline phosphatase-1.4%, and decreased WBC-1.2%. Those occurring less frequently were elevated BUN, serum creatinine, and LDH, and decreased hematocrit.

Dosage and Administration: (Page 24, lines 1-12) Revise this section to read as follows:

"Norfloxacin should be taken orally one hour before or two hours after a meal with a glass of water. Patients receiving norfloxacin should be well hydrated to prevent crystallization of norfloxacin in the urinary tract.

"Normal Renal Function

"The recommended norfloxacin dose is 400 mg twice daily for adults with normal renal function, and for patients with creatinine clearance rates greater than 30 mL/min/1.73 m².

For uncomplicated urinary tract infections, the recommended treatment period is 7 to 10 days.

For complicated urinary tract infections, the recommended treatment period is 10 to 30 days.

Doses higher than 800 mg/day are not recommended.

Animal Pharmacology: The Anti-Infective Advisory Committee has recommended that labeling for members of the quinolone drug class have an Animal Pharmacology section. The following text is recommended:

Animal Pharmacology: Norfloxacin and related drugs have been shown to cause arthropathy in immature animals of most species tested (See Warnings).

Crystalluria occurs in laboratory animals treated with norfloxacin. In dogs, needle-shaped drug crystals were seen in the urine at doses as low as 50 mg/kg/day. In rats, crystals were reported following doses of 200 mg/kg/day. In cynomolgus monkeys, drug crystals were seen in the urine at doses of 50 mg/kg/day and higher.

Embryolethality and slight maternotoxicity were observed in cynomolgus monkeys at doses of 50 mg/kg/day or higher.

Oculotoxicity, seen with some related drugs, was not observed in any norfloxacin-treated animal."

Memoranda of Telephone Conversations: A number of telephone conversations were held with Dr. David W. Blois, Senior Director of Regulatory Affairs (215-661-2304) to discuss these amendments and proposed labeling.

April 16, 1986 I called to dictate labeling recommendations. Dr. Blois will edit the brain function paragraph.

April 17, 1986 I called to discuss adverse reaction data. Dr. Blois discussed the Indications section. Dr. Blois wants E. cloacae, C. freundii, and indole positive Proteus listed in the Indications section.

April 19, 1986 In a conference call, Mr. Norton and I gave them comments on the Microbiology section. We agreed to add E. cloacae and C. freundii with asterisks. These pathogens are exquisitely susceptible to norfloxacin. Indole positive Proteus, however, represents a group.

Conclusion: All requests have been answered satisfactorily and the applicant has responded to all comments except a few labeling comments.

Recommendation: This application should be made approvable. Labeling is unsatisfactory but labeling discussions are progressing very well.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc
Orig NDA
HFN-815
HFN-815/Reed
HFN-815/CSO
4731b

BRD 22 Apr 86

4/28/86 Division Director's Comment
Wording of the "asterisk footnote" should be consistent with that in other recent drug labeling - preferred identical. S. Tabor

NDA 19-384

May 2, 1986

MEDICAL OFFICER'S REVIEW OF LABELING
and MEMORANDUM OF TELEPHONE CONVERSATIONS
Amendment ()

Applicant: Merck Sharp & Dohme Research Laboratories
West Point, Pennsylvania

Name of Drug: Trade: NOROXIN

Generic: Norfloxacin

Pharmacological Category: Fluoroquinolone

The applicant submits another revised version of proposed labeling.

Medical Officer's Comments: Revised proposed labeling has greatly improved and we are essentially in agreement. This new version was discussed with Mr. Norton. There are a few recommended sentences that have been omitted and there are a number of suggestions regarding sentence structure.

April 29 and 30, 1986: I called Dr. David Blois to discuss labeling.

May 2, 1986: I received the new version and I called Dr. David Blois, Senior Director of Regulatory Affairs (215-834-2304), to discuss these changes and to dictate my recommendations. Dr. Blois will consider these changes with his staff and will file revised proposed labeling in two or three days.

Recommendation: Approval is recommended but labeling is still unsatisfactory.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc

Orig NDA

8/SHFN-340

HFN-840/Reed

HFN-845/CSO

4783b

JRD 5/11/86

8:5 E.T. 5/23/86

IND 18,718 and NDA 19-384

April 25, 1986

MEDICAL OFFICER' REVIEW OF IND 18,718

Adverse Reaction Reports Dated 4-8-86 and 8-27-85 (Received 4-17-86)

Sponsor-Applicant: Merck Sharp and Dohme Research Laboratories

Name of Drug: Generic - Norfloxacin
Trade - NOROXIN^R

Amendment Dated August 27, 1985 (Just received on April 17, 1986): We are notified on Form 1639 of a third convulsion in a patient taking norfloxacin. This 32-year old Australian female suspected of having multiple sclerosis for about four years, received 200 mg bid of marketed norfloxacin for the prevention of urinary tract infection. She experienced a grand mal seizure after 1.4 years of prophylaxis and treatment continued. The investigator felt it was related to her multiple sclerosis and was not drug related.

Medical Officer's Comment: Until more information becomes available, a cause-effect relationship cannot be determined. Proposed labeling will address the problem of potential seizure activity.

Amendment Dated August 27, 1985: In Germany, a 32-year old pregnant female received 800 mg/day of marketed norfloxacin for treatment of acute pyelonephritis. She delivered a congenitally malformed infant girl with a suspected diagnosis of Opitz-Trigonocephalia.

Chromosome analysis revealed a female karyotype with deletion in the short arm of both chromosomes #7 (partial monosomes 7p). The breakpoint was located at the band 7p15. The chromosome abnormality was identified by using the R-bands technique, G-bands technique, and fluorescence with Mithramycin Colony. Subsequently, blood samples obtained from both parents were examined for chromosomal analysis. The karyotypes of the mother and father were normal without identifiable structural changes. Therefore, it was concluded that a reciprocal translocation between the short arm of chromosome #7 and any other chromosomal segment may be excluded as the cause of the infant's partial monosome #7. The geneticist stated the deletion in the short arm of chromosome #7 in this infant must have originated spontaneously during meiosis from the germ cells in one of the parents. He felt it very unlikely that the infant's anomalies were a result of possible teratogenic effects of norfloxacin and that the patient's experience was consistent with eight other cases of monosome 7p as reported in the literature.

Medical Officer's Comment: No conclusion can be drawn from one case. Proposed labeling indicates that norfloxacin is not recommended in pregnant women because of the arthropathy problem and because of embryoletality and slight maternotoxicity in monkeys.

Recommendation: No change. Approval will be recommended when labeling becomes satisfactory

cc Orig IND
Orig NDA

EL 5/20/86
HFN-845
HFN-845/Reed

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

HFN-845/Buko HFN-845/CSO 4769b

IND 25 Apr 86

NDA
19.384

May 16, 1986

MEDICAL OFFICER'S REVIEW OF LABELING
and MEMORANDUM OF TELEPHONE CONVERSATION
Amendment ()

Applicant: Merck Sharp & Dohme Research Laboratories
West Point, Pennsylvania

Name of Drug: Trade: NOROXIN

Generic: Norfloxacin

Pharmacological Category: Fluoroquinolone

The applicant submits another revised version of proposed labeling.

Medical Officer's Comments: Revised proposed labeling is satisfactory.

Telephone Conversation May 16, 1986: I called Dr. Blois (215-834-2304) to tell him that I had received this amendment. He told me that the safety update is ready and will be delivered to me Monday, May 19, 1986.

Recommendation: Approval is recommended.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc
Orig NDA, HFN-815, HFN-815/Reed, HFN-815/CSO, HFN-815/Norton, 4802b

ET 5/23/86
MK 16 May 30

MEDICAL OFFICER'S REVIEW OF NDA 19-384

Safety Update Dated May 19, 1986

Applicant: Merck Sharp and Dohme Research Laboratories
West Point, Pennsylvania 19486

Name of Drug: Trade: NOROXIN
Generic: Norfloxacin

In keeping with our request, the applicant files a safety update report covering the period from the NDA cut-off date, June 26, 1984, through September 30, 1985. This report gives adverse clinical and laboratory events from domestic and international controlled trials and compassionate therapy. Also, serious adverse experiences from the period since September 30, 1985 are presented. Since the NDA was compiled, an additional 1,797 patients have been treated with norfloxacin in controlled clinical trials, and over 17 million patients have been treated in worldwide marketing experience.

The following patients have been treated with norfloxacin since June 27, 1984:

Study	Approximate Number to 3-31-86
MSDRL controlled (domestic)	708
MSDRL controlled (international)	1,089
Japan Marketing Experience	11,900,000
Local Registration Studies	30,000
Clinical Development Study Program (CDSP)	1,945
MSDI Marketing Experience (excluding Japan)	5,600,000

Domestic and Foreign Applicant-Sponsored Studies: Between June 27, 1984 and Sept. 30, 1985, case report forms were received for the following 806 patients and volunteers who received norfloxacin in MSDRL-sponsored clinical trials:

Program	Dosage	No. Pts/Volunteers
Urinary tract infection (UTI)	400 mg bid	327
Travelers diarrhea (prophylaxis)	400 mg qd	60
Gastroenteritis (treatment)	400 mg bid	10
Gastroenteritis (treatment)	400 mg tid	30
Neutropenia (infection prophylaxis)	400 mg bid	27
Neutropenia (infection prophylaxis)	400 mg gid	9
Gonorrhea (treatment)	600 mg x 2 doses	8
Gonorrhea (treatment)	800 mg single dose	222
Compassionate program (U.S.)	400 mg qd, bid, tid	14
Compassionate program (Intern't)	400 mg bid	57
Pharmacology study	400 mg x 2 doses	24
Pharmacology study	400 mg single dose	18
	Total	806

(The number 806 differs from the number 708 because there were different cut off dates.)

Adverse reactions which were not seen in the NDA patients treated for urinary tract infections are listed below:

Adverse Reaction	No. Pts.	No. Drug Related
Malaise	5	0
Jaundice	1	0
Stomatitis	1	1
Muscle cramps	1	0
Hypertonia	1	0
Irritability	1	1
Lung cancer	1	0
Hyperhydrosis	1	1

Among post-NDA urinary tract infection cases, the most frequent adverse reactions were those related to the digestive system. Nausea was the most common complaint. The second most common complaint was neuropsychiatric in nature, namely, headache. Most common complaints are shown below:

System	All NDA	Drug Related NDA	All Post-NDA	Drug Related Post-NDA
Digestive:				
Nausea	2.75%	1.15%	2.45%	0.92%
Dyspepsia	0.44%	0.35%	0.31%	0.31%
Neuropsychiatric:				
Headache	2.66%	0.35%	1.83%	0.61%
Dizziness	1.77%	0.53%	0.61%	0.61%
Skin/Allergic:				
Rash	0.53%	0.27%	0.61%	0
Erythema	0.27%	0.17%	-	-

Adverse reactions with frequencies greater than five in combined data from the NDA and safety update and the total number are shown in the next table.

Adverse Experience	NDA UTI & Volunteer N=1127	Safety Update UTI N=327	Combined NDA & Safety Update N=1454	Combined % of pts. with AEs	Combined % with drug- related AEs
Constipation	4	2	6	.41	0
Diarrhea	3 (1)	2 (1)	5 (2)	.34	.14
Dry mouth	3 (2)	2 (1)	5 (3)	.34	.21
Dyspepsia	5 (4)	1 (1)	6 (5)	.41	.34
Nausea	31 (13)	8 (3)	39 (16)	2.68	1.10
Depression	4 (1)	1 (1)	5 (2)	.34	.14
Dizziness	20 (6)	2 (2)	22 (8)	1.51	.55
Headache	30 (4)	6 (2)	36 (6)	2.47	.41
Somnolence	5 (1)	-	5 (1)	.34	.07
Rash	6 (3)	2	8 (3)	.55	.21

(The number that were drug related is shown in parentheses.)

In the NDA, there were 196 adverse reaction reports for 1127 UTI patients and volunteers: 55 were drug related. In the safety update, there are 61 adverse reaction reports for 327 patients: 21 were drug related. Combined, there were 256 reactions of which 76 were drug related.

There were ten deaths. None of the deaths were considered to be drug related. Adverse experiences that were considered to be serious were convulsive disorders in two patients, intracerebral hemorrhage, jaundice, and confusion. One convulsive disorder and the intracerebral hemorrhage were probably not drug related. The other three were definitely not drug related.

Adverse clinical experiences resulted in discontinuation of therapy in 14 of 534 (2.6%) of all safety update report patients (including patients treated for diagnoses other than UTI), excluding the two-dose and single-dose gonorrhea studies. The most common reasons were nausea and rash.

The most common laboratory adverse experiences were elevated AST, ALT, followed by eosinophilia, elevated creatinine, elevated alkaline phosphatase, and leukopenia. None of the leukopenias or elevated creatinines were drug-related while one each of the other aforementioned observations were considered related to norfloxacin. Others were thrombocytosis (2 cases), increased serum GGT (1), increased blood glucose (2), decreased serum sodium (2), and decreased creatinine clearance (1). None of these were considered drug-related.

As with clinical adverse experiences, the types of laboratory adverse experiences from NDA and post-NDA patients are similar.

Adverse laboratory experiences resulted in discontinuation of therapy in 6 of 534 (1.1%) of safety update report patients, excluding the two-dose and single dose gonorrhea and pharmacology studies. The most common reasons for discontinuation were elevated liver function tests. None of the adverse laboratory experiences were considered related to norfloxacin therapy.

The applicant concludes that the safety profile for norfloxacin during the post-NDA period covered by this report is consistent with that seen in NDA data and described in the package circular.

Safety Update Report - Japan: The applicant reports that safety data from Japan have been derived from the post-marketing surveillance study (PMS) and spontaneous reports from prescribing physicians using marketed drug. The PMS study is a compulsory study required for all drugs after launching, maintained for three years after approval, and reported annually. Adverse experiences are looked for and reported in accordance with Koseisho Regulations. As of February 14, 1986, 8,827 patients had been enrolled in the PMS study. Between March 1984 and March 31, 1986, it is estimated that approximately 11,900,000 people received treatment with norfloxacin manufactured by Kyorin and Torii Pharmaceutical Companies.

Two deaths are listed: the cause was unknown for one and the other was due to acute renal failure which was reported as probably drug related. The patient had a history of hypertensive cerebral hemorrhage and asthma. The attacks led to a pulmonary infection followed by disseminated intravascular coagulation.

Twenty-four serious adverse experiences are listed in the report. The most frequent clinical AR's were allergic-type reactions, while the most frequently reported laboratory adverse events were elevated liver function tests. Their frequency is far below those described in clinical trials.

Local Registration Studies: In addition to the Japanese and clinical development studies, local studies to support product registration are on-going worldwide. The studies are conducted by the local Merck subsidiary and do not have case report forms. Approximately 30,000 patients had been treated in these local studies as of March 31, 1986. Prompt reporting of any deaths or serious adverse experiences are required and these are the only data that are available for the period between June 27, 1984 and March 31, 1986.

There are 21 reports. Eleven were deaths: ten of the eleven deaths were definitely not drug related. One death was due to interstitial nephritis and was listed as probably drug related. Other reactions are consistent with previous information.

Clinical Development Study Program: The Clinical Development Study Program supplements Merck's program in which the drug has been established as safe and effective. It gives physicians overseas an opportunity to form their own opinion concerning the efficacy and safety of norfloxacin. A total of 1,945 patients have received treatment with norfloxacin in CDSP studies through March 31, 1986. Three deaths have been reported to FDA on Forms 1639. None were drug-related. No serious adverse laboratory experiences were reported.

Marketing Experience (Excluding Japan): In addition to Japan, norfloxacin was being marketed in the following countries as of March 31, 1986:

Argentina	El Salvador	Mexico
Austria	Germany	New Zealand
Belgium	Guatemala	Pakistan
Brazil	Holland	Peru
Columbia	Honduras	Portugal
Costa Rica	Italy	Spain
Ecquador	Lebanon	Switzerland

Excluding Japan, approximately 5,600,000 patients have received marketed norfloxacin worldwide. As with the clinical studies, deaths and serious adverse experiences occurring within 14 days of norfloxacin therapy are promptly reported to FDA on Form 1639. One death due to exfoliative dermatitis has been reported. Reports which were possibly or probably drug related included one anaphylactic reaction, thrombocytopenia, and thrombophlebitis. Drug relationship was not stated for one case of anuria, and one case of increased prothrombin time and hematuria. A congenital malformation was definitely not drug related.

Recommendation: Approval of norfloxacin is recommended.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc Orig NDA HFN-815, HFN-815/Reed, HFN-815/CSO, HFN-815/Norton, 4806b

Dr. J. H. ...

August 18, 1986

MEDICAL OFFICER'S REVIEW OF NDA 19-384
and MEMORANDUM OF TELEPHONE CONVERSATION

Labeling amendment dated July 25, 1986

Applicant: Merck Sharp & Dohme Research Laboratories
West Point, Pennsylvania

Name of Drug: Trade: NOROXIN^R
Generic: Norfloxacin

Pharmacological Category: Fluoroquinolone antibacterial agent

The applicant submits revised proposed labeling to comply with comments from Dr. Ed Tabor which were given to the firm by Mr. Robert Linkous in a telephone conversation on July 21, 1986. Revised proposed labeling is satisfactory except for the following recommendations:

1. Microbiology Section (page 7, line 3) Insert "of the organism" after the first word. The new sentence will read, "Resistance of the organism has developed during therapy with norfloxacin in less than 1% of patients treated."
2. Indications and Usage Section (page 13, lines 14-16) Revise the sentence after the asterisk to read, "* Efficacy for this organism in this organ system was demonstrated in fewer than ten infections."
3. Precautions Section (page 18, lines 10-13) The last sentence in the Pregnancy paragraph should be revised to read, "Since norfloxacin, like other drugs in this class, causes arthropathy in immature animals, it should not be used in pregnancy (see WARNINGS)."
4. Precautions Section (page 19, lines 5-6) The Pediatric Use sentence should be revised to read, "NOROXIN should not be used in children (See WARNINGS)."

