DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21158/S-018

SUPPLEMENT APPROVAL

Cornerstone Therapeutics, Inc.
Attention: Ashlie Adams, M.S.
Manager, Regulatory Affairs
1255 Crescent Green Drive, Suite 250
Cary, NC 27518

Dear Ms. Adams:

Please refer to your Supplemental New Drug Application (sNDA) dated December 15, 2010 and received December 16, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for FACTIVE® (gemifloxacin mesylate) Tablets.

We acknowledge receipt of your amendment dated January 21, 2011.

(b) (4)

We also refer to our letter dated November 15, 2010, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for all fluoroquinolone products. The new safety information pertains to the risk of fluoroquinolone-associated myasthenia gravis exacerbation, which is a potentially life-threatening event and may require ventilatory support.

This supplemental new drug application provides for revisions to the labeling for FACTIVE® (gemifloxacin mesylate). The agreed upon changes to the language included in our November 15, 2010, letter are as follows (additions are noted by underline and deletions are noted by ~~strikethrough)~~.

I. BOXED WARNING

WARNING:
Fluoroquinolones, including FACTIVE®, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (See WARNINGS).

Fluoroquinolones, including FACTIVE®, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid FACTIVE® in patients with known history of myasthenia gravis (See WARNINGS).

II. The following sub-section has been added after the **WARNINGS/Tendinopathy and Tendon Rupture** sub-section:

Exacerbation of myasthenia gravis
Fluoroquinolones, including FACTIVE, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Postmarketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid FACTIVE in patients with known history of myasthenia gravis. [See **PRECAUTIONS/Information for Patients and ADVERSE REACTIONS/Post-Marketing Adverse Reactions]**

III. **PRECAUTIONS/Information for Patients** has been revised as follows:

Information for Patients:
Patients should be counseled:

- to contact their healthcare provider if they experience pain, swelling, or inflammation of a tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and discontinue FACTIVE treatment. The risk of severe tendon disorder with fluoroquinolones is higher in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.

- that fluoroquinolones like FACTIVE may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Patients should call their healthcare provider right away if they have any worsening muscle weakness or breathing problems.

IV. **ADVERSE REACTIONS/ Post-Marketing Adverse Reactions** section has been revised as follows:

Post-Marketing Adverse Reactions: The majority of the post-marketing adverse events reported were cutaneous and most of these were rash. Some of these cutaneous adverse events were considered serious. The majority of the rashes occurred in women and in patients under 40 years of age.

The following are additional adverse reactions reported during the post-marketing use of FACTIVE. Since these reactions are reported voluntarily from a population of uncertain size, it is impossible to reliably estimate their frequency or establish a causal relationship to FACTIVE exposure:

- anaphylactic reaction, erythema multiforme, skin exfoliation, facial swelling;

- exacerbation of myasthenia gravis
- hemorrhage, increased international normalized ratio (INR), retinal hemorrhage;
- peripheral edema;
- renal failure;
- prolonged QT, supraventricular tachycardia, syncope, transient ischemic attack;
- photosensitivity/phototoxicity reaction (See **PRECAUTIONS**);
- antibiotic-associated colitis.

V. Medication guide:

a. In the section "**What is the most important information I should know about FACTIVE**? The following has been added as the last bulleted paragraph:

- **Worsening of myasthenia gravis (a disease which causes muscle weakness).** Fluoroquinolones like FACTIVE may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Call your healthcare provider right away if you have any worsening muscle weakness or breathing problems.

See the section **"What are the possible side effects of FACTIVE?"** for more information about side effects

b. The section **"What should I tell my healthcare provider before taking FACTIVE?"** has been revised as follows:

What should I tell my healthcare provider before taking FACTIVE?
See **"What is the most important information I should know about FACTIVE?"**

Tell your healthcare provider about all your medical conditions, including if you:

- have tendon problems
- have a disease that causes muscle weakness (myasthenia gravis)
- have central nervous system problems (such as epilepsy)
- have nerve problems
- have or anyone in your family has an irregular heartbeat, especially a condition called "QT prolongation."
- have low blood potassium (hypokalemia) or magnesium (hypomagnesemia)
- have history of seizures
- have kidney problems. You may need a lower dose of FACTIVE if your kidneys do not work well.
- have rheumatoid arthritis (RA) or other history of joint problems
- are pregnant or planning to become pregnant. It is not known if FACTIVE will harm your unborn child.

- are breast-feeding or planning to breast-feed. It is not known if FACTIVE passes into breast milk. You and your healthcare provider should decide whether you will take FACTIVE or breast-feed.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

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 Hyun Son, Pharm.D., Safety Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Ozlem Belen, MD, MPH
Deputy Director for Safety
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

OZLEM A BELEN
02/25/2011