DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-158/S-011

Oscient Pharmaceuticals Corporation
Attn: Michael S. Luck, Ph.D.
Director, Regulatory Affairs
1000 Winter Street, Suite 2200
Waltham, MA 02451

Dear Dr. Luck:

Please refer to your supplemental new drug application, dated June 25, 2007, received on June 26, 2007, and submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA Number	Supplement Number	Drug Product
21-158	011	Factive® (gemifloxacin) Tablets, 320 mg

We also acknowledge receipt of your submission dated November 7, 2007.

This "Special Supplement - Changes Being Effected" supplemental application proposes revising the content of labeling for the package insert to ensure consistency in the communication of the risk of phototoxicity associated with the use of fluoroquinolones, including gemifloxacin.

We have 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 text and with the minor editorial revisions listed below (~~strikethrough~~ = deleted and double-underline = added):

1. The third paragraph of the **PRECAUTIONS/*Rash*** subsection was modified as follows:

   Moderate to severe photosensitivity/phototoxicity reactions, the latter of which may manifest as exaggerated sunburn reactions (e.g., burning, erythema, exudation, vesicles, blistering, edema) involving areas exposed to light (typically the face, "V" area of the neck, extensor surfaces of the forearms, dorsa of the hands), can be associated with use of quinolone<u>s</u> ~~antibiotics~~ after sun or UV light exposure. Therefore, excessive exposure to these sources of light should be avoided. Drug therapy should be discontinued if phototoxicity occurs. (See **ADVERSE REACTIONS** and **ADVERSE REACTIONS/Post-Marketing Adverse Reactions**.)

2. The **PRECAUTIONS**/**Information for Patients** subsection was modified as follows:

   - that photosensitivity/phototoxicity has been reported in patients receiving quinolones ~~antibiotics~~. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while taking quinolones. If patients need to be outdoors while using quinolones, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. If a sunburn-like reaction or skin eruption occurs, patients should contact their physician; (See **CLINICAL PHARMACOLOGY: Photosensitivity Potential**);

Therefore, the overall revisions to the package insert were as follows (~~strikethrough~~ = deleted and double-underline = added):

1. The **CLINICAL PHARMACOLOGY**/**Photosensitivity Potential** subsection was modified as follows:

   Photosensitivity Potential
   In a study of the skin response to ultraviolet and visible radiation conducted in 40 healthy volunteers, the minimum erythematous dose (MED) was assessed following administration of either gemifloxacin 160 mg once daily, gemifloxacin 320 mg once daily, ciprofloxacin 500 mg BID, or placebo for 7 days. At 5 of the 6 wavelengths tested (295-430 nm), the photosensitivity potential of gemifloxacin was not statistically different from placebo. At 365 nm (UVA region), gemifloxacin showed a photosensitivity potential similar to that of ciprofloxacin 500 mg BID and the photosensitivity potential for both drugs were statistically greater than that of placebo. Photosensitivity reactions were reported rarely in clinical trials with gemifloxacin (0.039%). (See **ADVERSE REACTIONS**.)

   It is difficult to ascribe relative photosensitivity/phototoxicity among various fluoroquinolones during actual patient use because other factors play a role in determining a subject's susceptibility to this adverse event such as: a patient's skin pigmentation, frequency and duration of sun and artificial ultraviolet light (UV) exposure, wearing of sun screen and protective clothing, the use of other concomitant drugs and the dosage and duration of fluoroquinolone therapy. (See **ADVERSE REACTIONS** and **ADVERSE REACTIONS/ Post-Marketing Adverse Reactions**.)

2. The third paragraph of the **PRECAUTIONS/*Rash*** subsection was modified as follows:

   ~~Photosensitivity reactions have been reported rarely in clinical trials with FACTIVE. (See **CLINICAL PHARMACOLOGY.**) However, as with all drugs of this class, it is recommended that patients avoid unnecessary exposure to strong sunlight or artificial UV rays (e.g., sunlamps, solariums), and should be advised of the appropriate use of broad spectrum sun block if in bright sunlight. Treatment should be discontinued if a photosensitivity reaction is suspected.~~ Moderate to severe photosensitivity/phototoxicity reactions, the latter of which may manifest as exaggerated sunburn reactions (e.g., burning, erythema, exudation, vesicles, blistering, edema) involving areas exposed to light (typically the face, "V" area of the neck, extensor surfaces of the forearms, dorsa of the hands), can be associated with use of quinolones after sun or UV light exposure. Therefore, excessive exposure to these sources of light should be avoided. Drug therapy should be discontinued if phototoxicity occurs. (See **ADVERSE REACTIONS** and **ADVERSE REACTIONS/Post-Marketing Adverse Reactions**.)