In Dr. David Blois' absence, I called Dr. Gerard D. Picot, Assistant Director of Regulatory Affairs at Merck to give him these comments. Dr. Mike Corrado participated in the conversations. I also asked other questions that the Division Director has raised. Did all complicated UTI patients get 10-30 days of therapy? How many patients got 30 days? What were the eradication rates for indole-positive Proteus species (P. vulgaris, P. rettgeri, and M. morganii) and give the study numbers where these uropathogens were isolated? What were the eradication rates for S. aureus and what were these study numbers?

Some of these questions were answered in attachments to the second version of the proposed labeling.

1. The report gives microbiological outcomes for complicated and uncomplicated urinary tract infections after cases which were originally classified as unevaluable had been deleted.

	Norfloxacin			TMP/SMZ		
	Eradi- cated	Pers- isted	Total	Eradi- cated	Pers- isted	Total
Complicated Cases						
Gram Positive Cocci	15 (94%)	1	16	8 (88%)	1	9
Gram Neg. Bacilli	149 (89%)	18	167	34 (87%)	5	39
Uncomplicated Cases						
Gram Positive Cocci	30 (88%)	4	34	7 (88%)	1	8
Gram Negative UTIs	290 (97%)	9	299	174 (91%)	18	192

2. The majority of complicated urinary tract infections were treated for 10-30 days.

Treatment Period	Number of Evaluable Cases
1-9 days	9
10-30 days	147 (92.5%)
31-99 days	3
Total	159

Approximately 90% of all adverse reactions occurred within the first four days of norfloxacin therapy. Dyspepsia, nausea, headache, dizziness, etc. appeared to occur very early in the course of treatment and continued therapy did not seem to appreciably increase the incidence of adverse experiences. Three adverse experiences occurred in patients treated beyond ten days for complicated urinary tract infections: rash on day 12 was probably related to treatment, hemorrhagic shock on day 31 was definitely not related to treatment, and eosinophilia on day 11 was probably not related to treatment. Of the 150 patients receiving therapy beyond 10 days, 147 did not experience adverse reactions.

Dr. Picot will confer with his coworkers and respond as soon as possible.

Recommendation: Approval is recommended but labeling is still unsatisfactory.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc Orig NDA, HFN-815, HFN-815/Reed, HFN-815/CSO 5008b

WAD 19 Aug 86

ET 8/19/86

August 18, 1986

AMENDMENT TO MEDICAL OFFICER'S REVIEW OF NDA 19-384

Applicant: Merck Sharp & Dohme Research Laboratories
Division of Merck & Co., Inc.
West Point, Pennsylvania 19486

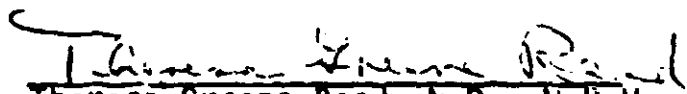
Name of Drug: Generic: Norfloxacin, MSD

Trade: NOROXIN™

The reader is referred to page 24 of the Medical Officer's Review dated Nov. 14, 1985. This is a review of the domestic multiclinic randomized controlled trial to compare norfloxacin with TMP/SMZ in the treatment of uncomplicated and complicated urinary tract infections. This review is amended to add the following information taken from Volume 2.6, page 1-01667:

CLINICAL RESPONSE

UTI	Susceptible to both drugs		Regardless to Susceptibility		Susceptible to Drug Received	
	Norflox.	TMP/SMZ	Norflox.	TMP/SMZ	Norflox.	TMP/SMZ
Complicated	95% (19)	83% (12)	81% (37)	87% (15)	85% (34)	83% (12)
Uncomplicated	94% (33)	82% (38)	95% (42)	82% (39)	95% (39)	82% (38)


Theresa Greene Reed, M.D., M.P.H.

cc
Orig NDA
HFN-815
HFN-815/Reed
HFN-815/CSO
5040b

OKS for E.T. 18 Aug 86

August 26, 1986

MEDICAL OFFICER'S REVIEW OF NDA 19-384

Amendment ~~XXXXXX~~

Applicant: Merck Sharp & Dohme Research Laboratories
West Point, Pennsylvania

Name of Drug: Trade: NOROXIN^R
Generic: Norfloxacin

Pharmacological Category: Fluoroquinolone antibacterial agent

The applicant submits revised proposed labeling and answers to Dr. Tabor's questions in response to my telephone conversation August 18, 1986.

Labeling:

1. Microbiology Section (page 7, line 3) The phrase "of the organism" has been inserted as requested.
2. Indications and Usage Section (page 13, line 12) An asterisk (*) has been added following the listing of the organism "Staphylococcus aureus."
3. Indications and Usage Section (page 13, lines 14-16) The sentence after the asterisk has not been revised to add "in this organ system" as requested. The applicant feels that this addition would lead the reader to think that norfloxacin was indicated for more organ systems than the urinary tract.
4. Precautions Section (pages 18 and 19) These two paragraphs have not been revised as requested to say that norfloxacin should not be used in pregnancy or in children. The applicant indicates that the wording is identical to that used in the approved labeling for cinoxacin, a related drug. It is felt that the reasons for the wording in these sections is the same for both drugs and, therefore, that the wording should be identical.

Medical Officer's Comment: The wording in the Precautions section of the cinoxacin labeling, that use of norfloxacin in pregnancy and in children is not recommended, was one of several recommended wordings for quinolones given us by the Anti-Infective Drug Advisory Committee.

Microbiological outcome:

In response to our request, the applicant reports the microbiological outcome for norfloxacin in Study No. 2 according to organism for both complicated and uncomplicated urinary tract infections as follows:

Study No. 2	Number Eradicated/Total Number	
	Complicated UTI	Uncomplicated UTI
<u>S. epidermidis</u>	1/1	2/2
<u>Group D streptococci</u>	5/6	4/4
<u>Citrobacter species</u>	1/1	
<u>C. freundii</u>	1/2	1/1
<u>E. coli</u>	13/13	24/24
<u>K. pneumoniae</u>	2/4	4/5
<u>M. morgani</u>	1/1	
<u>P. vulgaris</u>	1/1	
<u>P. mirabilis</u>	3/3	3/3
<u>P. rettgeri</u>	2/2	
<u>P. aeruginosa</u>	9/12	1/1
<u>Corynebacterium</u>		0/1
<u>Group B streptococci</u>		1/1
<u>E. aerogenes</u>		1/1
<u>Lactobacillus species</u>		1/1
Total	39/46 (85%)	42/44 (95%)

A similar table is provided for all evaluable norfloxacin cases as follows:

All evaluable norfloxacin cases	Number Eradicated/Total Number	
	Complicated UTI	Uncomplicated UTI
<u>Gram Positive Bacteria</u>		
<u>Corynebacterium sp.</u>		0/1
<u>Lactobacillus sp.</u>		1/1
<u>Micrococcus species</u>		1/1
<u>Staphylococcus species</u>		1/1
<u>S. aureus</u>	1/1	5/6
<u>S. epidermidis</u>	2/2	7/7
<u>S. saprophyticus</u>	2/2	4/4
<u>Coag. Neg. Staph.</u>		1/1
<u>Gp. B Streptococcus</u>		1/1
<u>Gp. D streptococci</u>	10/11	9/11
<u>Beta hemolytic Strep.</u>	1/1	
Total	15/16 (94%)	30/34 (88%)

(Continued on next page)

All evaluable norfloxacin cases	Number Eradicated/Total Number	
	Complicated UTI	Uncomplicated UTI
<u>Gram Negative Bacteria</u>		
<u>Acinetobacter sp.</u>	0/1	
<u>Alcaligenes species</u>		1/1
<u>Citrobacter species</u>	2/2	1/1
<u>C. diversus</u>	1/1	
<u>C. freundii</u>	3/4	4/4
<u>Enterobacter species</u>	1/1	1/1
<u>E. aerogenes</u>	1/3	2/2
<u>E. agglomerans</u>		3/3
<u>E. cloacae</u>	2/4	3/3
<u>E. coli</u>	66/68	207/210
<u>Klebsiella species</u>		1/2
<u>K. oxytoca</u>	1/1	2/2
<u>K. pneumoniae</u>	11/14	15/19
<u>M. morgani</u>	1/1	
<u>Proteus species</u>	1/1	1/1
<u>Proteus indole pos.</u>	1/1	1/1
<u>Proteus rettgeri</u>	2/2	
<u>P. vulgaris</u>	2/2	2/2
<u>P. mirabilis</u>	21/21	27/27
<u>Providencia rettgeri</u>	2/2	
<u>P. stuartii</u>	1/1	
<u>Providencia species</u>		1/1
<u>P. aeruginosa</u>	27/34	16/17
<u>P. cepacia</u>	1/1	
<u>S. liquifaciens</u>	1/1	
<u>S. marcescens</u>	1/1	
<u>Total</u>	149/167 (89%)	290/297 (98%)

Duration of Treatment:

In response to one of the questions, the applicant gives the duration of treatment in days for all patients who received norfloxacin for complicated urinary tract infections as follows:

<u>Duration of Treatment</u>	<u>Number of Norfloxacin Cases</u>
1-9 days	39
10-20 "	221
21-24 "	2
25-30 "	12
31-99 "	4
<u>Total</u>	<u>278</u>

No. with 10 days or more 239

Since only three adverse experiences occurred beyond 9 days of therapy, it appears that prolonging norfloxacin therapy up to 30 days does not significantly increase the rate of adverse experiences.

NDA 19-384

4

Indole-positive Proteus cases:

The following seven indole-positive cases were reported in the NDA:

<u>Protocol No.</u>	<u>Study No.</u>	<u>Alloc. No.</u>	<u>Micro-organism</u>
002	8	810	<u>Morganella morganii</u>
504/505	529	1093	<u>Proteus rettgeri</u>
504/505	529	1099	<u>Proteus rettgeri</u>
506/508	516	2002	<u>Proteus, indole pos.</u>
506/508	516	2009	<u>Proteus, indole pos.</u>
506/508	533	2028	<u>Proteus vulgaris</u>
506/508	535	2150	<u>Proteus vulgaris</u>
		Total	7 of 7 eradicated

Recommendation: Revised proposed labeling is satisfactory. Approval is recommended.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc Orig NDA, HFN-815, HFN-815/Reed, HFN-815/CSO 5008b

DRD 27 Aug 86

ST 8/27/86

NDA 19-384

November 18, 1986

MEDICAL OFFICER'S REVIEW OF PROPOSED ADVERTISING

Response to Consultation Request Dated Nov. 4, 1986

Applicant: Merck Sharp & Dohme

Name of Drug: Generic: Norfloxacin

Trade: NOROXIN^R

(The approval letter for norfloxacin application, NDA 19-384, was dated October 31, 1986.)

Mr. T. W. Cavanaugh (FFN-240/244) sent the proposed 68-page monograph for norfloxacin, 400 mg tablets, to this division for review. My comments are listed below.

Page 26: The applicant should reconsider the need to give both MIC₅₀ and MIC₉₀ values for each organism for the five drugs in Table 4. It seems that the MIC₅₀ has little clinical value and that the MIC₉₀ is the more clinically significant of the two.

Page 30: Under Drug Interactions, add that there is reduced absorption of norfloxacin in the presence of antacids. There is moderate loss of antibacterial activity where there are increasing concentrations of fecal material.

Page 31: Delete the word "acute" in the second sentence.

Page 33: Revise the clinical outcome criteria to delete references to bacteriological eradication or persistence. Correct the numbers accordingly. Clinical outcome should give the response of signs and symptoms only. Microbiological outcome gives eradication and persistence information. These are included in the next table.

Page 35: Delete the word "open" in the last sentence in the first paragraph or change it to "non-blinded."

Page 36: In Table 8, delete the word "suppressed." Suppression is not an outcome category. The pathogen either persists or is eradicated. Revise figures accordingly.

Page 37: Insert the word "agents" so that the revised sentence will read, "Most strains are highly resistant to the antibacterial agents typically utilized..."

Page 37: Change the word "sensitive" in the fourth line from the bottom to "susceptible."

Page 39: Change the word "sensitive" to "susceptible" in the 2nd paragraph.

Page 39: Since six parenteral regimens are listed, the ones that had the two failures (E. coli and P. aeruginosa) should be identified in Table 11.

Page 41: Revise Table 12 to give clinical outcome (symptoms and signs) only and revise the numbers accordingly. Revise the criteria, cured, improved and failed, to give resolution of symptoms and signs and to delete eradication and presence of the infecting organism. Bacteriological outcome is given in the preceding table. Revise the title of Table 12 to read "Clinical outcome for 94 evaluable patients with..."

Page 42: End the third paragraph with either "the enterococcus" or "enterococci."

Page 45: The first paragraph should be revised to insert a new sentence after the first sentence to give the total number of adverse reactions experienced by the 1127 patients and then should give the number of these that were considered to be drug related.

Page 46: The applicant should be requested to use other studies than the ones that were used here to illustrate adverse reactions. The three that are shown are not acceptable.

1. The applicant should be requested to further identify the 106-subject, placebo-controlled study by Zinney. I am not able to locate such a study. Zinney conducted three Phase I studies, Study No. 45 in 27 subjects, Study No. 66 in 26 subjects, and Study No. 13 in 15 subjects.

2. The Cohn study should not be considered in the evaluation of adverse effects because the very adverse effects that one would watch for are symptoms of the disease. Symptoms of gastroenteritis, besides diarrhea that were used in the evaluation of outcome, were abdominal cramps, nausea, vomiting, anorexia, etc. Gastrointestinal-type adverse effects that would be anticipated with norfloxacin are gastrointestinal cramps, nausea, vomiting, heartburn, flatulence, anorexia, abdominal pain, dyspepsia, etc.

3. The applicant should be requested to identify further the 54-subject placebo-controlled study conducted by Talbot/Derezinski/Karp. In Study No. 15, Talbot in Philadelphia studied 19 patients who received either a regimen of norfloxacin plus nystatin or a regimen of placebo plus nystatin. This study was analyzed with Study No. 19 conducted by Rubin in Boston. The 75% norfloxacin adverse-reaction rate in these studies and the 64% placebo adverse-reaction rate were unacceptable. The adverse reaction rate of 64% for placebo is not consistent with what would be expected for placebo so these studies should not be used as illustrations for adverse reactions.

The discussion about adverse reactions should say that since norfloxacin may cause dizziness or lightheadedness, patients should know how they react to the drug before they operate an automobile or machinery or engage in activities requiring mental alertness and coordination.

It would be helpful for the prescriber if the document would say somewhere that photosensitivity (sunburn) has been a troublesome adverse reaction with some quinolone products. Convulsions have been reported with at least one quinolone product: they are believed to be associated with the fact that when

NDA 19-384

3

there is concomitant administration with theophylline the fluoroquinolone raises plasma theophylline levels to toxic levels.

Page 55: Somewhere in the Dosage and Administration section the document should say that norfloxacin should not be used in children and in pregnant women.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc
Orig NDA
HFN-815
HFN-815/Reed
HFN-815/CSO
HFN-244/Cavanaugh
5124b

ST 12/12/86
MAD 2004-86

November 25, 1986

MEDICAL OFFICER'S REVIEW OF NDA 19-384 LABELING

Amendment Dated November 6, 1986

Applicant: Merck Sharp & Dohme Research Laboratories
West Point, Pennsylvania

Name of Drug: Trade: NOROXIN^R
Generic: Norfloxacin

Pharmacological Category: Fluoroquinolone antibacterial agent

Material Submitted: Final Printed Labeling

Final printed labeling is satisfactory. I have the following proofreading comments:

1. Clinical Pharmacology - Line 7, paragraph 4: The word "approximately" is misspelled.
2. Microbiology - Providencia alcalifaciens is misspelled in the list of susceptible organisms.
3. Hyphens should be inserted as follows:

Description - Line 1, paragraph 2: "400-mg tablets"

Clinical Pharmacology - Line 2, paragraph 4: "400-mg dose"

Line 1, paragraph 5: "400-mg dose"

Line 5, paragraph 5: "400-mg dose"

Last line, paragraph 6: "200-mg doses"

Microbiology - Line 3, paragraph 4: "nalidixic acid-resistant organisms"

- Line 5, paragraph 4: "nalidixic acid-susceptible organisms"

Susceptibility Tests - Line 1, par. 2: "single-disc susceptibility test"
and "10-mcg norfloxacin disc"

- Line 10, par. 6: "10-mcg norfloxacin disc"

Indications and Usage - Line 6, par. 1: "indole-positive Proteus species*"

Precautions - Line 1, paragraph 1: "Needle-shaped crystals"

Pregnancy - Lines 7-8: "well-controlled studies"

Nursing Mothers - Line 1, par. 2: "200-mg dose"

Adverse Reactions - Line 1, par. 2: "drug-related adverse experiences"

Dosage and Administration -

Renal Impairment - Line 4, par. 1: "one 400-mg tablet"

Animal Pharmacology - Line 2, par. 2: "needle-shaped drug crystals"

NDA 19-384

2

I called David W. Blois, Ph.D., Senior Director of Regulatory Affairs at Merck Sharp and Dohme to give him these comments. They are proofreading comments only. There are no comments regarding the content of the labeling. He will review them with his staff and include them in the next printing.

