

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-158

CORRESPONDENCE

28 March 2003

Renata Albrecht, MD, Director
Division of Special Pathogens and
Immunologic Drug Products (HFD-590)
Document Control Room
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

APPEARS THIS WAY
ON ORIGINAL

Re: NDA 21-158
Factive[®] (Gemifloxacin mesylate) Tablets, 320 mg
Response to Request for Information – Pharmacovigilance Plan

Dear Dr. Albrecht,

Reference is made to the Resubmission submitted on October 4, 2002 for Factive[®] (Gemifloxacin mesylate) Tablets, 320 mg, NDA 21-158.

The purpose of this letter is to provide written confirmation of the agreements reached during the telephone conference call on 27 March 2003 between the Division and LG Life Sciences related to a *post-marketing* pharmacovigilance plan for gemifloxacin. A summary of the various components of the agreements follows.

LG Life Sciences commits to conducting a vigorous post-marketing pharmacovigilance program in order to maximize the safe use of gemifloxacin. This program will entail multiple components including conducting a phase 4 safety study, monitoring for prescribing patterns and use, ongoing evaluations of particular adverse events, and conducting case control studies when indicated.

Phase 4 Study

LG Life Sciences will conduct a phase 4 safety study of gemifloxacin. The design will be a prospective, randomized, active control trial. Randomization will be at a ratio of two gemifloxacin patients (n=5,000) to one active control patient (n=2,500). Inclusion criteria will include the presence of community acquired pneumonia (CAP) or acute bacterial exacerbation of chronic bronchitis (AECB). In addition, LG Life Sciences will strive to ensure that the patient population enrolled consists of at least 10% of the following ethnic minorities: people of African origin, Asian origin and Hispanic origin so

as to achieve a better understanding of the clinical course – specifically as relates to rash – of these patient populations. CAP patients will be treated for seven days; AECB patients will be treated for five days. Patients will be monitored for efficacy and safety. Safety evaluations will include monitoring for adverse events – with particular emphasis on rash – as well as monitoring for laboratory abnormalities: liver function tests, CPK, and ECG in patients at risk for cardiac arrhythmias.

There will be annual interim analyses of the data from this trial. The timing of the interim analyses will be such as to allow for their results to be included in gemifloxacin Annual Reports to the FDA.

LG Life Sciences commits to forward to the FDA, within two months of NDA approval for gemifloxacin, a draft Phase 4 protocol for this trial and to incorporate changes requested by the FDA and agreed with LG Life Sciences within one month of their finalization. LG Life Sciences commits to initiate the study by the winter of 2004 and to complete the study within three to four years.

Prescribing Patterns and Use

LG Life Sciences commits to obtaining data on the prescribing patterns and use of gemifloxacin. These data will include the number of prescriptions issued as well as the rate of refills. To obtain these data, LG Life Sciences will utilize various databases from HMOs, governmental agencies, and pharmacy organizations. These data will be submitted in the gemifloxacin NDA Annual Reports and will be utilized to estimate not only the quantity of gemifloxacin being utilized, but also the appropriateness – as defined by the gemifloxacin label – of the prescribing patterns.

Evaluation of Spontaneous Adverse Event Reports

LG Life Sciences commits to including in the NDA Annual Reports enhanced sections on adverse events related to the following organ systems: hepatic, skeletal muscle, cardiac conducting system, and cutaneous. For each of these organ systems, spontaneous adverse events will not only be categorized and quantified, but there will also be an effort made to estimate the rates of these adverse events by estimating the rate of underreporting of these events and the amount of patient exposure. In addition, results from the interim analyses of the Phase 4 study will be incorporated into the appropriate sections of the Annual Report related to these four organ systems. These analyses will thus allow for a reanalysis of the risk/benefit ratio of gemifloxacin and will enhance the ability to discern a safety signal related to one or more of these organ systems.

Case Control Studies

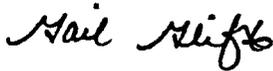
If a safety signal is identified for a rare but serious toxicity – especially severe hepatotoxicity, torsades des pointes, TENS or Steven Johnson Syndrome, or rhabdomyolysis – LG Life Sciences commits to conducting a retrospective case control study. The goal of such a study will be to estimate the relative risk for this toxicity

occurring among patients receiving gemifloxacin compared to other therapies. For this case control study, LG Life Sciences will utilize readily available patient databases, such as are available through various HMOs or governmental agencies. The case control protocol will be developed using standard accepted principles and will be sent for FDA review and input prior to initiation.

LG Life Sciences believes that, through the use of this proposed pharmacovigilance program, the safe and effective use of gemifloxacin can be optimized.

If there are any questions or comments regarding this plan, please contact me at 919-294-5099. Thank you.

Sincerely,



Gail Glifort
Senior Regulatory Associate
PAREXEL International

**APPEARS THIS WAY
ON ORIGINAL**

cc: LGLS: Youn Sung Choo, Vice President and Director, Product Development
GeneSoft: Gary Patou, President

**APPEARS THIS WAY
ON ORIGINAL**

PAREXEL International

PAREXEL

2520 Meridian Parkway, Suite 200
Durham, North Carolina 27713
+1 919 544 3170 Fax: +1 919 544 3410
www.parexel.com

April 1, 2003

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Park Building, Room 2-14
12420 Parklawn drive
Rockville, MD 20857

**APPEARS THIS WAY
ON ORIGINAL**

Re: **NDA 21-158**
Submission of Patent Information

Reference is made to Factive® (gemifloxacin mesylate) Tablets, 320mg, NDA 21-158, currently under review at the Division of Special Pathogens and Immunologic Drug Products.

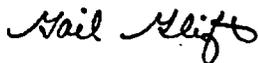
Further reference is made to the original NDA 21-158 submission of December 15, 1999, wherein SmithKline Beecham submitted information regarding patents in sections 13 and 14 of that NDA. The information on those patents (5,633,262, 5,776,944 and 5,962,468) remains in effect, also with regard to the NDA Resubmission filed on October 4, 2002.

