



NDA 21-158/S-003

Parexel International  
Attention: Gail Glifort  
Senior Regulatory Associate  
2520 Meridian Parkway, Suite 200  
Durham, NC 27713

Dear Ms. Glifort:

Please refer to your supplemental new drug application dated March 26, 2004, received March 30, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for FACTIVE<sup>®</sup> (gemifloxacin mesylate) Tablets, 320mg.

This “Changes Being Effected” (CBE) supplemental new drug application provides for the addition of quinolone class labeling in **WARNINGS** and **PRECAUTIONS, Information for Patients** as was requested in the supplement request letter dated November 26, 2003 and the facsimiles from the Division dated March 10, 2004 and July 28, 2004.

We acknowledge receipt of your submissions dated August 17, 2004 and August 31, 2004.

This CBE supplemental new drug application provides for the following revisions to the package insert:

#### 1. **WARNINGS**

- The following paragraph was revised, unbolded and changed from capital letters to lower case letters in the *QT Effects* subsection:

***QT Effects:*** **GEMIFLOXACIN** Fluoroquinolones may prolong the QT interval in some patients. Gemifloxacin should be avoided in patients with a history of prolongation of the QTc interval, patients with uncorrected electrolyte disorders (hypokalemia or hypomagnesemia), and patients receiving Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic agents.

- The following subsection was added:

***Peripheral Neuropathy:*** Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones.

- The *Tendon Effects* subsection was revised to read:

~~***Tendon and Cartilage Effects:*** Fluoroquinolones as a class have been shown to cause arthropathy and osteochondrosis in immature rats and dogs. The relevance of these findings to humans is unknown. Tendonitis and rupture of the shoulder, hand, and Achilles tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving fluoroquinolones. Gemifloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been confidently excluded. Tendon rupture can occur either during or after treatment. Elderly patients, athletes, and patients taking corticosteroids are more prone to tendonitis.~~

***Tendon Effects:*** Ruptures of the shoulder, hand, Achilles tendons or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones. Post-marketing surveillance reports indicate that this risk may be increased in patients receiving concomitant corticosteroids, especially the elderly. Gemifloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been excluded. Tendon rupture can occur during or after therapy with quinolones.

## 2. PRECAUTIONS

- The **Information for Patients** subsection was revised to read:

Patients should be counseled:

- that FACTIVE may ~~produce~~ cause changes in the electrocardiogram (QTc interval prolongation);
- that FACTIVE should be used with caution in patients receiving drugs that ~~may~~ affect the QTc interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants;
- to inform their physicians of any personal or family history of QTc prolongation or proarrhythmic conditions such as ~~recent~~ hypokalemia, ~~significant~~ bradycardia, or recent myocardial ischemia;

We completed our review of this application, as amended, and it is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling (text for the package insert submitted August 31, 2004).

The electronic labeling rule published December 11, 2003 (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format - NDAs (January 1999)* and *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004). The guidances specify that labeling is to be submitted in pdf format. To assist in our review, we request that labeling also be submitted in MS Word format.

If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper. For administrative purposes, these submissions should be designated "**FPL for approved supplement NDA 21-158/S-003.**" Approval of this submission by FDA is not required before the labeling is used.

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, HFD-410  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

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, call Robin Anderson, R.N., M.B.A., Labeling Reviewer at (301) 827-2127.

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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Renata Albrecht  
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