Recommendation: Final printed labeling is satisfactory.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc

Orig NDA

HFN-815

HFN-815/Reed

HFN-815/CSO

HFN-244/Cavanaugh

5008b

GT 12/12/86

BAD 26 Nov 86

19-384

APR - 6 1988

(See IND and NDA numbers below)

March 2, 1988

AMENDMENT TO MY MEDICAL OFFICER REVIEWS OF FLUORINATED QUINOLONES

Sponsors and Products:

Merck & Co.	IND 18,718 & NDA 19-384	Norfloxacin tablets
Warner-Lambert Co.	IND 20,898 & NDA 19-616	Enoxacin tablets
	IND 26,102	Enoxacin Acetate Parenteral
Rhone Poulenc	IND 20,095	Pefloxacin oral (If active)
	IND 29,060	Pefloxacin mesylate dihydrate parenteral
Ortho Pharmaceuticals	IND 21,033 & NDA 19-735	Ofloxacin tablets
	IND 29,107	Ofloxacin Injection
Miles Pharmaceuticals	IND 21,804 & NDA 19-537	Ciprofloxacin tablets
	IND 25,173	Ciprofloxacin Intravenous
Sterling Winthrop	IND 27,651	Amifloxacin capsules
	IND 24,090	Amifloxacin mesylate injection
Abbott Laboratories	IND 26,444	Difloxacin HCl capsules
	IND 26,498	A-56,620 HCl capsules
	IND 31,102	Temafloxacin HCl capsules
Searle Pharmaceuticals	IND 31,034	Lomefloxacin HCl capsules
Hoffmann La Roche	IND 27,760	Fleroxacin (Megalone) tablets
	IND 30,133	Fleroxacin (Megalone) parenteral

It has been known since the first quinolone, nalidixic acid, was approved that quinolones can affect vision in varying degrees during treatment. The same thing occurs with the fluoroquinolones. There has been no consistent pattern and some have more reports than others. Patients report blurred vision, changes in color perception, double vision, overbrightness of light, and difficulty in focusing. All are reversible when therapy is discontinued and in some cases when dosage is reduced. Cataracts have been reported with at least one fluoroquinolone. We have also been very interested in determining what these drugs do to alter brain function (headaches, convulsions, sensation of "jumping off a cliff," excitation, drowsiness, vertigo).

Past Animal Data: Ocular lesions were reported in animal studies of a nalidixic acid metabolite approximately twelve years ago. There was increased reflectivity of the tapetal retina in four of six dogs after 7 days of treatment and in one other by Day 16. The intensity of tapetal reflectivity gradually increased during the two weeks after it was first observed. Attenuation of the retinal vasculature was also observed. One dog became clinically blind. Retinal changes were observed in five of the six dogs. These changes consisted of atrophy of the rod and cone layers, loss of nuclei and disorientation of the outer nuclear layer. One area was spared in four dogs. Similar findings have been reported from studies in cats. These findings occurred in animals with a tapetum and did not occur in animals that do not have a tapetum.

Labeling: In recognition of this problem, labeling for cinoxacin has a full paragraph to say that drug administration results in retinal degeneration and other ocular changes in cats. Labeling for nalidixic acid says that the hydroxy metabolite when given orally in high doses has oculotoxic potential in dogs and cats. The animal pharmacology section of current labeling of ciprofloxacin and norfloxacin ends with the sentence, "Ocular toxicity seen

with some related drugs has not been observed in (generic name)-treated animals."

Current Animal Data: Pefloxacin penetrates the aqueous humor and the lens in beagle dogs, rats, and humans and lens opacities have been found in dogs. More information is needed on the role light plays in pefloxacin-induced cataract formation.

A confidential report in IND 29,494 for Ofloxacin ophthalmic solution suggests that there may be prolonged elimination of ofloxacin from aqueous humor. Dogs received oral doses of 32 mg/kg for three weeks. Elimination from the aqueous humor was biphasic, the half-lives being about 20 and 55 hours. This elimination was markedly longer than elimination from the plasma: the compound levels measured in the aqueous humor after the 21st dose amounted to 24% of the respective plasma level after 2 hours, 82% after 2 days, and 500% after 7 days. From the concentrations in the eye lenses, an elimination with a half-life of about 60 hours can be estimated.

Ofloxacin eye drops in a concentration of 0.3% were instilled into the eyes of the pigmented and albino rabbits for two weeks, and time-course ofloxacin concentrations in ocular tissues were measured starting from two hours after the last instillation. The concentrations in the iris/ciliary body and retina/choroid of the pigmented rabbits were higher than those of the albino rabbits, and were detected at low levels even after nine weeks. As for ofloxacin concentrations in the other ocular tissues, there was no great difference between the pigmented rabbits and the albino rabbits. From these results, it is presumed that when ofloxacin eye drops are instilled, ofloxacin may be transferred to the melanin-containing tissues such as the iris/ciliary body and the retina/choroid at relatively high concentrations and be retained, though at very low levels, for a long time.

Furthermore, ofloxacin was reported to be distributed to the melanin-containing tissues, uvea and skin, at high concentrations for a long time in dogs and monkeys after oral administration. It is, therefore, considered that in general, ofloxacin has a relatively high affinity for melanin pigment.

(I would like to add here that there is concern about phototoxicity due to the quinolones. One IND was halted by FDA because phototoxicity prohibited the continuation of clinical trials.)

Chloroquine: Some drugs (e.g. chloroquine, phenothiazines) can produce deposits in the cornea and, also, produce a retinopathy that can seriously affect vision when given at high doses given over prolonged periods. Chloroquine administration results in a pigmentary retinopathy which consists first of a perifoveal change in the granularity of the retinal pigment layer. Subtle changes in paracentral retinal function are demonstrable, while central visual acuity may still be entirely normal. Later, there is a bull's-eye pattern of thinning and clumping of retinal pigment in the macular area around the fovea. The rods and cones are destroyed in this area, but the cones tend to survive longer at the fovea. Central vision is lost if damage is allowed to progress. Peripheral visual field changes and peripheral pigmentation develop later. Also narrowing of retinal arteries is generally considered to

be a secondary late effect appearing in some cases. Chloroquine can seriously injure the retina without the patient being aware of the change. In most cases, lost vision due to chloroquine is not recovered.

Clinical Considerations: More information on the toxic effects of the fluoroquinolones on the human eye, and what can be done to detect them early before irreversible damage to vision occurs if toxic effects occur, is needed. Electrodiagnostic measures, particularly electroretinography and electro-oculography may be useful in providing information. Electro-oculography measures any increase in potential with light adaptation to evaluate the condition of the retinal pigment epithelium. Electrodes are placed at each canthus, and the changes in the electrical potential between these electrodes are recorded as the eyes move. Electroretinography provides a record of the action potential superimposed upon the resting potential when the retina is stimulated with light. It demonstrates the presence of fluorescent materials such as deposits in the retinal pigment epithelium.

Sponsors of quinolone and fluoroquinolone INDs should be requested

1. To file funduscopy and histological reports from one-year studies of the drug in the pigmented (rather than the albino) rabbit. Histological reports should include sections of the retina, pigment epithelium, choroid, and macula.
2. To file reports of electro-oculography (EOG) and electroretinography (ERG) studies from clinical trials. EOG measurements should be obtained before treatment, at approximately 7 days, at 14 days, and again 30 days after treatment has been discontinued. Both EOG and ERG procedures are non-invasive and may be performed on outpatients.

These studies are requested in addition to other ophthalmic studies which FDA has already requested.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc

Orig INDs listed above

Orig NDAs listed above

HFN-815

HFN-815/Reed

HFN-815/DeSantis

HFN-815/McCormick

HFN-815/Chambers

0058R

add 3/3/88

all 2/11/88

N19384 -5

February 2, 1989

FEB 21 1989

MEDICAL OFFICER'S REVIEW OF NDA 19-384

Monitored Adverse Reaction Report dated January 3, 1989
from the Division of Epidemiology and Surveillance

Applicant: Merck Sharp & Dohme Research Laboratories
West Point, PA

Name of Drug: Trade: Noroxin Tablets

Generic: Norfloxacin

The Division of Epidemiology and Surveillance has notified the review team that six patients with thrombocytopenia were found in the agency's Spontaneous Reporting System. In all six cases, the thrombocytopenia was reported to have resolved after norfloxacin was stopped.

Thrombocytopenia is not listed in the Adverse Reactions section of the insert.

Recommendation: The last paragraph of the Adverse Reactions section should be revised. The paragraph now reads as follows:

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

Hypersensitivity Reactions

Hypersensitivity reactions have been reported including anaphylactoid reactions, angioedema, urticaria, Stevens-Johnson syndrome and arthralgia.

Skin

Photosensitivity

Gastrointestinal

Pseudomembranous colitis"

The applicant should be notified by letter to add the following text:

"Hematological
Thrombocytopenia"

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

Attachment

Orig NDA 19-384

cc

HFD-520

HFD-520/Reed

HFD-520/Nazario

HFD-520/Casola

HFD-520/Buko

HFD-735/Green

\Norflox

msd 2/21/89

CHEM REV

Division of Anti-Infective
Drug Products
Chemist's Review
Date Completed: 3/14/85

A.1. NDA 19-384

Sponsor: Merck Sharp & Dohme Research Laboratories
Division of Merck & Co., Inc.
West Point, PA 19486

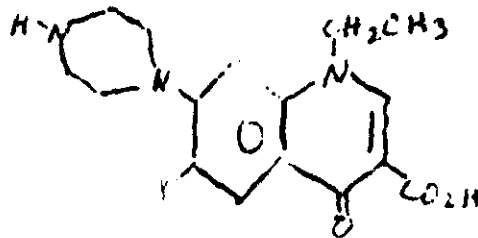
2. Product Names:

Proprietary: Noroxin
USAN: Norfloxacin
Code: MK-366, L-643, 316-00J; AM-715

3. Dosage Form & Route of Administration: 200, 400 mg. film-coated oral
Tablets.

4. Pharmacological Category and/or Principal Indication: For treatment
of UTI (complicated or uncomplicated) uncomplicated gonococcal
infections, acute gastroenteritis caused by susceptible organisms.

5. Structural Formula and Chemical Name(s):



m.w. 319.34

1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic
acid.

B. 1. Initial Submission: 12/5/84; Rec'd in Bureau: 12/7/84
Rec'd by Chemist: 12/20/84

2. Amendments: None

3. DMF Referrals:

4. Related Material: (

NDA 19-384
Page 2

C. Remarks:

There have been a number of formulation changes during drug development which require explanation by the sponsor as to their impact if any on clinical, biopharmaceutic and stability parameters.

The controls section of the application appears basically adequate, but due to formulation changes additional information is required to permit a scientific appraisal.

D. Conclusions and/or Recommendations:

John W. Taylor
John W. Taylor, Ph.D.

cc: Orig. NDA

~~HFN-815~~

R/D Init. by: ARCasola 3/15/85

HFN-815/MO

3433b

HFN-815/CSO

HFN-815/Taylor; gm 3/15/85

ARC 3/21/85

NDA 19-384
Page 3

1&2. Components and Composition: Adequate with comment.

(

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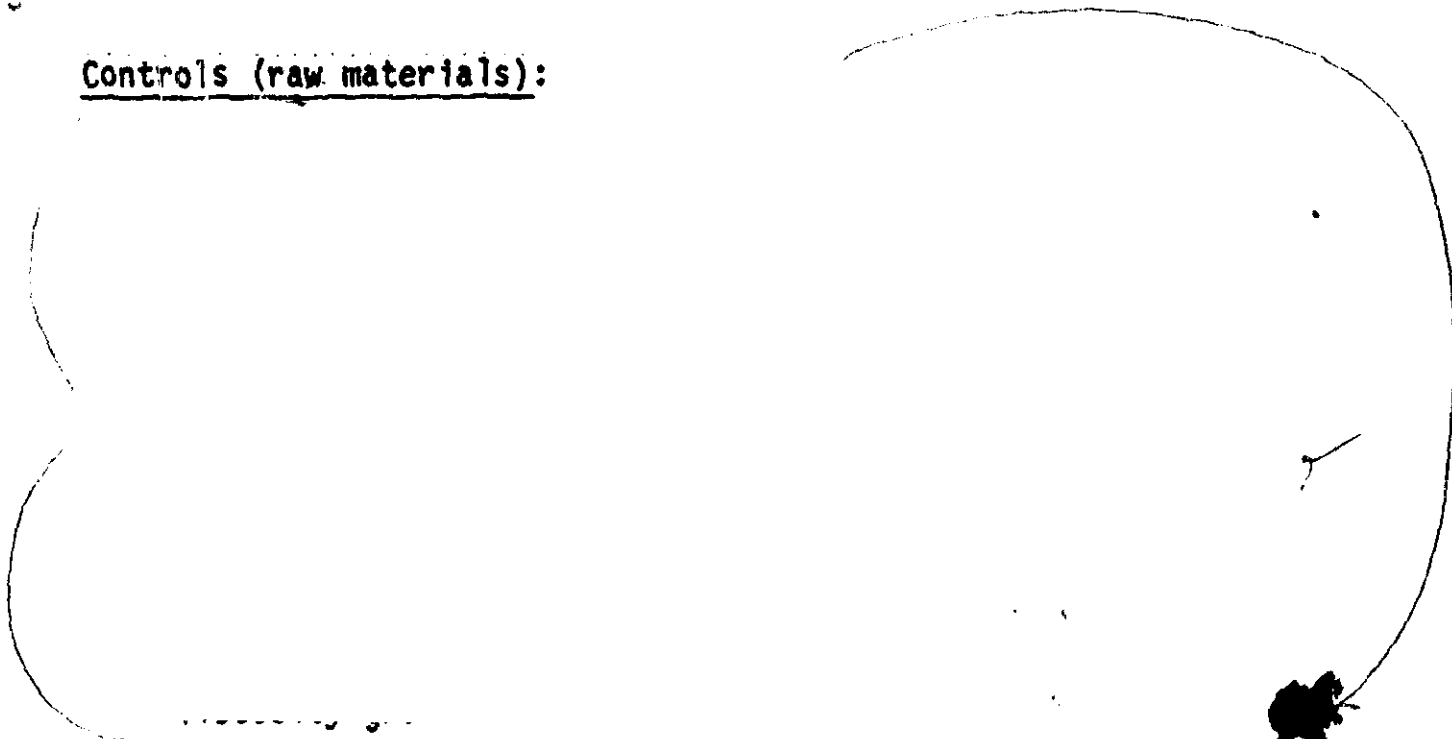
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5

3. Facilities:

4. Personnel: Adequate.

5.

6. Controls (raw materials):



7. Other Facilities: See item 3.

8. Manufacturing and Processing:

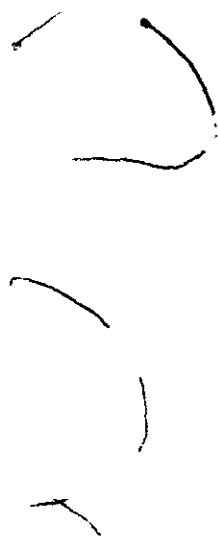


9. Packaging and labeling: Adequate.

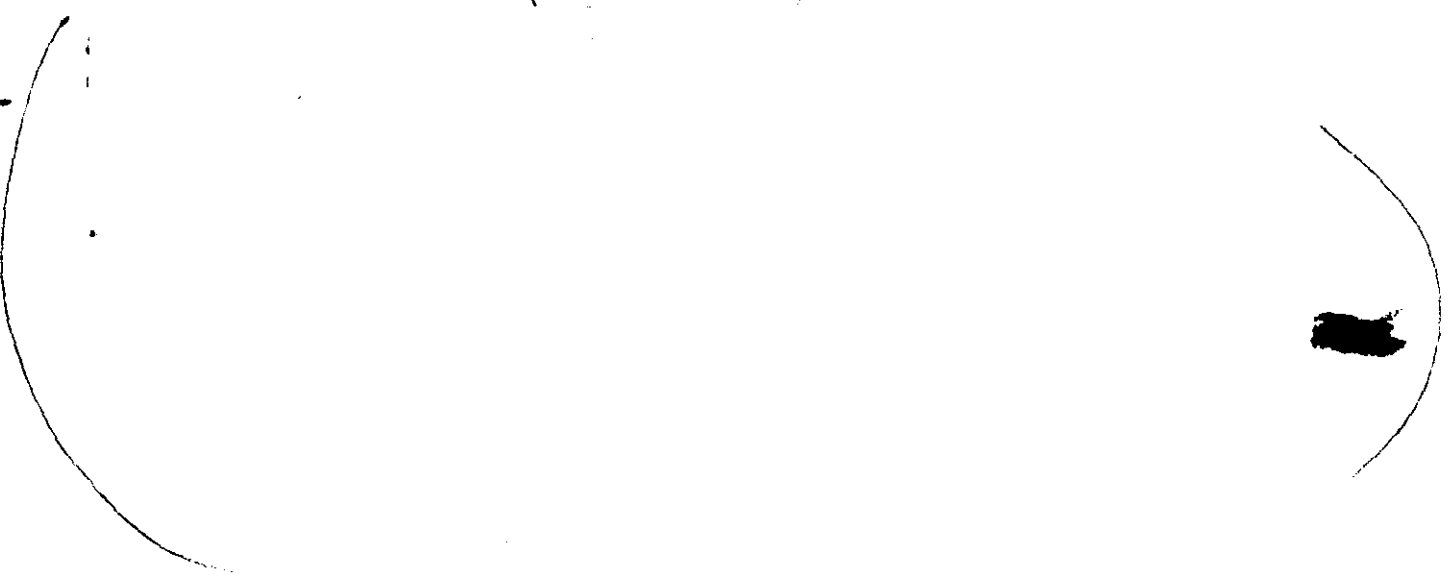
10. Container/Closure Systems:

a)

b) Unit Dose:



11. Controls (dosage form): ([REDACTED])



NDA 19-384
Page 6

12. Stability Data:

Division of Anti-Infective
Drug Products
Chemist's Review
Date Completed: 3/11/86

A.1. NDA 19-384

Sponsor: Merck Sharp & Dohme Research Laboratories
Division of Merck & Co., Inc.
West Point, PA 19486

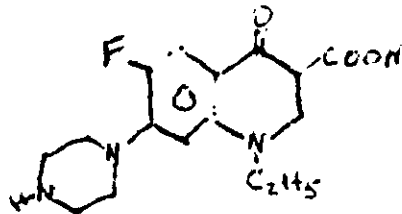
2. Product Names:

Proprietary: Noroxin
USAN: norfloxacin
Code: MK-366, 6-643, 316-00J, AM-716

3. Dosage Form & Route of Administration: 200 mg, 400 mg. FC tablets for oral use.

4. Pharmacological Category and/or Principal Indication: For treatment of VTI, uncomplicated gonococcal infections, acute gastroenteritis caused by susceptible organisms.