Please note that the sponsor has changed since the original filing from SmithKline Beecham (GlaxoSmithKline) to LG Life Sciences, Ltd (Seoul, Korea). A copy of the transfer letter has been submitted for your convenience. PAREXEL International is the Authorized U.S. Agent for the current sponsor of NDA 21-158.

Since the original submission of NDA 21-158, four new patents have been granted for the method of use for gemifloxacin. This new patent information is hereby submitted to the NDA.

If you have any questions regarding this submission, I may be contacted at 919-294-5099. Thank you for your attention to this matter.

Sincerely,



Gail Glifort
Senior Regulatory Associate
PAREXEL International

**APPEARS THIS WAY
ON ORIGINAL**

cc: LGLS: Youn Sung Choo, Vice President and Director, Product Development
GeneSoft: Gary Patou, President



LG Life Sciences

LG Life Sciences, Ltd.

LG Twin Towers
20, Yoido-dong, Youngdungpo-gu, Seoul, Korea.
TEL: (02) 3773-5114

September 19, 2002

**APPEARS THIS WAY
ON ORIGINAL**

Renata Albrecht, M.D.
Acting Director
Division of Special Pathogens and Immunologic Drug Products (HFD-590)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

**Re: U.S. NDA 21-158
Change of NDA Ownership
Factive (gemifloxacin mesylate) Tablets, 320 mg**

Dear Dr. Albrecht:

Effective September 26, 2002 SmithKline Beecham Pharmco Puerto Rico d/b/a GlaxoSmithKline (GSK), has formally transferred ownership of NDA 21-158 for Factive[®] (gemifloxacin mesylate) Tablets, 320 mg to:

LG Life Sciences, Ltd.
LG Twin Towers
20, Yoido-dong, Youngdungpo-gu
Seoul 150-721, Korea

LG Life Sciences, Ltd. (LGLS) has obtained a complete copy of the NDA from GSK including all submissions and official Agency correspondence, as required by § 314.81. LGLS commits to comply with all agreements, promises and conditions made by GSK and contained in the NDA.

LGLS wishes to inform the Division that PAREXEL International Corp. (PAREXEL) has been contracted to act as its U.S. Agent for activities related to this NDA, including its imminent resubmission.

**APPEARS THIS WAY
ON ORIGINAL**

Sincerely,



Youn-Sung Choo, Ph.D.
Vice President and Director, Product Development

**APPEARS THIS WAY
ON ORIGINAL**

cc: PAREXEL International: Alberto Grignolo Ph.D.
Senior Vice President and General Manager
Worldwide Regulatory Affairs

GlaxoSmithKline: Edward M. Yuhas, Ph.D.
Senior Director
U.S. Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
LG Life Sciences, Ltd.

DATE OF SUBMISSION
April 1, 2003

TELEPHONE NO. (Include Area Code)
781-487-9900

FACSIMILE (FAX) Number (Include Area Code)
781-487-0525

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code,
and U.S. License number if previously issued):
LG Life Sciences, Ltd.
LG Twin Towers
20, Yoido-dong, Youngdungpo-gu
Seoul 150-721, KOREA

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State,
ZIP Code, telephone & FAX number) IF APPLICABLE
PAREXEL International Corporation
195 West Street
Waltham, MA 02451-1163

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-158

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)
gemifloxacin mesylate

PROPRIETARY NAME (trade name) IF ANY FACTIVE®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) (±)-7-[3-(aminomethyl)-4-methyl-4-oxo-1-
pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, 7[^]4-(Z)-
(L-methoxy) methyl monomethanesulfonate

CODE NAME (If any) SB-265805 or
LB20304a

DOSAGE FORM: Tablet

STRENGTHS: 320mg

ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE: Treatment of infections caused by susceptible strains of designated organisms in the following
conditions: acute exacerbations of chronic bronchitis and; community-acquired pneumonia

APPLICATION INFORMATION

APPLICATION TYPE
(check one)

NEW DRUG APPLICATION (21 CFR 314.50)

ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

505 (b)(1)

505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one)

ORIGINAL APPLICATION

AMENDMENT TO A PENDING APPLICATION

RESUBMISSION

PRESUBMISSION

ANNUAL REPORT

ESTABLISHMENT DESCRIPTION SUPPLEMENT

EFFICACY SUPPLEMENT

LABELING SUPPLEMENT

CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY

CBE

CBE-30

Prior Approval (PA)

REASON FOR SUBMISSION Patent Information requested by FDA

PROPOSED MARKETING STATUS (check one)

PRESCRIPTION PRODUCT (Rx)

OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

1

THIS APPLICATION IS

PAPER

PAPER AND ELECTRONIC

ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name,
address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing)
conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Not applicable

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA 21-376

APPEARS THIS WAY
ON ORIGINAL



This application contains the following items: (Check all that apply)

- 1. Index
- 2. Labeling (check one) Draft Labeling Final Printed Labeling
- 3. Summary (21 CFR 314.50(c))
- 4. Chemistry section
 - A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
 - B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
 - C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- 12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
- 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- 14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A))
- 15. Establishment description (21 CFR Part 600, if applicable)
- 16. Debarment certification (FD&C Act 306(k)(1))
- 17. Field copy certification (21 CFR 314.50(l)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Neil Smith for</i>	TYPED NAME AND TITLE Alberto Grignolo, President Worldwide Regulatory Affairs Services	DATE <i>April 1, 2003</i>
ADDRESS (Street, City, State, and ZIP Code) PAREXEL International, 195 West Street, Waltham, MA 02451		TELEPHONE NUMBER 781-487-9900

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-158

LG Life Sciences, Ltd
C/o PAREXEL International
Attention: Gail Glifort
2520 Meridian Parkway, Suite 200
Durham, North Carolina 27713

**APPEARS THIS WAY
ON ORIGINAL**

Dear Ms. Glifort:

Please refer to your new drug application (NDA) dated December 15, 1999, received December 16, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Factive (gemifloxacin mesylate) Tablets, 320 mg.