3. The **PRECAUTIONS**/**Information for Patients** subsection was modified as follows:

   - ~~that phototoxicity has been reported with certain quinolones. The potential for FACTIVE to cause phototoxicity was low. In keeping with good clinical practice, avoid excessive sunlight or artificial ultraviolet light (e.g., tanning beds). If a sunburn-like reaction or skin eruption occurs, contact your physician; (See **CLINICAL PHARMACOLOGY: Photosensitivity Potential**);~~ that photosensitivity/phototoxicity has been reported in patients receiving quinolones. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while taking quinolones. If patients need to be outdoors while using quinolones, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. If a sunburn-like reaction or skin eruption occurs, patients should contact their physician; (See **CLINICAL PHARMACOLOGY: Photosensitivity Potential**);

4. In the fourth and sixth paragraphs of the **ADVERSE REACTIONS s**ection, the following was modified:

   ~~FACTIVE appears to have a low potential for photosensitivity. In clinical trials, treatment-related photosensitivity occurred in only 0.039% (3/7659) of patients.~~

   Adverse Events with a Frequency of Less than 1%
   Additional drug-related adverse events (possibly or probably related) in the 8119 patients, with a frequency of >0.1% to ≤1% included: abdominal pain, anorexia, constipation, dermatitis, dizziness, dry mouth, dyspepsia, fatigue, flatulence, fungal infection, gastritis, genital moniliasis, genital pruritus, hyperglycemia, increased alkaline phosphatase, increased ALT, increased AST, increased creatine phosphokinase, insomnia, leukopenia, pruritus, somnolence, taste perversion, thrombocythemia, urticaria, vaginitis, and vomiting.

   Other adverse events reported from clinical trials which have potential clinical significance and which were considered to have a suspected relationship to the drug, that occurred in ≤0.1% of patients were: abnormal urine, abnormal vision, anemia, arthralgia, asthenia, back pain, bilirubinemia, dyspnea, eczema, eosinophilia, facial edema, flushing, gastroenteritis, granulocytopenia, hot flashes, increased GGT, increased non-protein nitrogen, leg cramps, moniliasis, myalgia, nervousness, non-specified gastrointestinal disorder, pain, pharyngitis, photosensitivity/phototoxicity reactions, pneumonia, thrombocytopenia, tremor, vertigo. (See **PRECAUTIONS**.)

5. The second paragraph of the **ADVERSE REACTIONS/Post-Marketing Adverse Events s**ection was modified follows:

   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;
   - 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.

6. In the **"Patient Package Insert"/** "**Factive® and other quinolone antibiotics may cause the following serious side effects"** was modified as follows:

   - ~~phototoxicity. **FACTIVE may rarely make your skin sunburn more easily. Do not use a sunlamp or tanning bed while taking FACTIVE. Use a sunscreen and wear protective clothing if you must be out in the sun.**~~ **Sun sensitivity (photosensitivity),** which can appear as skin eruption or severe sunburn can occur in some patients taking quinolones after exposure to sunlight or artificial ultraviolet light (UV) (e.g. tanning beds). Factive® has been infrequently associated with photosensitivity. You should avoid excessive exposure to sunlight or artificial UV light while you are taking Factive®. Use a sunscreen and wear protective clothing if out in the sun. If photosensitivity develops, contact your physician.

7. Minor editorial changes throughout the labeling.

CONTENT OF LABELING

As soon as possible, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert and text for the patient package insert). Upon receipt, we will transmit this version to the National Library of Medicine for public dissemination. For administrative purposes, please designate these submissions, "**SPL for approved NDA 21-158/S-011**."

LETTERS TO HEALTH CARE PROFESSIONALS

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

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

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 Rebecca D. Saville, 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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