DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-744/S-003

Esprit Pharma, Inc.
Attention: Richard J. Brown, M.D.
V.P., Regulatory Affairs
Two Center Boulevard
East Brunswick, NJ 08816

Dear Dr. Brown:

Please refer to your supplemental new drug application submitted on February 8, 2007, received on February 9, 2007, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Proquin XR® (ciprofloxacin hydrochloride) Tablets, 500 mg.

We also refer to your submission dated July 27, 2007.

This "Changes Being Effected" supplemental new drug applications, submitted in response to the Supplement Request letter issued by the Division on October 30, 2006, and the facsimile transmission on December 21, 2006, provides for changes to the **WARNINGS** section, the **PRECAUTIONS/ Information for Patients** subsection and the "**Patient Package Insert**," as follows (~~strikethrough~~ = deleted and <u>underlined</u> = added):

1. The seventh, eight and ninth paragraphs in the **WARNINGS** section (the paragraphs referring to pseudomembranous colitis) should be replaced with the underlined text below.

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

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

   ~~If a diagnosis of pseudomembranous colitis is established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against C. difficile colitis. Drugs that inhibit peristalsis should be avoided.~~

   <u>*Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including ProQuin XR, and may range in severity from mild diarrhea to</u>

fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

2. Under the **PRECAUTIONS/Information for Patients** subsection, please add the following text after the last bullet:

    a. that diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

3. In the **"Patient Package Insert,"** the following wording was included under "**What are the possible side effects of ProQuin XR?"**

    Diarrhea that usually ends after treatment is a common problem caused by antibiotics. A more serious form of diarrhea can occur during or up to 2 months after the use of antibiotics. This has been reported with all antibiotics including with ProQuin XR. If you develop a watery and bloody stool with or without stomach cramps and fever, contact your physician as soon as possible.

4. The subsection "**What are the ingredients in ProQuin XR**?" in the patient package insert has been moved above the subsection "**General information about ProQuin XR**".

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions agreed upon during the July 31, 2007, correspondence between Kristen Miller, Pharm.D. and Alexander Mironov listed below:

1. The word "ProQuin" listed throughout the labeling has been changed to "Proquin"

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Kristen Miller, Pharm.D., Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Renata Albrecht

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