We acknowledge receipt of your submissions dated as follows:

October 14, 2002	December 16, 2002	February 12, 2003
October 24, 2002	December 20, 2002	February 17, 2003
October 29, 2002	December 30, 2002 (2)	February 18, 2003
October 30, 2002	January 2, 2003	February 20, 2003
October 31, 2002	January 9, 2003	February 21, 2003
November 1, 2002	January 10, 2003	February 27, 2003 (2)
November 4, 2002	January 16, 2003	March 24, 2003
November 14, 2002	January 22, 2003	March 27, 2003
November 25, 2002	January 24, 2003	March 28, 2003 (2)
November 26, 2002	January 30, 2003	April 4, 2003
December 9, 2002 (3)	January 31, 2003	
December 12, 2002	February 11, 2003	

**APPEARS THIS WAY
ON ORIGINAL**

Your October 4, 2002 submission constituted a complete response to our December 15, 2000 action letter.

This new drug application provides for the use of Factive (gemifloxacin mesylate) Tablets for the treatment of community-acquired pneumonia and acute bacterial exacerbation of chronic bronchitis.

We have completed the review of this application, as amended. We 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. Accordingly, the application is approved for these indications, effective on the date of the letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert submitted April 3, 2003) and the agreed-upon labeling (immediate container and carton labels submitted March 28, 2003 to be amended as agreed during our April 2, 2003 teleconference and as stated in your April 3, 2003 submission). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the

FPL as soon as it is available but no more than 30 days after it is printed. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "FPL for approved NDA 21-158." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated March 28, 2003:

1. Comparative Safety Study

Conduct a prospective, randomized study comparing gemifloxacin (5,000 patients) to an active control (2,500 patients) in patients with community-acquired pneumonia (CAP) or acute bacterial exacerbation of chronic bronchitis (ABECB). At least 10% of patients should be of African origin, 10% of Asian origin and 10% of Hispanic origin to gain safety information in other minority or ethnic groups, specifically as it relates to rash. Patients should be evaluated for clinical and laboratory safety.

Protocol Submission:	Within 3 months of the date of this letter
Study Start:	Within 11 months of the date of this letter
Interim Report Submission:	Within 12 months of date of this letter (with the annual report)
Final Report Submission:	Within 4 years of the initiation of the study

2. Prescribing Patterns and Use

Conduct a study to evaluate the prescribing patterns and use of gemifloxacin. In this study, obtain data on the prescribing patterns and use of gemifloxacin for the first three years after initial marketing in the US. Include the number of prescriptions issued (as well as the rate of refills) and the diagnoses for which the prescriptions were dispensed. These data may be obtained from various databases such as HMOs, governmental agencies, and pharmacy organizations.

Protocol Submission:	Within 4 months of the date of this letter
Interim Report Submission:	Within 12 months of date of this letter (with the annual report)
Final Report Submission:	Within 5 years of date of this letter

The Division anticipates discussing the details of the above studies at your earliest convenience.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."

FDA's Pediatric Rule at 21 CFR 314.55 was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In

any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Special Pathogen and Immunologic Drug products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA 21-158 for this drug product. We also note that you agreed to evaluate spontaneously reported adverse events, particularly for the cutaneous, hepatic, musculoskeletal, and cardiac (conducting system) organ systems, annually for the first three years after initial marketing in the US.

If you have any questions, call Yon Yu, Pharm. D., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Mark J. Goldberger, M.D., M.P.H.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Mark Goldberger
4/4/03 03:23:47 PM

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-158

FACTIVE[®] (gemifloxacin mesylate) 320mg Tablets

Action Date: December 15, 2000

TL: Leissa

APPEARS THIS WAY
ON ORIGINAL

MO: Powers, Alivisatos, Cox

CHM: M. Sloan

PCL: Ellis

MIC: Dionne

APPEARS THIS WAY
ON ORIGINAL

BPH: Colangelo

STT: Higgins, Dixon, Silliman

RPM: Kimzey

APPEARS THIS WAY
ON ORIGINAL



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-158

SmithKline Beecham
Attention: Edward M. Yuhas, Ph.D.
Associate Director, U.S. Regulatory Affairs
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

**APPEARS THIS WAY
ON ORIGINAL**

Dear Dr. Yuhas:

Please refer to your new drug application (NDA) dated December 15, 1999, received December 16, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Factive (gemifloxacin mesylate) tablet, 320 mg.

We acknowledge receipt of your submissions dated as follows:

January 18, 2000	August 15, 2000	October 19, 2000
January 26, 2000	August 18, 2000	October 31, 2000
February 22, 2000	August 24, 2000	November 3, 2000
February 24, 2000	August 25, 2000	November 21, 2000
March 2, 2000	September 1, 2000	November 24, 2000
March 7, 2000	September 7, 2000	November 27, 2000
June 26, 2000	October 9, 2000	November 28, 2000
July 21, 2000	October 11, 2000	December 8, 2000
August 14, 2000	October 18, 2000	December 11, 2000

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.125(b). The deficiencies are summarized in the following categories:

DEFICIENCIES: CLINICAL SAFETY

In accordance with 21 CFR 314.125(b)(4), based on your NDA submission, we conclude, "There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended or suggested in its proposed labeling." Of particular concern is the lack of data available in your NDA to fully assess the potential risks posed by the high incidence of hypersensitivity/rash in the clinical trials in order to balance these with the efficacy profile of gemifloxacin. This and other safety deficiencies and possible remedies are discussed below.

**APPEARS THIS WAY
ON ORIGINAL**

Rash/Hypersensitivity

Rash, as a manifestation of hypersensitivity, is of greatest concern to us. While this toxicity has previously been reported for fluoroquinolones, it has not occurred with the frequency observed in the data submitted in your application. From these data it is clear that gemifloxacin administration is associated with a significantly increased rate of rash relative to the comparator drugs studied and that this toxicity is especially common in young women (e.g. rates as high as 25% in one of the clinical pharmacology studies). Limited skin biopsy data suggest that for many individuals the rash was consistent with Type IV hypersensitivity, although some had signs and symptoms suggestive of Type I phenomena.