5. Structural Formula and Chemical Name(s):



1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid.

B. 1. Initial Submission: 12/5/84

2. Amendments:

3. DMF Referrals: N/C

4. Related Material: N/C

C. Remarks:

Sponsor has replied to each concern adequately.

D. Conclusions and/or Recommendations:

Application is approvable from manufacture and controls standpoint pending a reply from the Division of Biopharmaceutics re adequacy of the dissolution specifications for the dosage form.

CSO to request copies of all draft labeling.

John W Taylor
John W. Taylor, Ph.D.

cc: Orig. NDA
HFN-815
HFN-815/MO
0240c

HFN-815/CSO
R/D initialed by: ARCSola 3/11/86
HFN-815/Taylor: gm 3/11/86
AKC 3/17/86

- 1&2. Components & Composition: N/C. A list of previously studied formulations has been provided.
3. Facilities: N/C.
4. Personnel: N/C.
5. Synthesis:
As requested information and data have been provided re the starting product, 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-chloro-3-quinoline carboxylic acid. Ten lots (5 from each supplier were examined) and TLC's were equivalent, UV, I.O.D. and assays $> 98\%$ av. All lots were homogeneous via TLC. The norfloxacin results are also equivalent.

The assays indicate an approximate ⁹88% purity.

6. Controls (raw material):
Total impurities have been revised to a max of 0.5% which is acceptable to this reviewer based on the USP proposals and the semiquantitative TLC method provided. Gradient elution HPLC results provided by Merck indicates consistent purity in the new drug substance and lack of dosage form degradation.

An in-process test of 3% total moisture by Karl Fischer has been added for the tablet form.

Excipients are tested per USP/NF.

7. Other Firms: N/C.
8. Manufacturing & Processing:
With the exception of moisture controls noted in 6. N/C.
9. Packaging and Labeling: N/C.
10. Container/Closure:
a) bottles: N/C
b) foil packet - outer to inner composition cellophane/0.007 PE/0.0007 Al foil/0.0015 PE
11. Stability:
Previously Kyorin data for the foil package, their formulation showed little or no degradation at 30 months; dissolution data were not provided.

The listing of tested formulations provided by Merck indicates relatively little difference in coating amounts which might influence dissolution slightly.

The data indicate in conjunction with the Kyorin data that the product should be quite stable. A tentative 30 month expiry is acceptable to this reviewer pending actual production lot data providing the dissolution specification is acceptable.

12. Controls (Dosage Form):
A TLC identity test is added for regulatory purposes.

A proposed justification for the dissolution Q value is presented which must be agreed to by the Division of Biopharmaceutics. The argument appears rational.
13. Control Numbers: N/C.
14. Methods Validation:
The methods were validated by DDC and PHI-DO and found adequate for regulatory purposes. Comments by DDC re centrifugation is regarded as gratuitous. The method now specifies a dried sample for IR.
15. Labeling: Foil strip labeling is required. Otherwise N/C.
16. Inspections:
Involved facilities are in compliance with CGMP regulations.
- 17-20. N/C.
21. Bioavailability:
Needs review and verification of adequacy of proposed dissolution value.

PHARM REV

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 19-384 (Original Submission, dated 1/14/85)

Date Review Completed: 2/3/86

Applicant: Merck Sharp & Dohme

Drug: NoroxinTM Coated Tablets

Code Names: Kyorin AM-157; NK-0366

Category: Quinolone urinary antibacterial

Related Drugs: All quinolone urinary antibacterials

PRECLINICAL STUDIES

Labs Performing Studies: Kyorin Pharmaceutical Co., Ltd., Japan; MSD, USA; and various Italian, French, Canadian res. institutes & universities.

Note: "#" is used to designate foreign studies.

ACUTE TOXICITY

These studies follow the order of Vol. 2.43, from page III-00510 on.

Animals Used: Rats; dogs; mice; monkeys

#1. Acute Toxicity [Kyorin]

IV LD₅₀: 220 mpk in mice
Oral LD₅₀: 4000 mpk in rats & mice

#2. Acute Toxicity & Lethality in Rats & Mice [Institute Gen. Path., Italy]

MLD for both species: 3000 mpk, PO; 1500 mpk, SC; 300 mpk, IV

#3. Oral Toxicity of the 6 Metabolites of the Drug [Kyorin]

Oral LD₅₀s: M-1, M-4 (2), M-5: Greater than 2000 mpk
M-2, M-3, M-4 (1): Greater than 4000 mpk

SUBACUTE TOXICITY

#1. 1-Month Oral Toxicity in Rats [Kyorin]

Doses: 250, 500 & 1000 mpk/day. A slight but stat. sig. increase in urinary K excretion was seen in F rats at the MD & HD, but no concurrent decrease in serum K level. Besides enlargement of the cecum at the HD, which is usual in these studies, no toxic signs were seen.

#2. 1-Month Oral Toxicity in Rats [Institute Gen. Path., Italy]

Doses employed were the same as in the previous study. There was no appreciable toxicity; not even potassuria.

#3. 1-Month Oral Toxicity in Dogs [U. of Cagliari, Italy]

Doses: 50, 100 & 200 mpk/day. No drug related changes observed.

#4. Subacute Oral Toxicity Study in Dogs [Kyorin]

Doses: 25, 50 & 100 mpk b.i.d. The only abnormality was slightly increased glucose-6-phosphatase activity in the liver of most drug-treated groups; the biological sig. of this change is not known. No other drug-induced changes were observed.

Reviewer's Comment: Regarding the enzyme changes, I don't know how to interpret this finding either.

5. 14-Week Oral Toxicity in Dogs Receiving NH₄Cl [MSDRL, USA]

This is a repetition of a French study in which, at the same doses as in this study, crystalluria and/or urinary obstruction occurred. Based on the knowledge that in vitro, the solubility of the drug is substantially increased under pH 6, the study was repeated in the USA with simultaneous administration of NH₄Cl (oral). No detailed write-up of that study was provided. Since the MSD study is pivotal, a detailed review will be presented here.

Animals, Doses, Route & Duration: Beagles, 43-45 wks of age; 4 groups, 3/sex/gp - Controls, 50, 150 & 300 mpk/day; oral (gavage); 14 wks, with acidification by adding 1% ammonium chloride to the drinking water.

Results

Mortality: Four in all gps due to aspiration.

<u>Week 3</u>	<u>Week 6</u>	<u>Week 8</u>
T M @ 300mpk	T M @ 150mpk	T F @ 150mpk; 1 F @ 300 mpk

The following dogs had aspiration pneumonia as a result of vomiting and regurgitation: Controls, 2/6; LD, 5/6; MD, 4/6; HD, 4/6. [Reviewer's Comment: Since the controls did not receive the drug, but only the vehicle, apparently the vehicle itself was irritating to the stomach of some control dogs, resulting in this reaction.]

Body Wt: All animals at the HD and several from other gps (including controls) lost body wt. The mean total wt change (kg/gp) was: Controls, +0.2; LD, -0.4; MD, -0.1; HD, -0.8.

Crystalluria: The admin. of ammonium chloride to drinking water was routinely effective in reducing urine pH to an approx. range of 5.5-6.5.

Drug crystals shaped like sea urchins and/or fine needles were occasionally seen in urine from dogs in each drug-treated gp. Those found during Drug Weeks 11, 12 & 13 were shown by high performance liquid chromatography to be MK-366. The severity & incidence of crystalluria was greatest in the HD gp.

No evidence of urinary tract obstruction was observed. Chronic tubulointerstitial nephritis (unilateral, slight-moderate) was present in 1 M each in the MD & HD gps. This lesion is not typical of a toxic change and its association to treatment is unknown.

Other: No other drug-related changes were seen in urinalysis, hematology or serum chemistry determinations.

No dose-related changes were seen in organ wts or on gross exam or histomorphologic exam of tissues.

6. Urinary Drug Disposition Study in Dogs [MSDRL, USA]

An oral study was initiated in beagle dogs with MK-366 to determine whether crystals of MK-366 or its metabolites can be isolated from the urine. The drug was administered to 4 dogs (2/sex) @ 300 mpk/day for 4 days, by oral gavage (as a suspension in aq. methylcellulose). A similar gp of dogs received 0.5% methylcellulose and served as controls. Urine samples were collected 2, 4, 6 & 24 hrs following dosing and were analyzed for undissolved MK-366-related material; 24-hr urine samples were also examined microscopically for crystals & cells. All dogs were killed at termination and both kidneys & urinary bladders removed and samples from each fixed in 10% neutral buffered formalin.

Results: One drug-treated dog showed large numbers of needle-shaped crystals on microscopic exam, suggestive of drug crystals. Three or 4 types of crystals were detected by HPLC in the urine of the dogs. The majority of the crystals seen were MK-366.

#7. Subacute Toxicity Study in Monkeys [Kyorin]

Material Tested: MK-366 administered as oral suspension

Animals, Doses & Duration: Macaca fascicularis; 4 groups, 2 M/gp; Controls (sterile dist. water), 25, 50 & 100 mpk b.i.d.; 4 wks

Schedule of Parameters Measured: Food & water intake, daily; body wt prior to treatment and day of sacrifice; hematological & serum biochem. parameters, pretest and after 2 & 4 wks of treatment; urinalysis, at necropsy. The following enzyme activities were determined in all animals at termination: ATP; glucose-6-phosphatase; B-glucuronidase; heart ATP; kidney ATP; bone marrow alkaline phosphatase; skeletal muscle ATP.

Wts of brain, pituitary, submandibular gland, thyroid, thymus, heart, lung, liver, pancreas, cecum, spleen, kidneys, adrenals, testes & epididymides were recorded at necropsy. Various tissues were fixed in

10% formalin. May-Giemsa stained bone marrow smears were prepared from all monkeys. Microscopic exam was done on hematoxylin- & eosin-stained sections from an extensive list of tissues.

Results: No changes attributable to treatment were seen.

8. Subacute Oral Toxicity Study in Immature Rats

Animals, Doses, Route & Duration: Immature (age under puberty) white Laboratory rats (strain not specified); 4 groups - Control, 250, 500 & 1000 mpk/day; orally in suspension; 7 days/week for 4 weeks

Schedule of Parameters Measured: Observation of signs of toxicity & body wt gain daily; food & water intake weekly; hematology, serum biochemistry, enzyme activity of kidney, heart & skeletal muscle, urinalysis, organ wt and gross & microscopic exams of various tissues near or at the end of the study.

Results

Body Wt; Food & Water Intake: No drug-related changes.

Hematologic & Serum Biochemical Parameters; Urinalysis: Stat. sig. changes in some of these parameters; however, the differences were small, within the limits of normal variation, and generally not dose-dependent.

Reviewer's Comment: The applicant does not consider these changes treatment-related. This might be true, but where are the reports on the expected arthropathy, at least clinically?

The following is a verbatim quotation from the report. Note: It does not even mention joint involvement.

"An increase of absolute and relative weights of cecum was found in drug-treated males and females. This is not an uncommon finding in animals treated with antibacterial agents for long periods. There were no other organ weight changes or gross or microscopic changes attributable to treatment with NK-366."

CHRONIC TOXICITY

#1. 6-Month Chronic Toxicity Study in Rats [Kyorin]

Animals, Doses, Route & Duration: Laboratory white rats (strain not specified); 4 gps, 10/sex/gp - Controls, 125, 250 & 500 mpk/day; orally in suspension; 7 days/week for 6 mos. The age of the rats was 7 weeks at the start of the study. [Note: Puberty onset is at the end of the 10th wk of life in rats. Thus, for 3 wks this was a study in immature (juvenile) rats. I wonder if arthropathy was experienced during the first 3 wks of the study. However, since it is difficult to observe it clinically in the rat, and since the histopathology at the end of the 6-mo. treatment period might be negative (if they paid any attention to

the articular cartilage of the weight bearing joints), this study might indicate negative results with respect to arthrosis, although it could occur but remain unnoticed clinically during the first 3 wks of treatment.]

Schedule of Parameters Measured: Body wt, prior to the study and weekly thereafter; clinical signs, daily; food & water intake, once/week; ophthalmic exam, at 3 mos. & 6 mos. after start of treatment; hematology & urinalysis on all rats 2, 4 & 6 mos. after initial treatment; serum biochemistry on all rats 6 mos. after start of the study; glucose-6-phosphatase & B-glucuronidase, kidney ATP, bone marrow alkaline phos. activity in 5/sex rats from control & hD gps at study termination. All animals were terminally necropsied, and organ wts (heart, spleen, thymus, pituitary, adrenal, liver, pancreas, lung, brain, kidneys, testes, epididymides, prostate, ovaries & uterus) were recorded. Various tissues were fixed in 10% formalin. Microscopic exam was done on hematoxylin & eosin-stained sections of extensive tissues of all rats. Samples of liver & kidney were examined by using transmission electron microscopy. In addition, cochlea were examined using a scanning electron microscope to determine ototoxic potential.

Results: Slight body wt retardation was seen in M rats at the MD & HD. This did not occur in F. Serum albumin/globulin ratio showed tendency to increase in M at all dose levels and in F at the MD & HD. This was considered not to be treatment-related. There were no other changes attributable to treatment, including ototoxicity.

#2. Chronic Toxicity Study in Rats [Institute Gen. Path., Italy]

This study is identical to the previous study, but performed in Italy.

Results: No treatment-related changes in any of the parameters examined.

#3. 26-Week Oral Toxicity Study in Rats [MSD, Chibret, France]

Animals, Doses, Route & Duration: Laboratory white rats, 5 wks of age at study initiation; 4 gps - Controls, 50, 200 & 600 mpk/day; orally (gavage), suspended in aq. methylcellulose; controls received methylcellulose sol'n only.

Results

Signs: Grey feces (unabsorbed drug) in all treated gps; slight salivation occasionally in the hD gp.

Food & Water Intake: No significant effects.

Mortality: None

Body Wt Gain: Slight, but stat. insig. decrease in body wt gain in the hD M which could be treatment-related.

Hematology, Serum Biochemistry & Urinalysis: (weeks 4, 8, 12, 18 & 25)
No drug-related hematological changes. Very slight but stat. sig. dec. in serum proteins were observed in M at the HD at all scheduled exams and in M at the MD in drug wks 8 & 12 (significance unknown).

Crystalluria, consisting of needle-shaped and "sea urchin" shaped crystals (dihydrate & magnesium salt of MK-366), occurred in rats from the MD & HD gps. Crystalluria was most common in M at the HD. There was no crystalluria in LD rats. A high incidence (40-100%) of cecal enlargement was seen at all dose levels. This is not an uncommon finding in rats treated with antibiotics for a prolonged periods. There were no other treatment-related changes seen at necropsy including organ wt & histopathology.

#4. 54-Week Oral Toxicity Study in Rats [Bio Research Labs, Ltd., Canada]

Animals, Doses, Route & Duration: Albino rats [CrI:CD (SD) Br strain]; 20/sex - Controls, 50, 200 & 600 mpk/day; orally by gavage as a suspension; up to 54 wks; controls rec'd dist. water. The age of the rats at study initiation was 7 wks. N.B.: This age is one week short of the onset of puberty, i.e., 8 wks.

Schedule of Parameters Measured: Physical exam of all rats, daily; more detailed physical exam of abnormal animals, weekly; body wts twice/week for 2 wks during the pretreatment period, the first 13 wks of feeding, and thereafter once/week & preterminally; ophthalmic exam of all animals prior to treatment and of control & HD rats during drug weeks 27 & 52; hematology, serum biochem. & urinalysis, drug weeks 6, 12, 25 & 51 using the first 10/sex rats of each gp. Necropsy was performed on all rats dead or sacrificed during the course of the study, and on the rest at termination. At necropsy: body wt measurement; histopathology on all dead & sacrificed rats, 10/sex from control & HD gps, and any rat from any group showing gross lesions at necropsy.

Results

Physical Exam: No abnormalities.

Mortality or Sacrifice of Moribund Rats: Total of 19 (controls, 4; LD, 2; MD, 7; HD, 6). None were considered to be treatment-related.

Body Wt: Lower than that of controls in all treated gps at termination; however, it was sig. different in the MD & HD F.

Ophth. Exam: No abnormalities attributable to treatment.

Hematology, Serum Biochem. & Urinalysis: Normal biological variations

Gross Pathology: Findings not indicative of drug treatment (normal abnormalities).

