**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-384/S-037, S-038, S-039

Merck & Co., Inc.
Attention: Ms. Virginia G. Snyder
Manager, Regulatory Affairs
P.O. Box 4
Sunneytown Pike, BLA-20
West Point, PA 19486

Dear Ms. Snyder:

Please refer to your supplemental new drug applications dated August 19, 1998, December 30, 1998 and December 23, 1999, received August 21, 1998, January 4, 1999 and December 23, 1999, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Noroxin® (norfloxacin) Tablets, 400 mg.

We acknowledge receipt of your submissions dated October 29, 1998 and March 19, 2001.

These supplemental new drug applications provided for the following changes to the Noroxin® label:

1. The word "children" was changed to "pediatric patients" throughout the label.

2. **CLINICAL PHARMACOLGY**

•The second paragraph in this section was revised and a third paragraph was added to read:

> "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. Following a single 400 mg dose of norfloxacin, the mean (± SD) AUC and $C_{max}$ of 9.8 (2.83) μg•hr/mL and 2.02 (0.77) μg/mL respectively, were observed in healthy elderly volunteers. The extent of systemic exposure was slightly higher than that seen in younger adults (AUC 6.4 μg•hr/mL and $C_{max}$ 1.5 μg/mL. Drug absorption appears unaffected. However, the effective half-life of norfloxacin in these elderly subjects is 4 hours.
>
> There is no information on accumulation of norfloxacin with repeated administration in elderly patients. However, no dosage adjustment is required based on age alone. In elderly patients with reduced renal function, the dosage should be adjusted as for other patients with renal impairment (see DOSAGE AND ADMINISTRATION, *Renal Impairment*)."

•The following sentence was added to what is now the fifth paragraph in this section:

> "(Average creatinine clearance was 91 mL/min/1.73m$^2$.) In elderly subjects approximately 22% of the administered dose was recovered in urine and renal clearance averaged 154 mL/min."

3. **PRECAUTIONS**

•In the General subsection, a fifth paragraph was added to read:

> "Quinolones, including norfloxacin, may exacerbate the signs of myasthenia gravis and lead to life threatening weakness of the respiratory muscles. Caution should be exercised when using quinolones, including NOROXIN, in patients with myasthenia gravis (see ADVERSE REACTIONS)."

•In the Information for Patients subsection, the following phrase was revised to add information concerning Videx®:

> "— that multivitamins or other products containing iron or zinc, antacids or Videx® (Didanosine), chewable/buffered tablets or the pediatric powder for oral solution, should not be taken within the two-hour period before or within the two-hour period after taking norfloxacin. (See PRECAUTIONS, Drug Interactions.)"

•In the Information for Patients subsection, the following phrase was added to the end of this subsection to include information concerning convulsions to read:

> "— that convulsions have been reported in patients taking quinolones, including norfloxacin, and to notify their physician before taking this drug if there is a history of this condition."

•In the Drug Interactions subsection, the following sentence was revised to add information concerning Videx®:

> "Videx® (Didanosine) chewable/buffered tablets or the pediatric powder for oral solution should not be administered concomitantly with, or within 2 hours of, the administration of norfloxacin, because these products may interfere with absorption resulting in lower serum and urine levels of norfloxacin."

•A Geriatric Use subsection was added to the end of this section to read:

> "Of the 340 subjects in one large clinical study of NOROXIN for treatment of urinary tract infections, 103 patients were 65 and older, 77 of whom were 70 and older; no overall differences in safety and effectiveness were evident between these subjects and younger subjects. In clinical practice, no difference in the type of reported adverse

experiences have been observed between the elderly and younger patients; however, increased risk for adverse experiences in some older individuals cannot be ruled out (see ADVERSE REACTIONS).

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

A pharmacokinetic study of NOROXIN in elderly volunteers (65 to 75 years of age with normal renal function for their age) was carried out (see CLINICAL PHARMACOLOGY)."

4. **ADVERSE REACTIONS**

•In the Post Marketing subsection, the following sentence was revised to include tremors, and now reads:

"CNS effects characterized as generalized seizures, myoclonus and tremors have been reported with NOROXIN (see WARNINGS)."

•In the Post Marketing subsection, the following sentence, "A causal relationship to Noroxin has not been established," was deleted.

•In the Gastrointestinal subsection, the first sentence was revised to include elevated liver function tests and now reads:

"Pseudomembranous colitis, hepatitis, jaundice including cholestatic jaundice and elevated liver function tests, pancreatitis (rare), stomatitis."

•In the Musculoskeleteal subsection, the word "possible" was deleted before "exacerbation of myasthenia gravis" and now reads:

"Tendinitis, tendon rupture; exacerbation of myasthenia gravis (see PRECAUTIONS)"

•In the Special Senses subsection, "dysgeusia" was added to the first sentence to read:

"Transient hearing loss (rare), tinnitus, diplopia, dysgeusia"

4. **DOSAGE AND ADMINISTRATION**

•The second sentence in the first paragraph was revised to include information about Videx to read:

"Multivitamins, other products containing iron or zinc, antacids containing magnesium and aluminum, sucralfate, or Videx® (Didanosine), chewable/buffered tablets or the

pediatric powder for oral solution, should not be taken within 2 hours of administration of norfloxacin."

5. **HOW SUPPLIED**

•The storage statement was revised to read:

"Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed."

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text and with the minor editorial revision listed below. Accordingly, these supplemental applications are approved effective on the date of this letter.

At the time of printing please make the following minor editorial revision and replace:

"(Average creatinine clearance was 91 mL/min/1.73m$^2$.) In elderly subjects approximately 22% of the administered dose was recovered in urine and renal clearance averaged 154 mL/min."

with:

"In elderly subjects (average creatinine clearance was 91 mL/min/1.73m$^2$) approximately 22% of the administered dose was recovered in urine and renal clearance averaged 154 mL/min."

The final printed labeling (FPL) must be identical and include the minor editorial revision indicated to the submitted labeling (package insert submitted March 19, 2001).

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved supplements NDA 19-384/S-037, S-038, S-039." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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

If you have any questions, call Robin Anderson, Regulatory Review Officer at (301) 827- 2127.

Sincerely,

*{See appended electronic signature page}*

Mark J. Goldberger, M.D., M.P.H.
Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research