In order for us to adequately assess the risk and benefit balance for Factive for the proposed indications, the following issues must be addressed. First, is the risk of rash or other forms of hypersensitivity higher upon re-exposure to gemifloxacin than first exposure? Second, does re-exposure in patients who experienced a type IV hypersensitivity rash cause more severe or serious dermatologic or systemic reactions than the prior exposure? Finally, what is the risk or rate of individuals with hypersensitivity to Factive developing cross-sensitivity to other drugs in the fluoroquinolone class?

To address these deficiencies you should develop investigations or clinical studies in consultation with experts in dermatology and clinical immunology. We offer the following suggestions, mindful that alternatives or modifications may be appropriate following such consultation.

- 1) You should conduct a clinical pharmacology study in several hundred patients to more accurately assess the risks associated with and characteristics of skin rash, the effect of re-challenge, and the possible role of the N-acetylated metabolite of gemifloxacin (SB-414000) in association with rash. This study should include a substantial sample of young women, the population that appears to be most at risk for rash/hypersensitivity. Patients should receive 320 mg gemifloxacin once daily by mouth for a minimum of 10 days duration (unless rash occurs earlier). Those who experience a non life-threatening rash should undergo a washout period followed by re-challenge with gemifloxacin in a carefully monitored re-challenge study (such as the study outlined in 2) below. A sampling of patients who do not experience a rash should also be re-challenged in this first study, following a similar washout period. We recommend that you measure the peak plasma concentrations of both parent gemifloxacin and N-acetyl gemifloxacin for all subjects, sampling from 0.5 to 6.0 hours after the first dose of gemifloxacin and at steady state.
- 2) You should conduct a gemifloxacin re-challenge study in patients who experienced a gemifloxacin-associated rash in prior, ongoing, or future clinical studies in order to determine the rate of recurrence, as well as describe the spectrum of hypersensitivity phenomena associated with rash. In order to minimize risks to the study subjects, individuals who previously experienced a rash where signs and/or symptoms were suggestive of Type I hypersensitivity (e.g., bronchospasm, hypotension, edema) should be excluded. Re-challenges should be conducted in an appropriately monitored setting. Findings suggestive of further increased rates of rash or more serious forms of hypersensitivity than have been observed to date would require that future decisions on this

NDA be brought before the Anti-Infective Drugs Advisory Committee.

- 3) If the above studies confirm a high rate or increased severity of rash, in particular upon re-challenge, then a follow-up cross-sensitization study with other commonly marketed fluoroquinolones should be conducted. Alternatively, a cross-sensitization assessment could be incorporated into one or both of the above studies.

In the above studies and in other ongoing and future studies of gemifloxacin, you should collect the following information on all patients who develop a rash: skin biopsy histopathological slides, pathology reports (read by a dermatopathologist), photographs of the rash, and clinical assessments from board-certified dermatologists. You should also submit this information (where available) for patients who experienced a gemifloxacin-associated rash in the past (i.e., subjects included in the current NDA submission).

Liver

Based on the pre-clinical and clinical data submitted in your application, we remain concerned that a liver toxicity signal is present for gemifloxacin, particularly at doses exceeding 320 mg. Because of the overlap in the pharmacokinetic profiles of the 320 mg and higher doses and the possibility of dose intensification or prolongation of therapy by clinicians, it is likely that many individuals will achieve systemic exposure similar to that observed with the 640 mg dosing. In addition, the findings observed in gemifloxacin recipients do not appear consistent with the liver toxicity mechanism suggested by the animal toxicology studies (i.e., "cholate stasis"). We are concerned that the hepatic findings in patients may represent a manifestation of an immunologically mediated mechanism similar to that manifesting as rash, in spite of the fact that patients with rash were not necessarily those with abnormal liver test results. To address this concern, as part of the recommended studies to assess hypersensitivity/rash, you should also monitor patients for hepatic abnormalities (e.g. elevations in liver enzymes, bile acids, etc.). An effort should be made to correlate these abnormalities with plasma levels of gemifloxacin or its metabolites.

DEFICIENCIES: CLINICAL EFFICACY

Based on our review of the clinical trial data submitted in your NDA, we have concluded that gemifloxacin is effective in treating community-acquired pneumonia (CAP) of mild to moderate severity, acute bacterial exacerbation of chronic bronchitis (ABECB), acute bacterial sinusitis (ABS), and uncomplicated urinary tract infection (UUTI) due to selected susceptible pathogens. Approval of these indications is dependent on completion of the above studies with demonstration of an acceptable safety profile. You have not provided adequate information to support the efficacy of gemifloxacin for the use outlined below:

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Acute pyelonephritis (AP)

The data provided in support of the AP indication are inadequate, because the population studied represents a subset of the larger complicated urinary tract infection (CUTI) population in which non-

inferiority was not demonstrated. To obtain approval for AP you should conduct a prospective, comparative, randomized, double blind controlled study in patients with signs and symptoms consistent with acute pyelonephritis. Any patients with a CUTI should be excluded from this study. We also note that the population most affected by AP is comprised of the same patients who seem to be at greatest risk for hypersensitivity to gemifloxacin, young women. Any future AP study, which should include a predominance of women, will therefore need to be closely monitored for the development of hypersensitivity. As for all indications, the approval of an AP indication is dependent on completion of the above studies to address safety with demonstration of an acceptable balance of benefit and risk.

Because concerns about gemifloxacin's efficacy in CUTI exist, we anticipate that a future potential approval for any urinary tract infection indication will require language in product labeling advising the healthcare provider of the lower efficacy rates observed in patients with CUTI. If you believe such a labeling approach is unreasonable, one option is for you to conduct a label comprehension study to assess clinicians' understanding and ability to differentiate acute pyelonephritis from CUTI. This study should survey all medical specialties, with a focus on primary care physicians.

LABELING ISSUES

In addition to the deficiencies listed above, we have the following comments on labeling. This list is not all-inclusive, but represents current information we wish to provide to help guide your drug development.

Community-Acquired Pneumonia (CAP) - _____

To obtain approval of a treatment duration longer than _____ you should obtain clinical safety and efficacy data that demonstrate added efficacy provided by such a dose extension. To obtain labeling for severe CAP, you should conduct additional studies in patients who meet accepted standardized criteria. We recognize that clinicians may not be likely to enroll patients with severe CAP in an oral drug study. Therefore, studies involving gemifloxacin injection may be needed to garner a severe CAP labeling claim.