Organ Wt: Stat. sig. dec. in mean abs. wts of liver, spleen, heart & brain of the HD M, compared to controls. "The differences for the liver, spleen and heart were reflected in the organ weight relative to brain weight. Liver and spleen weights relative to body weight were also statistically significantly decreased. These findings are not considered to be biologically significant since all mean values are within the 95% range of controls values and since there were no histomorphological changes that could account for these organ weight changes."

Histopathology: No drug-related changes.

#5. 13-Month Chronic Toxicity Study in Dogs [Kyorin]

Animals, Doses, Route & Duration: Dogs (breed not specified), 6 mos. old; 4 gps, 4/sex/gp - Controls, 25, 50 & 100/200* mpk/day; orally as a coated tablet; 6 days/wk for 13 mos; controls rec'd placebo tablets.

* "Dogs given 100 mpk/day for 10 months of the study were given 200 mpk/day for the remainder of the study."

Schedule of Parameters Measured: Clinical signs, daily; body wt, weekly; hematology, serum biochemistry, prior to study initiation and 3, 6, 9 & 13 mos. after the initial dose; urinalysis, 13 mos. after initial dose; ECG & ophth. exam, 13 mos. after initial dose. Organ enzymes monitored at termination were: liver ATP, glucose-6-phos. & B-glucuronidase, heart ATP, creatinine phosphokinase, kidney ATP, skeletal muscle ATP, creatinine phosphokinase, bone marrow alkaline phos. Similarly, drug metabolizing enzymes of the liver (cytochrome P-450; aminopyrimidenethylase; aniline hydroxylase) were examined at termination. Sera of all dogs were examined for specific antibodies vs. the drug at termination. All dogs were necropsied at termination and examined histologically.

Results: All of the above parameters remained normal.

Reviewer's Comment: The initial age of the dogs is the minimal age of puberty in this species. This explains the lack of degenerative joint disease.

#6. Chronic Oral Toxicity in Dogs [U. of Cagliari, Italy]

This is a shorter version of the previous (Kyorin) study. However, it lacks the wealth of parameters measured of the Kyorin study. Since this is not a pivotal study, it will be narratively reviewed.

MK-366 was administered orally as a susp. in distilled water, to gps of dogs (1/sex/gp) for 20 wks at dose levels of 25, 50 & 100 mpk/day. A control gp was established and rec'd distilled water. The animals were observed for general condition & behavior. Body wts were recorded weekly. Hematology, blood chemistry & urinalysis were done at the beginning and at the end of treatment. All animals were necropsied and major organs weighed. Histopath. exam of selected organs was performed.

Results: There were no treatment-related changes in any parameter examined. N.B.: No crystalluria.

#7. 26-Week Oral Toxicity Study in Dogs [MSD, Chibret, France]

Animals, Doses, Route & Duration: Beagle dogs, approx. 11 mos. old; 4 gps, 3/sex/gp - Controls, 50, 150 & 300 mpk/day; 7 days/wk for 26 wks. The drug was suspended in 0.5% methylcellulose and administered in gelatin capsules up to Drug Week 6, and thereafter by oral gavage. Controls were treated with empty gelatin capsules or methylcellulose suspension.

Schedule of Parameters Measured: Clinical signs, daily; body wt, 2x/wk up to week 12, then once/week; ophth. exam, ECG, hematology, serum biochemistry & urinalysis, weeks 3, 8, 12, 17 or 18 & 25. F were sacrificed after receiving 182 doses, M after 183 doses. Routine histologic exam was done on all dogs from the control & HD gps, as well as those that died or were sacrificed prior to scheduled termination. In addition, heart, kidneys, and all gross changes observed were examined microscopically in all dogs.

Results

Mortality: Total of 4; 1 & 3 in the MD & HD, respectively - found dead or sacrificed because of deteriorating physical condition.

Clinical Signs

- dose-related emesis post-dose and salivation pre- & post-dose in all treatment gps; less frequent in the LD gp;
- gray or clay-colored feces (unabsorbed drug) in all treatment gps;
- anorexia in HD dogs that died or were sacrificed during the study;
- dehydration in 2 HD dogs;
- marked wt loss in the same 2 HD dogs;
- slight retardation of body wt gain in surviving MD & HD dogs.

Ophthalmologic Exam; EKG: No changes or abnormalities attributable to treatment.

Hematology; Serum Biochemistry: Treatment-related changes characteristic to uremia & nephropathy, secondary to intra-renal or urethral obstruction (MK-366 crystals). These changes occurred in those dogs that were sacrificed during the study, e.g., (1) neutrophilic leucocytosis & slight lymphopenia; (2) monocytosis & slight lymphopenia.

Biochemical studies in sacrificed dogs showed moderate-marked increases in BUN & creatinine and moderate decreases or increases in serum electrolytes. Slight-moderate increases in activity of SGOT, SGPT, and/or alkaline phos. were also seen in these dogs and were probably secondary to uremia. There was also slight-moderate stress-related inc'd serum glucose in these dogs.

There were very slight transient inc's in BUN & creatinine in one surviving HD dog. Blood was present in the urine of one surviving MD & 2 HD dogs. There were no macroscopic and/or microscopic changes to account for these.

Crystalluria was evident in all treated gps. The crystals were needle-shaped or "sea urchin" shaped and identified as the dihydrate or magnesium salt of MK-366, respectively. Crystalluria was seen in most dogs at the HD & occasionally at the LD & MD. Microscopic changes were seen in the 2 sacrificed MD & HD dogs. Urethral obstruction, as well as hemorrhages in the urinary bladder wall & renal capsule, congestion of renal parenchyma, renal tubular dilatation & hemorrhagic prostatitis were also evident upon gross examination of these dogs. Acute pyelitis, pyelonephritis & nephrocalcinosis were also seen in one of these dogs. The 3rd dog sacrificed, a HD F, had no sig. gross changes in the urinary tract. Renal tubular dilatation, pyelonephritis and very slight unilateral papillary necrosis were apparent in this dog and were considered secondary to obstruction of the ducts of Bellini. Other microscopic changes occurring in the GI tract of one dog, also considered secondary to uremia, included gastritis & a pyloric ulcer. Marked lymphoid depletion in the thymus was apparent in all HD dogs that died or were sacrificed during the study and was considered related to stress.

One HD dog found dead at Week 12, showed no renal or urinary tract changes, but did show slight lymphoid cell depletion related to stress. The changes were present in the lymph node, spleen & Peyer's patches. There were no signs of toxicity in dogs given the MK-366 LD. Crystalluria was seen occasionally in this group.

Reviewer's Comment: Except for occasional crystalluria, the LD appears to be safe. Since crystalluria is an inherent toxic effect of this group of drugs, the final answer should come from human clinical experience. However, in the HD, a new effect surfaced which has not previously been found to be part of the spectrum of toxicity of drug of this class. This is the lymphoid depletion induction. The sponsor interprets this as a stress-induced change. I question this, since during a 6-month stress period, the adrenal cortex is either exhausted or undergoes hypertrophy. None of these are mentioned in the report. I suspect a peculiar endocrine related effect inherent to the drug or its metabolite(s), since the drug has another endocrine related effect on pregnant Cynomolgus monkeys. The lymphoid depletion, at least of the thymus, can be experimentally accomplished by parenteral admin. of either estrogens or progesterone & its synthetic derivatives, by simultaneous administration of both, or by testosterone alone in F rats. It is also well known that the admin. of exogenous glucocorticoids leads to the same effect, without stress. The importance of this lymphoid-depleting effect of the drug is that it may indicate an, as yet unsurfaced, potentially hazardous effect of this class of drugs. If the lymphoid depletion is a nonspecific stress-related effect, then any carcinogenicity study in laboratory animals should start with a report on "stress-related immunosuppression." Indeed, this is sometimes the case. However, I don't know if, from a sample statement on the presence of "allegedly

indirect immunosuppression" anyone can say that it is strictly stress related. A xenobiotic alone could be directly immunosuppressive, and at the same time, be responsible for the "treatment-induced chronic stress." Who can estimate the rate of contribution of the 2 factors from a simple histologic recognition of lymphoid depression? I wonder what a stress expert would say about this?

#8. 53-Week Oral Toxicity Study in Dogs [Bio Research Labs, Ltd., Canada]

Animals, Doses, Route & Duration: Beagle dogs (avg. age = 24-28 wks; age of replacement = 30-32 wks; the 24-28 wks of age coincides with the minimal age of puberty; the replacement dogs were already post-pubertal); 4 groups, 4/sex/gp - Controls, 50, 100 & 150 mpk/day of MK-366; gavage in aq. suspension; 7 days/week for 53 wks; controls rec'd distilled water.

Schedule of Parameters Measured: Physical exam of all dogs, daily; more detailed physical exam of abnormal dogs, weekly; body wt, pretest & weekly during treatment & just before sacrifice; food intake, daily prior to & during treatment; ophth. exam & EKG on all dogs, prior to treatment and at wks 12, 24 & 51; hematology, serum biochem. & urinalysis on all dogs, prior to treatment in at drug wks 6, 12, 23 & 50. At completion of the treatment period, all surviving dogs (except 5, fed by oversight) were fasted overnight, then killed by IV overdose of pentobarbital Na followed by exsanguination via incision of the axillary arteries. In dogs killed at study termination, the adrenals, brain, heart, kidneys, liver & testes were weighed. In addition, a necropsy was performed on all dogs sacrificed during the study. Hematoxylin & eosin-stained sections of tissues from all dogs were prepared for histopathological exams. Oil red O-stained frozen sections of liver & kidney from the same dogs were examined histopathologically by the applicant. Prepared & stained femoral bone marrow smears and reticulocyte counts for all sacrificed dogs were not evaluated, since hematological findings did not warrant these examinations.

Results

Clinical Signs: Silver-gray colored feces (unabsorbed drug) daily in the HD M & F, from wk 27 to termination.

Mortality: One HD M at wk 7, attributed to intussusception of cecum into the colon; one control F at wk 5, [dermatitis (demodicosis), undefined pulmonary pathology (abnormal respiratory sounds & congestion)].

Body Wt Gain: The HD dogs had lower wt gain than controls; wt gain in the LD & MD dogs was comparable to controls.

Food Intake: No adverse effect in any gp.

Ophth ; EKG; Hematology; Serum Biochem.; Urinalysis: No treatment-related effects.

Gross Path.; Organ Wts; Histopath.: No treatment-related findings.

Reviewer's Comment: This study contradicts the French study. The dose levels, except for the 300 mpk dose of that study (French), are identical.

The duration of treatment in this study is approx. double that of the French study and the age range of the animals is the same; yet this study is incredibly clean. Where is the crystalluria, nephropathology, lymphoid depletion, at least at 150 mpk? The applicant should explain this. [Is the French dog (whichever breed) reacting differently than the Canadian dog? Where is the stress effect?]

I also wish to note that, in my experience, the final outcome of a toxic effect depends not only on the dose, but on the duration of treatment. In other words, toxicity is the result of a multiplication of the daily dose with the no. of the days of admin. In this case, 300 mpk for 26 wks should result in the same sort & severity of toxicity as 150 mpk for 53 wks (in terms of lymphoid depletion). Lymphoid depletion (immunosuppression) is particularly bad for an antimicrobial drug. Although this cosmetic mistake is not severe enough to hold up approval of this drug, an acceptable explanation should be submitted by the applicant. The 50 mpk/day "no effect dose level" is high enough for the calculation of an acceptable and efficacious human dose.

SPECIAL STUDIES

These studies follow the order in Vol. 2.51.

Arthropathy Studies

#1. Effect on the Diarthroidal Joint of Immature Dogs [Kyorin]

Animals, Doses, Route & Duration: Beagle & mongrel dogs, 3-5 mos. of age; 2/group and a neg. control gp. The treated dogs received orally:

- MK-366 @ 30, 60, 100, 250 & 500 mpk/day for 7 days, recovery study - 200 mpk/day for 99 days;
- Pipemidic Acid @ 30, 60, 100, 250 & 500 mpk/day for 7 days;
- Nalidixic Acid: 30, 60 & 100 mpk/day.

Results: This is the best report I have ever seen on this subject. The summary is excellent and worthy of a verbatim quote. [At the end, I will make some comments on certain aspects of this study; however, is there any study which cannot be made better or more comprehensive?]

"Clinical signs of lameness appeared from the second day of treatment in dogs given doses of MK-0366 greater than 60 mpk/day which persisted through the duration of the study (7 days). In the 99-day study there was recovery from clinical signs within 6-8 weeks after initiation of the study. The degree of lameness was related to dose administered. In dogs administered PPA (pipemidic acid) and NA (nalidixic acid), similar dose related lameness was seen at dose levels greater than 30 mpk/day.

An increased amount of synovial fluid was found at necropsy in dogs at doses at 100 mpk/day or greater for all three compounds in the 7-day study. The synovial fluid was sometimes yellow & semiopaque with white suspended matter. The abnormality in the synovial fluid was dose dependent for all three compounds. No abnormality was seen in the synovial fluid of dogs in the 99-day study at the time of necropsy.

The joint lesions were characterized by blister formation in the articular cartilage. At higher doses ruptured blisters (erosions) were common. The chondrocytes adjacent to the blisters and erosions were hypertrophied. Although there was recovery from clinical signs in dogs in the 99-day study, gross and microscopic changes were evident in the articular cartilage at termination. Synovial membranes and epiphyseal plates were not affected by any of the three compounds tested.

No abnormalities related to treatment were detected in the hematologic and serum biochemical parameters, urinalysis or tissue enzymes."

Reviewer's Conclusions

- a) The study shows that the very left-hand ring of the quinolone, which is a fused substituted benzene in MK-366, could be modified by exchanging 1 carbon of the ring with a N-atom (NA) or 2 carbons with 2 nitrogen atoms (PPA) without losing the arthrotoxicity of the drug.
- b) The molar conc'n of the same dose is higher for NA (m.w. 232.23), less for PPA (m.w. 303.33) and even less for norfloxacin. Though the minimal arthropathogenic dose is not known for any of the drugs, from the available data, a conclusion based on the ratio of molecular size (no. of moles) and severity of the lesions cannot be drawn.
- c) No other organs or systems were affected by MK-366 from a 500 mpk/day dose for 7 days, or from 200 mpk/day for 99 days.
- d) Conspicuous is the finding in the synovial fluid at 100 mpk/day and higher. Unfortunately, it is not stated that this change included increased viscosity; cloudiness was due to inflammatory cellular exudate and/or increased protein content. The most important aspect of protein content would be its enzyme activity, which was not investigated.
- e) It is also interesting that minor lesions in the articular cartilage are present, in the case of all these drugs, at doses not inducing changes in the synovial fluid; therefore, it is safe to assume that the synovial fluid change is not essential in the pathogenesis and that it appears to be secondary.
- f) The hypertrophy of the chondrocytes adjacent to blebs & fissures indicates something. Is this a desperate tendency to regenerate, or do these cells only appear to be hypertrophied since, in the neighborhood of the "lakes", they are not compressed as tightly as in normal cartilage?

- g) It is still not clear from this study (or any study) whether or not the chondrocytes or the matrix are primarily affected by the drug or vice versa. From one single photograph of Dr. Margett's, I am unable to conclude that the drug is deposited only in the chondrocytes in the case of NA in the rat.
- h) The drug does not appear to be an enzyme inhibitor in a general sense, since it did not show these effects in a number of visceral enzymes. The 3 enzymes that might play a crucial role in the articular toxicity of these drugs might be Mg-dependent topoisomerase, the Mg-dependent GPT-ase, and the group of lysosomalytic (proteoglycan) enzymes of the chondrocytes, which were not investigated.
- i) This study also proved that only the juvenile cartilage is sensitive to the arthrototoxic effects of the drug. Prior to this study, they tested mature rats & dogs for this purpose, with negative results.
- j) Finally, the study shows that MK-366 is less arthrototoxic (with a factor of 2) than the world-wide (USA involved) marketed NA, and the world-wide (except USA) marketed PPA.
- k) Although the applicant rightly determined the acute toxicity of the individual metabolites, it is unknown whether or not the drug per se, or one or several of the metabolites, with or without the drug in concert, are responsible for the arthrosis.
- l) This study does not identify any objection to the approval of the drug.

#2. Study in Immature Rabbits [Kyorin]

Animals, Doses & Duration: Japanese white rabbits, 8-10 wks old; 250 & 300 mpk/day of MK-0366 for one week or 100 & 300 mpk/day for 21 days; groups of 5-11 rabbits; 4 other groups were treated with NA (150 mpk) & PPA (250 mpk/day) for 7 days, as pos. controls.

Results: No gait abnormalities, hematologic, serum biochemical, urinary or tissue enzyme changes related to treatment in any group.

Pathology: Gross blisters were seen on the articular cartilage of the stifle, hip or elbow joints or some of the rabbits treated with NA, PPA & MK-366 for 7 days. The rabbits given MK-366 for 21 days had no blisters on the articular cartilage. However, 1/5 control rabbits also had blisters on the articular surface of the stifle joint. Histopathologically, activation was seen at the intermediate zone of the cartilage with matrix rarefaction & fibrillation in the immediately surrounding cartilage.

Reviewer's Comment: The study does not indicate the no-arthropathogenic-effect dose level in rabbits.

#3. Antigenicity Studies [Kyorin]

- MK-366 elicited no delayed hypersensitivity reaction on the skin of guinea pigs, whereas under the same conditions, 2,4-dinitrochlorobenzene elicited a positive response.
- Anaphylactic reaction was not observed in guinea pigs sensitized with MK-366 alone or in a mixture with Freund's complete adjuvant (FCA).
- Serum from guinea pigs sensitized with MK-366 induced no passive cutaneous anaphylaxis in recipient guinea pigs.
- Specific antibodies vs. MK-366 were not detected in sera of rabbits immunized with MK-366-BGG conjugate & FCA.

#4. Guinea Pig Skin Maximization Test [Kyorin]

There was no evidence (gross or microscopic) of sensitization in the MK-366 treated groups. On the other hand, the challenge sites of all animals in the DNCB group showed, as expected, characteristic sensitization reactions consisting of slight-marked dermal inflammation and slight-moderate epidermal thickening.

#5. Influence on the Retina of Cats [Kyorin]

Retinal toxicity of MK-366 was evaluated in cats by electroretinogram (ERG) & histopathological exam. NA was used as a reference substance. MK-366 or NA was infused IV (0.8 ml/min) at a dose of 40 mpk and ERGs were recorded during & after dosing. There were no sig. changes in latent times or amplitude of ERG waves during or up to 60 min. after dosing with MK-366, when compared with those before admin. NA, on the other hand, caused a prolongation of latency as early as 15 min. after the start of dosing, followed by complete loss of op- & b-waves of ERG.

In another experiment, MK-366 was administered orally at doses of 50, 100 & 200 mpk/day for 2 wks. NA was administered orally @ 100 & 200 mpk dose levels (varied doses, based on the presence or absence of toxicity) for 2 wks. ERGs were recorded at termination under anesthesia or while the animal was immobilized by a muscle relaxant. All animals were killed after recording of ERG and eyes were collected for histopathology. Results of histopathologic exam were negative.

#6. Auditory Toxicity in Rats [Kyorin]

Schedule: A daily dose of 500 mpk of the drug was given orally to Wistar rats for 7 mos. Other groups of rats were given 200 mpk b.i.d. of kanamycin & 400 mpk b.i.d. of streptomycin for 27 days (pos. controls). All groups were tested for auditory & vestibular function at the end of their period of treatment.

Upon completion of auditory & vestibular function tests, the animals were killed and cochleae were resected & processed for scanning electron microscopic exam.

There were no treatment-related changes in auditory or vestibular function in rats given MK-366 @ 500 mpk/day for 6 mos. There were also no histopathological changes in the organ of Corti.

The rats given streptomycin showed changes in vestibular function characterized by tremor, tilting of the head & decreased ability to balance on a bar; there were no abnormal auditory functions or histopath. changes in the organ of Corti. The rats treated with kanamycin showed auditory dysfunction, but no vestibular dysfunction. Histologically, there were dec's in the number, reaction & size of cilia of the inner hair cells and complete loss of cilia in the outer hair cells.

7. Acute Phototoxicity in Female Mice [Method of E.S. Copeland, et al., J. Invest. Dermatol. 64: 349-356, 1975]

In this study, chlorpromazine was used as a positive control. Oral admin. of MK-366 at doses of 625, 1250 & 2500 mpk produced no perceptible erythema in F mice after 20 hrs of exposure to long wave UV light. However, oral admin. of chlorpromazine, a known phototoxic agent, produced definite erythema of the ears at a dose of 120 mpk. All 6 animals in this group showed moderate erythema 3 hrs following exposure. By the 7th day, 4 of these had slight or no erythema, while the remaining 2 had marked erythema with scarring. Negative control animals (water) showed no evidence of erythema.

8. Ocular Irritation Study in Rabbits (Draize Method)

All rabbits showed a normal body wt gain during the study. Instillation of MK-366 powder into conjunctival sac produced a very slight conjunctival injection & moderate cloudy discharge at 15 min. The severity of ocular effects increased by 24 hrs with a moderate injection & discharge and a marked amount of chemosis; 2/4 eyes had corneal opacification & circumcorneal hemorrhage by the 4th day; 3/4 eyes appeared normal after 10 days; the remaining eye continued to show severe ocular irritation at day 14.

Applicant's Conclusion: MK-366 was found to be severely irritating to the rabbit eyes in a primary eye irritation study.

9. Drug Deposition Study in Dogs

Purpose of the Study: To determine in Beagle dogs (3 gps, 3/sex/gp), the conc'n of MK-366 in the plasma, aq. humor & lens of dogs after 1 & 21 oral doses of 7 days after cessation of treatment.

Conclusions

- a) Once daily oral admin. of 150 mpk of MK-366 for 21 days to dogs resulted in a small, though stat. sig., increase in aq. humor levels, ranging from 0.06-0.11 ug/ml.
- b) Three-week admin. of MK-366 resulted in a small, but stat. sig. inc.

in the lens content of the product. Such an observation would not be unexpected, as the product is present in low conc'ns in the aq. humor. What is clear is that the avidity of the lens for MK-366 is negligible as reflected by the very low value of 0.24 ug/g. The presence of low conc'ns of MK-366 in the lens most probably result from simple diffusion.

- c) The lack of sequestration of MK-366 by the lens is clearly shown by the rapidity of washout following cessation of treatment, conc'ns declining from 0.24 to 0.08 ug/g at 7 days.
- d) Once daily admin. of 150 mpk of MK-366 does not result in a marked, persistent accumulation of the compound in the dog lens.

REPRODUCTION STUDIES

#1. Effect of MK-366 on Fertility in M & F Mice [Kyorin]

Animals, Doses, Route & Duration: White laboratory mice (SLC:ICR strain); 4 gps, 21/sex/gp - Controls, 125, 250 & 500 mpk; oral; Days 6-15 of gestation. Prior to this an equal no. of M & F were kept together (1:1/cage) until the appearance of a vaginal plug (= day 1 of pregnancy).

Parameters observed were: maternal toxicity, embryotoxicity & lethality, functional & behavioral tests of newborn F₁ & F₂ generations and reproduction performance of F₁ & F₂ generations.

Results: No abnormalities were observed in any parameter.

#2. Teratogenic Effects in Mice [Institute of Gen. Path., Italy]

Animals, Doses, Route & Duration: Laboratory F white mice; 4 groups, 20/gp - Controls, 100, 200 or 400 mpk/day; oral; Days 5-16 of pregnancy.

Results: There were no drug-induced effects on the dams. There were also no treatment-related differences in gestation period, no. of corpora lutea, no. of implants, no. of resorptions, no. of live or dead fetuses, wts of fetuses or external malformations.

#3. Effects of Oral Admin. on Pregnancy in the Rat (Dose-Range-Finding Study) [Life Sciences Res., U.K.]

Animals, Doses, Route & Duration: Charles River CD rats; 5 groups, 20 F/gp - Controls, 200, 400, 600 & 800 mpk; oral; Days 6-17 of pregnancy.

Results: Treatment with MK-366 had no effect on the general condition of the animals or upon body wt gain during gestation. MK-366 had no adverse effect on pregnancy, as assessed by external exam of the uterine horns. It was concluded from this preliminary study that dose levels up to 800 mpk/day should be suitable for use in a main teratology study in rats.

#4. Effects of Oral Admin. on Pregnancy in Rats [Life Science Res., U.K.]

Animals, Doses, Route & Duration: Pregnant F SD/CD rats; 4 groups, 25/gp - Controls, 50, 200 & 800 mg/kg b.i.d.; oral; Days 6-17 of pregnancy.

Results: The general condition & body wt gain of treated animals were similar to those of the controls throughout the study.

At termination on Day 20 of gestation, there were no changes or trends in the nos. of implantations and viable young or in the extent of pre- & post-implantation losses that could be attributed to treatment. Fetal & placental wts were similar in all gps.

Fetal exam at necropsy, by free-hand serial sectioning or following skeletal processing, revealed a small no. of anomalies in all gps, including 4 abnormal fetuses, but no indication of any adverse effects could be related to treatment with MK-366.

#5. Teratogenicity Study of AM-715 in Rats [Kyorin]

AM-715 Chemical Formula: 1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-Pipreaziny)-3-quinolinecarboxylic acid

Animals, Doses, Route & Duration: JCL-SD rats (pregnant F only); 30/gp - Controls, 125, 250 & 500 mpk/day; oral; Days 7-17 of pregnancy. [Max. dose equiv. to 41.7x the proposed clinical dose (12 mpk/day).

Results: AM-175 showed no undesirable effect on pregnant rats. In the F₁ fetuses of the treated gps, it was determined that the gross malformations, visceral & skeletal abnormalities and variations observed were within the limit of spontaneous occurrence.

AM-715 produced no serious effect on growth, differentiation, functions, behavior or reproductive performance of the newborns. The drug showed no toxicity or any effect on F₂ fetuses.

From the above, it was concluded that admin. of AM-175 to rats during organogenesis, at the doses used in this study, had no adverse effect. Therefore, 500 mpk/day was assumed to be the maximum dose producing no overt teratological effect in rats.

#6. Effects of Oral Admin. on Pregnancy in Rabbits (Dose-Range-Finding Study) [Life Sci. Res., U.K.]

Animals, Doses, Route & Duration: Japanese white domestic rabbits (pregnant F only), 8/group; Controls, 50, 100 & 200 mpk; oral; Days 6-18 of gestation. All surviving rabbits were sacrificed on 2 days before expected parturition.

Results: Body wt loss or dec'd body wt gain and premature births or abortions were observed in all dosage gps.

Applicant's Comments: In view of the sensitivity of MK-366, the rabbit was considered unsuitable for use in a full teratology study. This sensitivity is due to the disturbance of the GI flora.

#7. Teratology Study in Rabbits [Kyorin]

Animals, Doses, Route & Duration: White domestic pregnant F rabbits; 4 groups, 12-13/gp; Controls, 25 & 100 mpk/day; oral; Days 6-18 of gestation. On day 29 of gestation, all dams were sacrificed for examination of uterine contents.

Results: Only at the HD, slight dec. in spontaneous movement, sig. reduction of appetite, diarrhea & reduction of body temp. were noted. Sig. wt gain reduction also in the same gp. One dam of this gp aborted dead fetuses on the 27th day of gestation.

Embryotoxicity: Noted in the HD only: inc'd no. of dead embryos and resultant dec. in the no. of surviving fetuses. There were no external, visceral or skeletal malformations that were considered related to the admin. of MK-0366.

8. Exploratory Plasma Profile Study in Rabbits [MSDRL, USA]

Reason for Study: As was suggested in the earlier rabbit studies, the oral route for teratogenicity studies in rabbits is not appropriate. Therefore, it was decided to determine the drug's toxicity in the absence of an effect on intestinal flora by administering the drug parenterally.

A comparative plasma profile study (oral vs. SC) was performed in rabbits, in order to aid in the selection of doses for parenteral admin.

Animals, Doses, Route & Duration: Nonpregnant F NZ albino rabbits; 2 groups, 3/gp; 100 mpk, once, orally; 20 mpk once, SC. Plasma was collected 0.5, 1, 2, 3, 4, 5, 6 & 24 hrs post-dose. Determination of plasma levels were done by microbiological assay. N.B.: This might indicate that in the case of oral admin., a great deal of microbiologically nonactive metabolites entered the blood stream (intestinal microbiological metabolism); but since they don't have antimicrobial effects, the assay does not indicate their presence.

Results: Plasma level of MK-366 peaked at 0.6-1.3 ug/ml within 3 hrs following oral admin. and at 6.8-6.9 ug/ml within 0.5 hr follow SC admin. At 24 hrs post-dose, there was no detectable amount of drug in plasma in either gp of animals.

Based on these results, 20 mpk/day SC is judged to be a more than adequate dose to attain blood levels as high & prolonged as 100 mpk/day orally.

9. Exploratory Biliary Excretion Study in Rabbits [MSDRL, USA]

Reason for Study: As is evident from earlier rabbits studies, oral MK-366 appears to be much more toxic to rabbits than to other laboratory animals (rats, mice). It appears that for teratogenicity studies, the parenteral route is the only available way for the rabbit. To avoid disturbing interference by enterohepatic circulation of the drug, its

biliary excretion had to be explored. The SC route is valuable only if biliary excretion is minimal; therefore, a substantial amount of the SC-administered dose does not enter the intestines, and after being metabolized by the GI bacteria, does not enter the blood stream as a highly toxic metabolite. (Urinary excretion is predominant in most species.)

Animals, Doses, Route & Duration: NZ albino rabbits; 4 groups (1/group) anesthetized; SC; 20 mpk of MK-366. Bile was collected continuously via a cannula in the common bile duct; blood samples were collected periodically for 4-6 hrs after dosing; determinations were done by microbiological assay.

Results: Plasma levels of MK-366 peaked at 3.84-14.4 ug/ml between 10 & 60 min. post-dose. Levels of MK-366 in the bile peaked at 33.3-93.5 ug/ml between 30 & 90 min. post-dose and inc'd & dec'd approx. in parallel with plasma levels. The total amount of drug excreted in bile during the 4-6 hr post-dose period represented 1.2-2.4% of the SC dose. By extrapolating from the decreasing rate of biliary excretion at the end of the collection period, it can be estimated that the total amount excreted in bile would have been 2-4%.

Applicant's Remarks: "The low rate of biliary excretion of MK-0366 in the rabbit makes it possible to design a study to test the hypothesis that the toxicity and fetotoxicity associated with oral dosing may be due to an effect on the intestinal flora."

10. Exploratory Toxicity Study in Nonpregnant Rabbits [MSDRL, USA]

Reason for Study: To prove the hypothesis that the maternotoxicity of MK-366 was secondary to an antibiotic effect on the GI flora, it was decided to administer the drug parenterally, and thereby determine its toxicity in the absence of an antibiotic effect on the intestinal flora. The results of the previous study proved that the biliary excretion rate is low (2-4%); therefore, the potential interference by that portion of the drug that re-enters the circulation after being excreted in the bile is negligible.

Study Objective: To determine whether SC admin. of MK-366 for 13 days at doses up to 20 mpk/day is tolerated in rabbits.

Methods: In this study, which used NZ albino rabbits, MK-366 was given SC to 3 groups of 5 F, at dosage levels of 5, 10 & 20 mpk/day. A 4th group of 5 F received 100 mpk/day of MK-366 orally by rubber catheter in 1 ml/kg of 0.1% methylcellulose. A 5th group of 5 F received 0.9% saline SC and served as controls. The drug (factor = 1.00) or control article was administered once/day for 13 days (day of 1st dose = Day 1). The dosing volume for the SC gps was 0.5 ml/kg. At the beginning of the study, the F were approx. 5-6 mos. of age & weighed 3680-4370 gm.

At the end of the 13-day dosing period, the F were observed for an additional 7 days. Body wts were recorded on Days 1, 4, 7, 10, 13, 14,

17 & 20. Food intake, at 24-hr intervals, was measured the day before the 1st dose and every 3rd day beginning at Day 1. At 0.5 & 3 hrs after the 1st & 13th doses, the rabbits were bled for determination of plasma levels of MK-366 by microbiological assay. On day 14, they were bled for determination of serum levels of urea nitrogen, creatinine, Na, K & Cl. On Day 20, they were sacrificed and discarded without further examination.

Results: There were no deaths. Toxicity was apparent @ 100 mpk/day PO as a mean body wt loss of 354 gm during the dosing period compared to a wt gain of 132 gm in controls. The wt loss was accompanied by dec's in food & water intake. Mean food intake @ 100 mpk/day PO dec'd during the dosing period to 20-30% of controls levels, then inc'd during the post-dose period, but remained below that of controls. Also, on Day 14, there were slight but sig. inc's (Day 14) in serum creatinine (up to 2.0 mg/dl) & urea nitrogen (up to 24.4 mg/dl) levels in the 100 mpk/day orally-treated gp. There was no evidence of toxicity with the SC route.

Orally dosed F had orange urine as early as Day 10 and as late as Day 20. There was no discolored urine in the SC-treated gp.

At 0.5 hr following the 1st dose, plasma levels of MK-366 in the 100 mpk/day PO gp (mean = 1.02 ug/ml) were much lower than those in the 5, 10 & 20 mpk/day SC gps (means = 2.25, 5.33 & 9.25 ug/ml, respectively). Following the 13th dose, however, the oral plasma levels had inc'd compared to those after the 1st dose. At 0.5 hr post-dose (PD), the oral levels (mean = 1.77 ug/ml) were almost as great as those @ 5 mpk/day SC (mean = 2.45 ug/ml). At 3 hrs post-dose, the oral levels (mean = 1.5 ug/ml) were greater than both the 5 & 10 mpk/day SC levels (means = 0.59 & 1.24 ug/ml, respectively). Only the 20 mpk/day SC gp had plasma levels (3.76 & 1.94 ug/ml @ 0.5 & 3 hrs after 13th dose) which exceeded those in the oral gp at all time points tested.

Applicant's Conclusion: "Since the toxicity seen with oral dosing was not seen with SC dosing, even though blood levels of drug were higher following SC dosing, it seems likely that the toxicity seen with oral administration of high doses is not due to a systemic effect of the drug but rather to an effect on the intestinal flora."

11. Exploratory Blood Level Study in Nonpregnant Rabbits

Study Objective: To determine plasma drug levels at many time points after the 1st & 13th doses in order to better define the kinetics of the plasma levels of the drug. In addition, the effect of dec'd food intake on plasma levels of MK-366 was examined in a 2nd gp of F.

Methods

Group A: 5 F NZ albino rabbits received 13 daily oral doses (= Days 1-13) of 100 mpk/day, and were provided with the normal daily allotment of 150 gm/day of food.