Penicillin-Resistant *Streptococcus pneumoniae* (PRSP)

Community-Acquired Pneumonia (CAP): To obtain labeling that highlights the role of _____ in the treatment of _____

Additional clinical trial experience in the treatment of patients with severe CAP due to *Streptococcus pneumoniae* (including cases of bacteremic pneumococcal pneumonia) should also be obtained.

Acute Bacterial Sinusitis (ABS): Before we would be prepared _____, you should establish clinical efficacy of _____ (e.g., CAP). _____ (or another agreed upon alternative serious treatment indication), _____

Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB): At this time, insufficient evidence exists to conclude that PRSP in ABECB poses a public health problem that merits a labeling claim



for PRSP.

Macrolide-Resistant *Streptococcus pneumoniae* (MRSP)

Microbiology

Based on the *in vitro* and clinical microbiology data provided,



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RECOMMENDATIONS

The following studies would provide useful information to assist in labeling Factive for safe and effective use. Some of these may be able to be conducted in the course of further development of Factive prior to approval. If you do not complete these studies prior to an approval, they would likely constitute requests for postmarketing commitments.

Assessment of Safety

1. You should conduct a large cohort (active surveillance) study to accurately assess adverse events associated with Factive once it is in general use. This study should include the monitoring and analysis of adverse event reports, including dermatologic, hepatic, and cardiac (e.g., QT interval) adverse effects.
2. You should conduct further clinical and preclinical investigations to characterize the mechanism and risk factors for the development of liver toxicity.
3. Non-clinical QT Interval Effects: You should conduct an *in vitro* study (or studies) to assess the

potential effect of gemifloxacin on IKr and include other fluoroquinolones as comparators (e.g. gatifloxacin, moxifloxacin, levofloxacin, ciprofloxacin, sparfloxacin.)

4. QT Interval Effects and Exposure-response: The potential for gemifloxacin to prolong the QT interval should be further evaluated in clinical pharmacology studies of otherwise healthy young (18 to 64 years) and elderly (65 years) male and female subjects. It is recommended that the studies be designed to:

Assess the effect of single escalating oral doses of gemifloxacin (320 mg, 640 mg, and 960 mg) and placebo on the QTc interval.

Compare the potential QTc prolonging effect of a single oral clinical dose of gemifloxacin (320 mg) with that of placebo and of fluoroquinolones.

Compare the effect of repeat oral doses of gemifloxacin at steady state (days) with that of repeat oral doses of a fluoroquinolone comparator at steady state.

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Hepatic Impairment

You should conduct an additional study to evaluate the pharmacokinetics and safety of gemifloxacin in individuals with severe hepatic impairment. This study should compare subjects with severe hepatic impairment to demographically matched subjects with normal hepatic function.

Sucralfate Drug Interaction

To provide accurate labeling information regarding the use of sucralfate with gemifloxacin, you should conduct a study to evaluate the optimal timing of sucralfate dosing prior to gemifloxacin administration.

Genotoxicity

You should conduct a rodent micronucleus study (or studies) to compare the *in vivo* clastogenic potentials of gemifloxacin to other fluoroquinolones, including toxicokinetic evaluations.

Finally, as a corollary to the safety concerns addressed in this letter, it is our belief that the risk/benefit of this drug could be improved by providing evidence of efficacy from adequate and well-controlled studies in patients with more serious infections, including those infected with resistant pathogens. This could be accomplished with further development of your intravenous formulation for Factive.

When you respond to the above deficiencies, include a safety update as described in 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse

events, and common adverse events, incorporate new safety data as follows:

Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

Present tabulations of the new safety data combined with the original NDA data.

Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with the Division of Special Pathogen and Immunologic Drug Products to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Rene Kimzey, RNC, M.Ed., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

**APPEARS THIS WAY
ON ORIGINAL**

M. Dianne Murphy, MD

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Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Sandra L. Kweder
12/15/00 06:52:27 PM
for M. Dianne Murphy

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ODS Consult Reviews

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 4, 2003

TO: Renata Albrecht, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
HFD-590

VIA: Yon Yu, Pharm.D., Regulatory Health Project Manager,
Division of Special Pathogens and Immunologic Drug Products
HFD-590

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Anne Trontell, M.D., M.P.H., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review Patient Information for Factive
(gemifloxacin mesylate), NDA 21-158

The patient labeling which follows represents the revised risk communication materials for the Factive (gemifloxacin mesylate), NDA 21-158, PPI. It has been reviewed by our Office and by DDMAC. We have simplified the wording, made it consistent with the PI, removed promotional language and other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

Comments to the review division are bolded, underlined and italicized. We can provide marked-up and clean copies of the revised document in Word if requested by the review division.

Please let us know if you have any questions.

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this page is the manifestation of the electronic signature.**

/s/

Jeanine Best
3/4/03 11:38:56 AM
CSO

Toni Piazza Hepp
3/4/03 05:07:42 PM
PHARMACIST
for Anne Trontell

Memo

**APPEARS THIS WAY
ON ORIGINAL**

To: Renata Albrect, M.D.
Director, Division of Special Pathogen and Immunologic Drug Products
HFD-590

From: Alina R. Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

Through: Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
HFD-400

CC: Yon Yu
Project Manager
HFD-590

**APPEARS THIS WAY
ON ORIGINAL**

Date: February 3, 2003

Re: PID D030042; Review of Risk Management Plan for Factive
(Gemifloxacin Tablets) dated January 9, 2003; NDA 21-158.

This memorandum is in response to a January 21, 2003 request from the Division of Special Pathogen and Immunologic Drug Products (HFD-590) for a review of the risk management plan for Factive Tablets.

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In the post-marketing period, GeneSoft proposes to optimize gemifloxacin's safety profile by monitoring spontaneous adverse event reports, minimizing the risks of off label use through the use of blister packs and physician education, and implementing a phase 4 safety study. DMETS has the following comments in response to the proposed risk management plan.