Group B: Received a single oral dose of 100 mpk on Day 13 and were provided with an amount of food approx. equal to the max. level consumed

by a gp identical to Group A in a previous study (130 gm, Day 1; 100 gm, Day 2; 70 gm, Day 3; 40 gm, Days 4-13). The base compound of the drug (factor = 1.0) was suspended in 0.1% aq. methylcellulose and administered orally via rubber catheter at a dose volume of 4 ml/kg. At the beginning of the study, the animals were approx. 5-6.5 mos. of age and weighed 3620-4180 gm. Body wts were recorded on Days, 1, 4, 7, 10, 13 & 14. Food intake was measured at 24-hr intervals beginning on Day 1. On Days 1 & 13 (Gp A) & Day 13 (Gp B), the F were bled at 0.5, 1, 2, 3, 4, 6, 8 & 24 hrs PD for plasma drug level determination by a microbiological bioassay procedure. Plasma drug levels were also determined for samples collected from Gp A just before dosing on Day 13. On Day 14, the animals were sacrificed and discarded without further examination.

Results: There were no deaths. Toxicity was apparent in the gp receiving multiple doses (Gp A) as dec'd food & water intake and a mean body wt loss of 266 gm. Some F in Gp A had dark or orange urine as early as Day 9 and as late as Day 13. F in the pair-fed Gp B consumed all food provided and had inc'd water intake, but had approx. the same overall body wt loss (mean = 304 gm) as F in Gp A.

Following the 1st dose, the highest plasma level in Gp A occurred at 0.5 & 1 hr PD (mean levels = 1.25 & 1.24 ug/ml, respectively). No drug was detected at 8 hrs PD. Following the 13th dose, the peak plasma level (mean = 3.5 ug/ml), occurring at 1 hr PD, was approx. 3-fold higher than that following the 1st dose. The drug had not been cleared from plasma, even at 24 hrs after the 12th & 13th doses (mean levels = 0.34 & 0.36 ug/ml, respectively).

In the pair-fed gp B, the highest plasma levels following the single dose on Day 13 occurred at 0.5 & 1 hr PD (mean = 0.92 & 0.89 ug/ml, respectively). The drug had been cleared from plasma by 6 hrs PD. Thus, a low level of food intake for 12 days did not cause inc'd plasma levels of MK-366 in Gp B and is not an explanation for the inc'd plasma level following the 13th dose in Gp A.

Other possible explanations which have not been tested include the following:

- MK-366 may be broken down in the gut to a greater extent with the normal flora than with the antibiotic-altered flora.
- The drug may be bound to intestinal contents to a greater extent with the normal gut flora compared to the antibiotic-altered flora.
- Transit time in the gut may be inc'd in MK-366-treated rabbits.
- The drug may cause an inc'd absorption rate or a dec'd excretion rate.
- The drug may inhibit its own metabolism in the liver.

12. SC/Oral Teratology Study in Rabbits [MSDRL]

Objectives: To determine if the fetal wastage observed with oral MK-366 dosing is also specific to the oral route and not correlated with drug plasma levels, a combined oral/SC teratology study was conducted.

Methods: MK-366 was administered to NZ albino rabbits orally at a dose of 100 mpk/day to a gp of 20 artificially inseminated F and SC @ 20 mpk/day to a 2nd gp of 20 inseminated F. A 3rd gp of 20 F received saline SC and served as controls. For oral dosing, the drug was suspended in 0.1% aq. methylcellulose and administered at a dose volume of 4 ml/kg. For SC dosing, the drug was dissolved in saline. The dose vol. for both SC gps was 0.5 ml/kg. The drug (factor = 1.00) or control article was given once/day on gestational Days 6 thru 18. At the beginning of the study the F were approx. 6-6.5 mos. of age and weighed 3870-4840 gm. Body wts were recorded on Days 0, 6, 8, 10, 12, 14, 16, 18, 19 & 28 of gest. Food intake was measured at 24-hr intervals every 3rd day beginning on Day 3 of gest. At 1, 4, 7 & 24 hrs after the 1st dose on Day 6 of gest., 5/gp were bled for drug plasma level determination. The same F (except for 1 orally dosed F that died after an intubation accident) were bled again for this purpose just prior to the last dose on Day 18 of gest. and at 0.5, 1, 2, 3, 4, 8 & 24 hrs after the last dose. Because of the possibly complicating effects of the bleedings, these F were sacrificed after the last bleeding on Day 19 of gest., then examined grossly. On Day 28 of gestation, the remaining F were sacrificed & evaluated.

Results: There were no treatment-related deaths or abortions. One F at 100 mpk/day PO was found dead on Day 14 of gest. following an intubation accident. There were 2 abortions @ 100 mpk/day PO on Days 26 & 27 of gest. The F @ 100 mpk PO that aborted on Day 27 of gest. had a small amount of blood stained fluid in the thoracic cavity and associated pulmonary telectaxis? At termination on Day 28 of gest., 4 F at 100 mpk PO had varying amounts of clear fluid in the thoracic and/or abdominal cavities compared to one in controls. The applicant feels that this was due to malnutrition.

In the gp dosed orally, maternotoxicity was seen as mean wt loss during the dosing period and inc'd wt gain at the end of dosing. Embryotoxicity was apparent @ 100 mpk/day PO, as evidenced by inc'd resorption, dec'd fetal wt & delayed ossification. There was no maternotoxicity or embryotoxicity in the SC-dosed group.

Applicant's Comment: Since embryotoxicity occurred in the gp with maternotoxicity & lower peak blood levels (100 mpk PO), it is concluded that embryotoxicity is not a direct effect of the drug on the embryo, but rather secondary to maternotoxicity.

Reviewer's Comment: The above explanation is acceptable.

#14. Fertility Study in Mice [Kyorin]

MK-366 was administered orally as a suspension in sterile distilled water at dose levels of 125, 250 or 500 mpk/day to ICR M mice (20/gp) for 61 days before mating & during mating, and to ICR F mice (20/gp) daily for 15 days before mating until the 6th day of pregnancy.

Two similar gps of mice served as controls and received distilled water.

The mice were examined daily for their general condition. Body wts were taken daily. Food & water intake were measured once/week for M and 2x/wk for F prior to mating. All M mice were sacrificed & necropsied after mating, and their reproductive organs weighed. On Day 18 of pregnancy, the F were sacrificed, and after fetuses were removed, the corpora lutea & no. of implantation sites were counted. The no. of surviving fetuses, dead fetuses & resorption sites were also counted. The body wts of surviving fetuses & placental wts were also counted. The fetuses were examined for external, visceral & skeletal abnormalities.

Results: No treatment-related effects on reproductive performance or differences in growth & differentiation of the fetuses were observed.

15. Peri/Postnatal Study in Mice

MK-366 was administered orally, suspended in distilled water to F mice (21/gp) from Day 15 of gest. to Day 21 postpartum at dose levels of 0, 125, 250 & 500 mpk/day. The purpose of this study was to determine the effect of the test compound on growth, function, behavior & reproductive performance of F₁ & F₂ offspring. General symptoms & body wt were checked daily during gest. and the nursing period. All pregnant F were allowed to deliver. The length of gest., the no. & sex of newborns and their external abnormalities were determined. The newborns (F₁) were tested for growth & various physiological functions, including reproduction. Major organs were weighed. F₂ offspring were treated in the same manner as the F₁ newborn.

Results: No abnormal signs induced by MK-366 were observed in dams. The body wt of the treated gps was similar to that of controls at all times except on day 18 of gest. in the 500 mpk gp. This was not considered biologically sig.

No sig. differences were observed in the newborns in treated gps compared to controls, in gestation length, sex ratio, birth rate & weaning rate. There was no difference in the no. of implantation sites. There were no external or skeletal abnormalities related to treatment in the F₁ or F₂ newborns. There was also normal body wt gain. Also, there were no abnormalities in function, behavior or reproductive performance of the F₁ or F₂ offspring that were considered related to treatment.

Addendum: In the presently ongoing teratology study in cynomolgus monkeys, preliminary evidence indicates embryoletality at relatively high doses (200 mpk). There is, however, no evidence of teratogenicity. The study is continuing to establish a no-effect level.

Reviewer's Comment: Among all the reproductive & teratology studies, the rabbit & the cynomolgus monkey studies are troublesome. The studies elucidating the maternal-toxicity-dependent embryotoxicity of MK-366 are convincing. By learning about this phenomenon, we are introduced to a new concept in teratology. The rabbit studies do not affect the approval of the drug.

Much more important are the results of the cynomolgus monkey studies which are only briefly mentioned in the NDA and therefore not reviewed above. We have discussed the findings with the applicant. In the present submission, the summary indicates that the drug decreases the serum progesterone level in this species so drastically that dead and/or aborted feti will be delivered by a sizeable portion of the treated group, or if the embryolysis happens quite early, the uterus appears empty at study termination in monkeys which, prior to study initiation, were definitely pregnant.

Since I do not have the final report of the study, I cannot commit myself to anything at this time. However, as I already mentioned, the serum progesterone level reducing effect of the drug should be tested in nonpregnant women. I understand that the progesterone level during pregnancy is much higher than before pregnancy, and that a female body might react differently during pregnancy. I cannot imagine the testing of the effect of the drug in pregnant women, unless it could be done in such cases where the woman is determined to have an abortion anyway. Without saying more about the medical problem, I leave the decision to the medical fora. I anticipate that the monkey findings will call for Pregnancy Category "C", but I cannot offer a final decision on labeling until all the monkey data are submitted (and/or the drug is tested in pregnant women, if this is determined to be ethically feasible by the reviewing MO.)

MUTAGENICITY

MK-366 was tested for mutagenicity in the following tests:

In Vivo Studies: Dominant Lethal Test; Chromosomal Test

In Vitro Studies: V-79 Mammalian Cell Mutagenesis; Rec-Assay Ames Test; Cytotoxicity Test; Chromosomal Aberration Test; Sister Chromatid Exchange; Unscheduled DNA Synthesis in Rat Hepatocytes; Autoradiographic Assay.

Results: Only the Rec-Assay was weakly positive. In view of this single positive finding, the applicant decided to run a special rat carcinogenicity study, using Fisher rats, 5 wks of age; 3 groups, 50/sex/gp - Controls, 0.05% & 0.2% MK-366 in the diet. Feeding period was 19 mos. followed by withdrawal period of 12-14 wks. Results: No evidence of carcinogenic effect has been observed thus far.

PHARMACOLOGY

MK-366 appears to be without marked pharmacological action in the central & peripheral nervous, GI, and cardiovascular systems. In general, activity was only observed at doses well in excess of those necessary for antimicrobial activity. Therefore, these results suggest that MK-366 is a well-tolerated antibacterial agent.

METABOLIC & PHARMACOKINETIC STUDIES

These subjects were already discussed during the review of the original IND. The spectrum of the metabolites (7) is very similar in various species to those of man. The toxicity of the mixture of the metabolites gives the same LD₅₀ value as the parent drug.

CONCLUSIONS & RECOMMENDATION

This drug appears the least troublesome of all in its group. The total lack of functional & morphological eye toxicity is an encouraging quality. The enigmatic studies are the rabbit & cynomolgus monkey teratogenicity studies. The answer is easy for the rabbit, since the peculiarity of the GI tract flora and its unexpected reaction to the drug make this species unfit as an animal model.

The study which aroused my concern with respect to its abortifacient effects in the cynomolgus monkey, implicitly expresses the great hazard for pregnant women. The final report of this study has not been submitted to us yet. I will recommend a Pregnancy Category only after seeing the final report.


Lorant Buko, D.V.M., M.Sc.

cc: ~~Orig.~~ NDA

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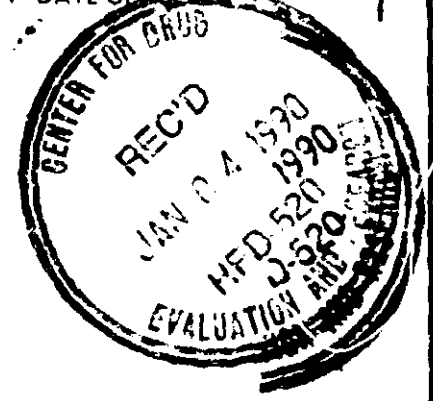
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ANNUAL REPORT

OATG

Noted 1-16-90 JMK REPORTS

TRANSMITTAL OF ANNUAL REPORTS FOR DRUGS FOR HUMAN USE (21 CFR 314.81)		DATE SUBMITTED 1/2/90	Form Approved: OMB No. 0910-0400 Expiration Date: August 31, 1989.	
NOTE: This report is required by law (21 USC 355; 21 CFR 314.91). Failure to report can result in withdrawal of approval of the New Drug Application.			1 NDA OR ANDA NUMBER N 1 9 3 8 4	
INSTRUCTIONS Complete a transmittal form for each application for which an annual report is being submitted. Retain the carbon copy labeled "applicant." Submit the remaining copies of the transmittal form along with two copies of the annual report to FDA. If any part of the annual report applies to more than one application, list in item 7 all other applications to which such parts apply.			2 Report No (FDA Complete) Y- 003 APPLICANT NOTE Reference NDA and Y numbers (entered on Acknowledgement Copy) in any subsequent correspondence regarding report	
4 APPLICANT Merck Sharp and Dohme Research Laboratories			3. CFR SECTION NUMBER (Antibiotic only)	
5 DRUG NAME Tablets NOROXIN® (Norfloxacin, MSD)			6 TYPE OF REPORT (Check one) ☒ ANNUAL ☐ OTHER	
7 OTHER NDA/ANTIBIOTIC APPLICATION NUMBERS (List all numbers if any part of report applies to more than one number.)			8 PERIOD COVERED BY REPORT FROM TO YEAR MONTH YEAR MONTH 88 11 89 10	
9 REPORT INFORMATION REQUIRED (See § 314.81 for description) (Enter type of information attached under "Identification." If you have nothing to report, enter None.) (INFORMATION IN "9b" and "9c" IS ALWAYS REQUIRED.)				
TYPE OF INFORMATION		IDENTIFICATION (Volume No. (s)/Tab(s)/Page(s) of Report)		
a SUMMARY OF SIGNIFICANT NEW INFORMATION		Item 1 Pages 1 - 2		
b DISTRIBUTION DATA		Item 2 Page 3		
c LABELING (Whether or not previously submitted)		Item 3 Pages 4 - 8		
d CHEMISTRY, MANUFACTURING AND CONTROLS CHANGES		Item 4 Pages 9 - 11		
e NONCLINICAL LABORATORY STUDIES		Item 5 Page 12		
f CLINICAL DATA		Item 6 Pages 13 - 99		
g STATUS REPORT POST-MARKETING STUDIES		Item 7 Page 100		
h STATUS OF OPEN REGULATORY BUSINESS (Optional)		Item 7 Page 100		
TYPED NAME AND TITLE OF RESPONSIBLE OFFICIAL OR AGENT Kenneth R. Brown, M.D. Group Director Regulatory Affairs			FDA USE ONLY	
SIGNATURE David E. Turner, MD for K.R.B.			10 REPORT FILED IN NDA NUMBER N 1 9 3 8 4	
APPLICANTS RETURN ADDRESS (Type within the window envelope tic marks) Merck Sharp and Dohme Research Laboratories Division of Merck & Co., Inc. West Point, PA 19486 Attention: Kenneth R. Brown, M.D.			11 DATE OF RECEIPT 	

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Certified No. P529431370

NOROXIN®
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ADVERSE REACTIONS

In clinical trials, NOROXIN was generally well tolerated. The incidence of subjects reporting drug related adverse experiences in clinical trials involving 1127 subjects was 3.4%. However, the incidence figures below were calculated without reference to drug relationship.

The most common adverse experiences (1% - 3%) were either gastrointestinal or neurological: nausea 2.8%, headache 2.7%, and dizziness 1.8%.

Additional reactions (0.3% - 1%) were: fatigue, rash, abdominal pain, dyspepsia, somnolence, depression, insomnia, constipation, flatulence, and heartburn.

Less frequent reactions included: dry mouth, diarrhea, fever, vomiting, and erythema.

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

Abnormal laboratory values observed in these 1127 subjects in clinical trials were eosinophilia 1.8%, elevation of ALT (SGPT) and AST (SGOT) 1.8%, increased alkaline phosphatase 1.4%, and decreased WBC or neutrophil count 1.2%. Those occurring less frequently included increased BUN, serum creatinine, and LDH, and decreased hematocrit.

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, urticaria, arthritis, arthralgia and myalgia.

Skin

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

Gastrointestinal

Pseudomembranous colitis, hepatitis

Nervous System/Psychiatric

Psychic disturbances including psychotic reactions and confusion, paresthesia

Hematologic

Neutropenia, leukopenia, thrombocytopenia

Special Senses

Transient hearing loss (rare)

OVERDOSAGE

The acute oral LD₅₀ values in male and female mice and male and female rats were greater than 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 one hour before or two hours after a meal with a glass of water. Patients receiving NOROXIN should be well hydrated (see PRECAUTIONS).

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Normal Renal Function

The recommended dosage of NOROXIN is:

Uncomplicated urinary tract infections: 400 mg twice daily for 7 to 10 days.

Complicated urinary tract infections: 400 mg twice daily for 10 to 21 days.

Maximum total daily dosage should not exceed 800 mg per day.

Renal Impairment

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

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

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

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

Elderly

Elderly patients with a creatinine clearance of greater than 30 mL/min/1.73m² should receive the dosages recommended under **Normal Renal Function**.

Elderly patients with a creatinine clearance of 30 mL/min/1.73m² or less should receive 400 mg once daily as recommended under **Renal Impairment**.

HOW SUPPLIED

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

NDC 0006-0705-68 bottles of 100

(6505-01-258-9542 100's)

NDC 0006-0705-20 unit of use bottles of 20

NDC 0006-0705-28 unit dose packages of 100.