A. Spontaneous Reports

The sponsor proposes to monitor spontaneous adverse events using routine solicitation and compilation of adverse event reports. However, the sponsor does not include any information or plans on monitoring medication errors. There is the potential for selection errors meaning an incorrect pack may be dispensed or there may be confusion associated with the proposed nomenclature of the packs (i.e., Façpac 5 and Façpac 7). DMETS encourages the sponsor provide a risk management plan that includes medication error monitoring as well (i.e., errors pertaining to nomenclature, labeling, and packaging).

B. Off Label Use Minimization

The sponsor proposes to design two separate blister packs containing gemifloxacin for either 5 days or 7 days of therapy: five for use in patients with acute exacerbations of chronic bronchitis (AECB) and seven for patients with community acquired pneumonia (CAP). The company has withdrawn bottle presentation of the drug from the NDA and limited the use of the 30 day dispensing packs to hospital pharmacies. The sponsor anticipates that the use of the blister pack will increase gemifloxacin's use according to its label, and thereby decrease the risks of toxicity.

Additionally, the sponsor has conducted a retrospective drug utilization demonstrating that fixed dose packs of drugs led to less than 1% prescribing of extended courses of treatment compared to 15 to 28 % with bottles of tablets or capsules. DMETS can not assess or comment on this study since it was not submitted for review.

DMETS acknowledges that the proposal to package the product in blister packs containing five or seven tablets may help to reduce the risk of off label use. However, it will not completely eliminate the risk of larger quantities being dispensed. For example, if a health care provider wishes to prescribe gemifloxacin for a longer duration of use, say 10 or 14 days, he or she will simply prescribe for two packs rather than one.

DMETS conducted a review for Factive on September 18, 2000 (see ODS consult 00-251) where the sponsor had proposed packages containing _____ The sponsor had proposed to name these packs as _____ DMETS did not recommend the use of this nomenclature at that time. The outcome of DMETS' recommendation is unknown. DMETS still maintains its position in discouraging this type of nomenclature for packaging configurations. Additionally, indication specific packaging, such as blister packs of 5 and 7 may introduce error and confusion among pharmacists and patients. For example, indication specific packaging will not prevent a pharmacist from dispensing the CAP blister pack (7 day therapy) if the stock for the AECB blister pack (5 day

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therapy) has been depleted. In this case, the patient may receive labels and labeling for the CAP indication rather than the AECB indication. Confusion and error may also be perpetuated if additional indications for gemifloxacin are approved by the Agency and indication specific packaging is utilized.

C. Phase IV Study



In summary, additional information regarding the risk management plan is necessary for review and comment. We acknowledge the use of two different packaging configurations which are indication specific may decrease the potential for off label use, however, it will not completely prevent the use of gemifloxacin for a duration greater than 7 days.

If you have any questions or need clarification, please contact Sammie Beam, Project Manager, at 301-827-3242.

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this page is the manifestation of the electronic signature.**

/s/

Carol Holquist
2/13/03 02:42:08 PM
PHARMACIST

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Jerry Phillips
2/13/03 03:10:51 PM
DIRECTOR

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CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: September 14, 2000	DUE DATE: September 30, 2000	OPDRA CONSULT #: 00-0251
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TO: Renata Albrecht, M.D.
 Director, Division of Special Pathogen and Immunologic Drug Products
 HFD-590

THROUGH: Rene Kimzey, Project Manager
 HFD-590

PRODUCT NAME: Factive (Gemifloxacin Mesylate Tablets) 320 mg	MANUFACTURER: SmithKline Beecham Pharmaceuticals
---	--

NDA #: 21-158

SAFETY EVALUATOR: Carol Holquist, R.Ph.

SUMMARY: In response to a consult from the Division of Special Pathogen and Immunologic Drug Products (HFD-590), OPDRA reviewed the proposed container labels, carton and insert labeling of Factive, for possible interventions that may help minimize medication errors.

OPDRA RECOMMENDATION:
 OPDRA recommends the Division request SmithKline Beecham Pharmaceuticals to revise their labels and labeling accordingly (See review).

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ON ORIGINAL**

/S/

9/25/2000

Jerry Phillips, R.Ph.
 Associate Director for Medication Error Prevention
 Office of Post-Marketing Drug Risk Assessment
 Phone: (301) 827-3242
 Fax: (301) 480-8173

/S/

MO
9/25/00

Martin Himmel, M.D.
 Deputy Director
 Office of Post-Marketing Drug Risk Assessment
 Center for Drug Evaluation and Research
 Food and Drug Administration

**APPEARS THIS WAY
ON ORIGINAL**

**Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B-03
Center for Drug Evaluation and Research**

Labels and Labeling Safety Review

DATE OF REVIEW: September 18, 2000 **APPEARS THIS WAY
ON ORIGINAL**

NDA: 21-158

NAME OF DRUG: Factive (Gemifloxacin Mesylate Tablets) 320 mg

NDA HOLDER: SmithKline Beecham Pharmaceuticals

I. INTRODUCTION

This consult is in response to a September 14, 2000, request from the Division of Special Pathogen and Immunologic Drug Products (HFD-590), to review the container labels, carton and insert labeling of Factive for interventions that might minimize medication errors.

OPDRA was originally consulted on April 13, 2000 for review of the proprietary name, Factive. OPDRA had no objections to the use of the proprietary name at that time, however, we did propose some labeling revisions (See OPDRA Consult 00-0122).

PRODUCT INFORMATION

Factive is a synthetic broad-spectrum potent antibacterial agent for oral administration which contains the active ingredient gemifloxacin mesylate. Gemifloxacin is a compound related to the fluoroquinolone class of antibiotics and is available as the mesylate salt in the sesquihydrate form. Factive can be administered with or without food and should be swallowed whole with a liberal amount of liquid. The recommended dose of Factive is 320 mg daily, however the duration of therapy is linked to the indication for use as follows:

INDICATION	DOSE	DURATION
Acute Bacterial Exacerbations of Chronic Bronchitis	320 mg daily	5 days
Community-acquired Pneumonia	320 mg daily	7 days

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Therapy can be extended _____ of therapy in cases of serious pneumonia. Dosage adjustments are not required for elderly patients and patients with mild to moderate renal impairment. However, dosage adjustments are required for patients with severe renal dysfunction (< 40 mL/min).