Storage

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

ANIMAL PHARMACOLOGY

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

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

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

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

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DIV OF MERCK & CO., INC., WEST POINT, PA 19380, USA

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response, 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 demonstrates activity against indicated organisms resistant to the aminoglycosides (including gentamicin), penicillins, cephalosporins, tetracyclines, macrolides, and sulfonamides, including combinations of sulfamethoxazole and trimethoprim. Antagonism has been demonstrated *in vitro* between norfloxacin and trimethoprim.

While *in vitro* studies have demonstrated the susceptibility of most strains of the following organisms, clinical efficacy for infections other than those included in the INDICATIONS AND USAGE section has not been documented.

Aerobic Bacteria

Gram-positive bacteria including:
Streptococcus faecalis (enterococcus)
Staphylococcus aureus (including both penicillinase-producing and methicillin-resistant strains)
Staphylococcus epidermidis
Staphylococcus saprophyticus
Bacillus cereus

Gram-negative bacteria including:

Acinetobacter calcoaceticus
Aeromonas species
Alicigenes species
Campylobacter species
Citrobacter diversus
Citrobacter freundii
Edwardsiella tarda
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Flavobacterium species
Hafnia alvei
Klebsiella oxytoca
Klebsiella pneumoniae
Klebsiella rhinoscleromatis
Morganella morganii
Neisseria gonorrhoeae
Proteus mirabilis
Proteus vulgaris
Providencia alcalifaciens
Providencia rettgeri
Providencia stuartii
Pseudomonas aeruginosa
Salmonella typhi
Salmonella species
Serratia marcescens
Shigella species
Vibrio cholerae
Vibrio parahaemolyticus
Yersinia enterocolitica

Other

Ureaplasma urealyticum
NOROXIN is not generally active against obligate anaerobes.

Susceptibility Tests

Diffusion Technique

Quantitative methods that require measurement of zone diameters give precise estimates of bacterial susceptibility.

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One such procedure has been recommended for use with discs to test susceptibility to norfloxacin.¹

Reports from the laboratory giving results of the standard single disc susceptibility test with a 10 mcg norfloxacin disc should be interpreted according to the following criteria:

Susceptible organisms produce zones equal to or greater than 17 mm, indicating that the test organism is likely to respond to therapy.

Intermediate (moderately susceptible) organisms produce zones of 13 to 16 mm, indicating that the test organism is expected to be susceptible to norfloxacin.

Resistant organisms produce zones equal to or less than 12 mm.

The standardized quality control procedure requires use of control organisms. The 10 mcg norfloxacin disc should give the zone diameters listed below for the quality control strains.

Organism	ATCC®	Zone Size Range
<i>E. coli</i>	25922	28 - 35 mm
<i>P. aeruginosa</i>	27853	22 - 29 mm
<i>S. aureus</i>	25923	17 - 28 mm

Dilution Technique

Broth and agar dilution methods may be used to determine the minimum inhibitory concentration (MIC) of norfloxacin.² MIC test results should be interpreted according to the following criteria:

Susceptible organisms have an MIC for norfloxacin equal to or less than 4 mcg/mL.

Intermediate (moderately susceptible) organisms have an MIC of 8 mcg/mL.

Resistant organisms have an MIC equal to or greater than 16 mcg/mL.

Dilution susceptibility tests should give MICs between the ranges listed below for the quality control strains.

Organism	ATCC®	MIC (mcg/mL)
<i>E. coli</i>	25922	0.03 - 0.12
<i>S. aureus</i>	29213	0.5 - 2.0
<i>S. faecalis</i>	29212	2.0 - 8.0
<i>P. aeruginosa</i>	27853	1.0 - 4.0

Based on urinary concentrations of norfloxacin achieved in man, breakpoint criteria have been established as listed below.

Category	Zone Diameter (mm)	Recommended MIC Breakpoint (mcg/mL)
Susceptible	≥ 17	≤ 4
Intermediate	13-16	8
Resistant	≤ 12	≥ 16

Norfloxacin susceptibility test results should not be used to predict susceptibility to other less potent quinolone antibacterial agents such as nalidixic acid.

INDICATIONS AND USAGE

Treatment

NOROXIN is indicated for the treatment of adults with complicated and uncomplicated urinary tract infections that are

¹National Committee for Clinical Laboratory Standards. Tentative Standard M2-T4. Performance Standards for Antimicrobial Disk Susceptibility Tests. 1988.

²National Committee for Clinical Laboratory Standards. Tentative Standard M7-T2. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically. 1988.

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caused by susceptible strains of the designated microorganisms listed below:

Escherichia coli; *Klebsiella pneumoniae*; *Enterobacter cloacae**; *Proteus mirabilis*; indole positive *Proteus* species* (which may include the organisms now called *Proteus vulgaris**, *Providencia rettgeri**, and *Morganella morganii**); *Pseudomonas aeruginosa*; *Citrobacter freundii**; *Staphylococcus aureus**, *Staphylococcus epidermidis**; and group D streptococci.

NOTE: Specimens for culture and susceptibility testing should be obtained prior to and during treatment if clinical response warrants. However, NOROXIN may be used to initiate therapy in urinary tract infections prior to the availability of laboratory results.

CONTRAINDICATIONS

NOROXIN is contraindicated in patients with a history of hypersensitivity to norfloxacin or the quinolone group of antibacterial agents (e.g., nalidixic acid and cinoxacin).

WARNINGS

Norfloxacin should not be used in children or pregnant women.

The oral administration of single doses of norfloxacin, 6 times the recommended human clinical dose, caused lameness in immature dogs. Histologic examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs (e.g., nalidixic acid and cinoxacin) also produced erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species.

PRECAUTIONS

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**).

Convulsions have been reported rarely with norfloxacin although no causal relationship has been established. Convulsions, increased intracranial pressure, and toxic psychoses have been reported with other drugs in this class. 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. Until more information becomes available, quinolones should be used with caution in patients with known factors which predispose to seizures.

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.

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

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

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.

Sucralfate or antacids should not be administered concomitantly with norfloxacin or within 2 hours of administration of norfloxacin.

Information for Patients

Patients should be advised to take NOROXIN one hour before or two hours after a meal. Patients should also be advised to drink fluids liberally and not to take antacids concomitantly or within 2 hours after dosing.

NOROXIN may cause dizziness or lightheadedness; 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.

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 0 - 9 times the usual human dose.

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 dose. 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 33 times the usual human dose.

Pregnancy

Pregnancy Category C: Norfloxacin has been shown to produce embryonic loss in monkeys when given in doses 10 times the maximum human dose (400 mg b.i.d.), with peak plasma levels that are 2 to 3 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 human dose. There were no adequate and well controlled studies in pregnant women. Since norfloxacin, like other drugs in this class, causes arthropathy in immature animals, it should not be used in pregnant women (see **WARNINGS**).

Nursing Mothers

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

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

Pediatric Use

Norfloxacin should not be used in children because it causes arthropathy in juvenile animals (see **WARNINGS**).

7465403

NOROXIN®
(Norfloxacin, MSD)

ADVERSE REACTIONS

In clinical trials, NOROXIN was generally well tolerated. The incidence of subjects reporting drug related adverse experiences in clinical trials involving 1127 subjects was 3.4%. However, the incidence figures below were calculated without reference to drug relationship.

The most common adverse experiences (1% - 3%) were either gastrointestinal or neurological: nausea 2.8%, headache 2.7%, and dizziness 1.8%.

Additional reactions (0.3% - 1%) were: fatigue, rash, abdominal pain, dyspepsia, somnolence, depression, insomnia, constipation, flatulence, and heartburn.

Less frequent reactions included: dry mouth, diarrhea, fever, vomiting, and erythema.

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

Abnormal laboratory values observed in these 1127 subjects in clinical trials were eosinophilia 1.8%, elevation of ALT (SGPT) and AST (SGOT) 1.8%, increased alkaline phosphatase 1.4%, and decreased WBC or neutrophil count 1.2%. Those occurring less frequently included increased BUN, serum creatinine, and LDH, and decreased hematocrit.

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, urticaria, arthritis, arthralgia and myalgia.

Skin

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

Gastrointestinal

Pseudomembranous colitis, hepatitis

Nervous System/Psychiatric

Psychic disturbances including psychotic reactions and confusion, paresthesia

Hematologic

Neutropenia, leukopenia, thrombocytopenia

Special Senses

Transient hearing loss (rare)

OVERDOSAGE

The acute oral LD₅₀ values in male and female mice and male and female rats were greater than 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 one hour before or two hours after a meal with a glass of water. Patients receiving NOROXIN should be well hydrated (see PRECAUTIONS).

NOROXIN®
(Norfloxacin, MSD)

Normal Renal Function

The recommended dosage of NOROXIN is:

Uncomplicated urinary tract infections: 400 mg twice daily for 7 to 10 days.

Complicated urinary tract infections: 400 mg twice daily for 10 to 21 days.

Maximum total daily dosage should not exceed 800 mg per day.

Renal Impairment

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

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

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

Females: = (0.85) x (above value)

Elderly

Elderly patients with a creatinine clearance of greater than 30 mL/min/1.73m² should receive the dosages recommended under *Normal Renal Function*.

Elderly patients with a creatinine clearance of 30 mL/min/1.73m² or less should receive 400 mg once daily as recommended under *Renal Impairment*.

HOW SUPPLIED

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

NDC 0006-0705-68 bottles of 100

(6505 01-258-9542 100's)

NDC 0006-0705-20 unit of use bottles of 20

NDC 0006-0705-28 unit dose packages of 100.

Storage

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

ANIMAL PHARMACOLOGY

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

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

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

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

MSD MERCK SHARP & DOHME
DIV. OF MERCK & CO., INC., WEST POINT, PA 19380, USA

Issued October 1989

Printed in USA

400 mg
(NORFLOXACIN, MSD)
NOROXIN®
TABLETS
100 | No. 3522

USUAL ADULT DOSAGE:
See accompanying circular.

This is a bulk package and not intended for dispensing.

Keep container tightly closed. Dispense in a tightly-closed container.

Avoid storage at temperatures above 40°C (104°F).

100 | No. 3522 7466102

NDC 0006-0705-68
6505-01-258-9542

100 TABLETS

NOROXIN®
(NORFLOXACIN, MSD)

400 mg

CAUTION: Federal (USA) law prohibits dispensing without prescription.

MERCK SHARP & DOHME
DIVISION OF MERCK & CO., INC.
WEST POINT, PA 19380, USA

400 mg

65592

USUAL ADULT DOSAGE:
See accompanying circular.
Keep container tightly closed. Dispense in a tightly closed container.

Avoid storage at temperatures above 40°C (104°F).

This is a bulk package and not intended for dispensing.

CAUTION: Federal (USA) law prohibits dispensing without prescription.

100 | No. 3522 7523902

NDC 0006-0705-68

100 TABLETS

NOROXIN®
(NORFLOXACIN, MSD)



400 mg

Lot Exp.

SUPPLEMENTS

OCT 16 1987

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October 14, 1987

MEDICAL OFFICER'S REVIEW OF NDA 19-384/S-006
and MEMORANDUM OF TELEPHONE CONVERSATION

Supplement dated September 15, 1987

Applicant: Merck Sharp & Dohme Research Laboratories
West Point, PA

Name of Drug: Trade: Noroxin Tablets

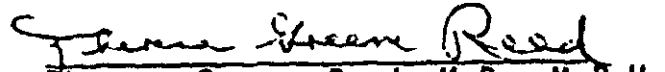
Generic: Norfloxacin

The applicant files final printed labeling that notifies FDA that the Adverse Reactions section has been revised. The applicant has added "Angioneurotic edema" and "urticaria" under the subheading Hypersensitivity Reactions.

This applicant-initiated revision of the labeling is acceptable.

I called David W. Blois, Ph.D., Senior Director of Regulatory Affairs at Merck (215-834-2304) to tell him that the term "angioneurotic edema" is an old term. The neurotic part of the name has been dropped. Currently the preferred name for giant urticaria is "angioedema." I asked him to use the preferred name at the next printing. Dr. Blois agreed.

Conclusion: The applicant-initiated labeling revision is satisfactory.


Theresa Greene Reed, M.D., M.P.H.

cc
Orig NDA
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Redd 10/14/87

August 28, 1989

**MEDICAL OFFICER'S REVIEW OF NDA 19-384/013 LABELING
AND MEMORANDUM OF TELEPHONE CONVERSATION**

Final Printed Labeling Dated July 20, 1989

Applicant: Merck Sharp & Dohme Research laboratories
West Point, Pennsylvania

Name of Drug: Generic: Norfloxacin
Trade: Noroxin[®] tablets

Pharmacological Category: Fluoroquinolone antibacterial agent for oral use.

THEOPHYLLINE INTERACTION: Final printed labeling does not comply with the labeling discussion between the MO and Dr. Kenneth R Brown of Merck and the proposed labeling filed May 5, 1989, and with the Division's letter to Merck on Aug. 22, 1989. (The reader is referred to my Memorandum of Telephone Conversation June 26, 1989.) As agreed, the Drug Interaction subsection of the Precautions section should, but does not, contain the following text:

"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."

However, final printed labeling does show that "thrombocytopenia" has been added to the Adverse Reactions section as requested.

Since the consideration of the above theophylline-interaction text and the addition of "thrombocytopenia," the medical officer has reviewed the computerized printout dated Aug. 15, 1989, of 615 adverse reactions that have been reported to FDA since the approval of norfloxacin Oct. 31, 1986. The norfloxacin labeling has been reviewed again with these reports in mind and we have the following additional requests for labeling changes.

1. CONVULSIVE SEIZURES: There are 30 reports of convulsive seizures. The recently-added paragraph about convulsions, now located in the Precautions section, should be moved to the Warnings section and the word "rarely" should be deleted. The Warnings paragraph will then read as follows:

"Convulsions have been reported with norfloxacin although no causal relationship has been established. Convulsions, increased intracranial pressure, and toxic psychoses have been reported with other drugs in this class. Quinolones may also cause central nervous system (CNS) stimulation which may lead to tremor, restlessness, lightheadedness, confusion, and hallucinations. Therefore, norfloxacin should be used with caution in patients with known or suspected CNS disorders, such as cerebral arteriosclerosis or epilepsy, or other factors which predispose to seizures (See Adverse Reactions). If these reactions occur in

patients receiving norfloxacin, the drug should be discontinued and appropriate measures instituted."

2. HYPERSENSITIVITY: For norfloxacin, there are 33 reports of urticaria/angioedema, 9 reports of anaphylaxis, and 11 reports of allergic reactions. For ciprofloxacin, a related fluoroquinolone, there are 48 reports of urticaria/angioedema, 39 reports of anaphylaxis, and 20 reports of allergic reactions. For the quinolone, cinoxacin, there are 26 reports of urticaria/angioedema, 38 reports of anaphylaxis, and 44 reports of allergic reactions. For nalidixic acid, these numbers are equivalent but consistent with a much earlier reporting period. Also, for norfloxacin, there are 93 reports of rash and 36 reports of pruritus.

Therefore, the following class labeling paragraph should be added to the Warnings section for norfloxacin, ciprofloxacin, cinoxacin, and nalidixic acid:

"Serious and occasionally fatal hypersensitivity (anaphylactoid) 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. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should be administered as indicated."

3. WARFARIN INTERACTION: There are eight cases of concomitant use of warfarin and norfloxacin. Significant reactions in these cases were prothrombin decrease, anticoagulation increase, drug interaction, anemia, increased effect, GI hemorrhage, and thromboplastin decrease. Three of the eight patients died. There are similar reports for ciprofloxacin. This interaction has been reported in medical literature. Therefore, the following class labeling paragraph should be added to the Drug Interaction section of the Precautions section:

"Quinolones, including norfloxacin, may enhance the effects of oral anticoagulants, warfarin or its derivatives, by displacing significant amounts from serum albumin binding sites. When concomitant administration of these products cannot be avoided, daily measurements of prothrombin time or other suitable coagulation tests are essential."

4. STEVENS-JOHNSON SYNDROME: There are six reports of erythema multiforme and/or Stevens-Johnson Syndrome. The following sentence should be added to the Adverse Reactions section:

"Erythema multiforme and Stevens-Johnson syndrome have been reported with norfloxacin and other drugs in this class."

5. The Adverse Reactions section should be revised to add dyspnea, pruritus, and a sentence to say that the most frequently reported adverse reaction post

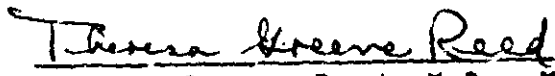
NDA 19-384

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marketing is rash. There were 19 reports of dyspnea, 36 reports of pruritus, and 93 reports of rash.

Memorandum of Telephone Conversation August 28, 1989: I called David W. Blois, Ph.D., Director of Regulatory Affairs at Merck, to dictate and discuss these labeling requests. He will proceed with labeling revisions and will check to see why the theophylline interaction paragraph was not included in the July 20, 1989, submission of FPL.

Conclusion and Recommendation: Proposed final printed labeling is unsatisfactory. Labeling change requests have been discussed with the applicant. Revised proposed labeling has been requested.


Theresa Greene Reed, M.D., M.P.H.

Orig NDA 19-384

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HFD-520/Reed

HFD-520/Szarfman

HFD-520/Nazario

HFD-520/Standard

HFD-520/Blum

HFD-520/Buko

HFD-520/Shetty

HFD-735/Green

HFD-340

\19-384 *mda 8/29/89*

END

R.A.M

J.H.M. Research & Development, Inc., 5776 Second Street, N.E., Washington, D.C. 20011