The package insert states the product will be supplied as bottles of 30s and 50s, SUP 30s and 100s and unit of use packages containing _____. Although all of these packaging configurations are listed in the HOW SUPPLIED section of the insert, OPDRA was provided labeling for the unit-of-use packages containing 5 or 7 tablets and bottles containing 30 tablets.

II. RISK ASSESSMENT

- A. _____ appears to be the *most prominent* name on the labeling inferring it is another *proprietary name* for the product and this is *misleading*.
- B. The use of the ' _____ ' is similar to that utilized by Pfizer for Zithromax/Z-Pak and Bayer most recently for Avelox/ABC Pack. Health care providers prescribe Zithromax Z-Pak simply as Z-Pak. OPDRA has safety concerns regarding the use of this nomenclature. "Z-Pak" and "ABC Pack" are not *approved* proprietary names and if a practitioner is unfamiliar with "Z-Pak" or "ABC Pack" and attempts to find a reference to these names, they will be unsuccessful.

Since Z-Pak or ABC Pack are not approved proprietary names, they do not exist in any reference text. OPDRA searched the PDR, Medline, Micromedex, Facts and Comparisons and American Drug Index for reference to Z-Pak and was unsuccessful. *OPDRA does not recommend the proliferation of such names for unit of use packaging configurations.*

- C. OPDRA discourages the use of a number in conjunction with a proprietary name or in this case the packaging nomenclature because *numbers* can often be *misinterpreted* for the *strength* of the product or *total number of tablets* to be administered on a prescription or inpatient order. Post-marketing experience with Percocet 5, demonstrated this problem. Patients were given 5 tablets rather than one 5 mg tablet.
- D. There are currently no directions for use on the carton. The patient may *misinterpret* the *number* as the *total daily dose* of the product rather than the net quantity. Recent post-marketing experience with Avelox packaged in a similar packaging configuration of 5 tablets, the patients administered all five tablets at once because the directions for use were not clearly communicated on the labeling.

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- E. There are several unit of use packages proposed: _____
_____ OPDRA questions the rational of the proposal to market a unit of use package that contains _____. We are concerned that this proposed packaging configuration may not be reasonable since _____ of therapy is only indicated for serious cases of pneumonia.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In addition to the above safety concerns, if the nomenclature is approved we then recommend the following revisions, which might minimize potential user error.

A. UNIT of USE CARTONS (3s, 7s) and OUTER CARTONS (3 Unit of Use Cartons)

1. The approved proprietary name of this product is Factive not '_____
_____ is the most prominent name on the labeling. We note that the "ASHP Guidelines on Preventing Medication Errors in Hospitals", Am J Hosp. Pharm, Vol. 50, Feb 1993, notes that important information such as drug name and strength should have the greatest prominence. Factive should be relocated to appear at the top of the carton and its prominence should be increased. _____ should be relocated and the font size should be reduced to appear less prominent than the proprietary name or deleted altogether.

2. 

3. 

B. _____

We recommend the net quantity statement be _____. The location and boxing gives more prominence to this amount than the product strength. Post-marketing experience has demonstrated confusion due to this same approach, with Remeron tablets. The Agency received several medication error reports due to confusion of the: _____ and strength.

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C. UNIT DOSE BLISTER

The unit dose tablet is technically misbranded because the product does not contain _____ We recommend revising to read as _____ or revising the label to read as follows:

FACTIVE
(Gemifloxacin Tablets)
320 mg

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D. UNIT DOSE CARTON

1. See comment 1 under CONTAINER.

2. 

[Note: The second sentence is optional.] 

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IV. RECOMMENDATIONS

OPDRA recommends the above labeling revisions, which might lead, to safer use of the product.

In addition, OPDRA recommends a consult be forwarded to the Division of Drug Marketing, Advertising and Communications (DDMAC) for comment on the proposed packaging nomenclature as well.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Carol Holquist at (301) 827-3244.

/S/

9-22-00

Carol Holquist, RPh.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/

9/25/2000

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

**APPEARS THIS WAY
ON ORIGINAL**

CC: NDA 21-158
HFD-590; Division Files/Rene Kimzey, Project Manager
HFD-590; Renata Albrecht, Division Director
HFD-400; Jerry Phillips, Associate Director, OPDRA

Electronic only cc:

HFD-002; Murray Lumpkin, Deputy Center Director for Review Management
HFD-400; Peter Honig, Director, OPDRA
HFD-040; Patricia Staub, Senior Regulatory Review Officer, DDMAC
HFD-440; Mary Dempsey, Project Manager, OPDRA
HFD-400; Sammie Beam, Project Manager, OPDRA

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NDA 21-158

FACTIVE[®] (gemifloxacin mesylate) 320mg Tablets

Action Date: December 15, 2000

TL: Leissa

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ON ORIGINAL**

MO: Powers, Alivisatos, Cox

CHM: M. Sloan

PCL: Ellis

MIC: Dionne

**APPEARS THIS WAY
ON ORIGINAL**

BPH: Colangelo

STT: Higgins, Dixon, Silliman

RPM: Kimzey

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT LG Life Sciences, Ltd.	DATE OF SUBMISSION March 28, 2003
TELEPHONE NO. (Include Area Code) 781-487-9900	FACSIMILE (FAX) Number (Include Area Code) 781-487-0525
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): LG Life Sciences, Ltd. LG Twin Towers 20, Yoido-dong, Youngdungpo-gu Seoul 150-721, KOREA	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE PAREXEL International Corporation 195 West Street Waltham, MA 02451-1163

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-158

ESTABLISHED NAME (e.g., Proper name, USP/USAN name) gemifloxacin mesylate	PROPRIETARY NAME (trade name) IF ANY FACTIVE®
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) (±)-7-[3-(aminomethyl)-4-methyl-4-oxo-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, 7 [^] 4-(Z)-(O-methylxime) monomethanesulfonate	CODE NAME (If any) SB-265805 or LB20304a
DOSAGE FORM: Tablet	STRENGTHS: 320mg
ROUTE OF ADMINISTRATION: Oral	

(PROPOSED) INDICATION(S) FOR USE: Treatment of infections caused by susceptible strains of designated organisms in the following conditions: acute exacerbations of chronic bronchitis and; community-acquired pneumonia

APPLICATION INFORMATION

APPLICATION TYPE
(check one) NEW DRUG APPLICATION (21 CFR 314.50) ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
 BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE 505 (b)(1) 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION (check one) ORIGINAL APPLICATION AMENDMENT TO A PENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT
 LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION Response to requests for information

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.
Not applicable

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
NDA 21-376

This application contains the following items: (Check all that apply)

- 1. Index
- 2. Labeling (check one) Draft Labeling Final Printed Labeling
- 3. Summary (21 CFR 314.50(c))
- 4. Chemistry section
 - A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
 - B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
 - C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- 12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
- 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- 14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A))
- 15. Establishment description (21 CFR Part 600, if applicable)
- 16. Debarment certification (FD&C Act 306(k)(1))
- 17. Field copy certification (21 CFR 314.50(l)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify) Pharmacovigilance Plan

CERTIFICATION

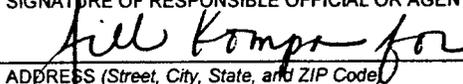
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Alberto Grignolo, President Worldwide Regulatory Affairs Services	DATE 03/28/03
ADDRESS (Street, City, State, and ZIP Code) PAREXEL International, 195 West Street, Waltham, MA 02451		TELEPHONE NUMBER 781-487-9900

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

DATE: February 3, 2003

FROM: Cynthia Kornegay, Ph.D., Epidemiologist
Division of Drug Risk Evaluation, HFD-430
Office of Drug Safety

**APPEARS THIS WAY
ON ORIGINAL**

THROUGH: Julie Beitz, M.D., Division Director
Division of Drug Risk Evaluation, HFD-430
Office of Drug Safety

TO: Renata Albrecht, M.D., Acting Director
Division of Special Pathogens and Immunologic Drug Products, HFD-590
Office of New Drugs

SUBJECT: Review of Risk Management Plan for Gemifloxacin (Factive) for Parexel Int. (LG Life Sciences, Ltd).

PID#: D030042

NDA#: 21-158

Executive Summary

The purpose of this document is to review and evaluate the risk management program (RMP) submitted for gemifloxacin (Factive). The submitted RMP has three sections, titled Spontaneous Reports, Off Label Use Minimization, and a

The RMP submitted does not contain adequate detail for either review or evaluation. The sponsor does not list any of the risks that may be of concern, nor do they present an approach of how to minimize those risks once gemifloxacin is available by prescription.

Post-Marketing Safety Plan for Gemifloxacin

The RMP submitted by the sponsor is composed of two short sections. In the first section, Spontaneous Reports, the sponsor proposes to collect and report all adverse events as required by regulation. The sponsor proposes to gather additional information if the adverse events are dermatologic in nature. The sponsor does not describe or detail the additional information they intend to obtain.

The second section of the RMP summarizes how the sponsor intends to minimize off-label use. "Off-label" is defined as use for more than seven consecutive days. The sponsor intends to provide gemifloxacin in 5- or 7-day blister packs, and to use marketing representatives to emphasize the importance of prescribing gemifloxacin according to labeled instructions.

Assessment of Post-Marketing Safety Plan

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The RMP submitted by the sponsor does not provide adequate detail for either assessment or evaluation. Specifically,

1. The sponsor does not define any potential risks associated with gemifloxacin use, particularly those that are to be addressed by the RMP. The sponsor does not summarize the relevant premarketing safety data needed to understand the extent and the manageability of the risk, nor do they provide any insight into the risk profile of individuals who take gemifloxacin.
2. The sponsor does not state the goals of the RMP.
3. Generally, the sponsor does not provide adequate information about the steps that they will take to minimize the risks associated with gemifloxacin. Although two approaches (spontaneous report monitoring and blister pack dispensing) are briefly described, it is not possible to evaluate their adequacy without knowing what the risks of interest are, or how they will relate to the goals of the RMP.
4. The sponsor does not describe how spontaneous report monitoring will directly relate to reducing the risks associated with gemifloxacin. The sponsor does provide data supporting their claim that providing gemifloxacin in 5- or 7-day reduces the incidence of prescribing for longer periods. However, it is not clear if prescribers will be able to dispense multiple blister packs. It is also not clear if extended prescribing is the only off-label use that is of concern to the division or the sponsor.
5. The sponsor does not describe any mechanism to evaluate the effectiveness or impact of the RMP or its individual components.
6. _____

Given these deficiencies, it is not possible to evaluate the submitted RMP, or to offer suggestions on how it might be improved.

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/s/

Cynthia Kornegay
2/3/03 03:58:29 PM
MEDICAL OFFICER

Julie Beitz
2/3/03 04:04:27 PM
DIRECTOR

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NDA 21-158
NDA ———

Edward M. Yuhas, Ph.D.
Director, U.S. Regulatory Affairs
GlaxoSmithKline
One Franklin Plaza, P.O. Box 7929
Philadelphia, PA 19101-7929

**APPEARS THIS WAY
ON ORIGINAL**

Dear Dr. Yuhas:

We received your January 8, 2002 correspondence on January 9, 2002, requesting a meeting to discuss the approvability of NDA 21-158 and NDA ——— based on new data for rash and community-acquired pneumonia studies. The guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000), describes three types of meetings:

- Type A: Meetings that are necessary before a company can proceed with a stalled drug development program.
- Type B: Meetings described under drug regulations [e.g., Pre-IND, End of Phase 1 (for Subpart E or Subpart H or similar products), End of Phase 2, Pre-NDA].
- Type C: Meetings that do not qualify for Type A or B.

The guidance can be found at <http://www.fda.gov/cder/guidance/2125fnl.htm>.

You requested a type A meeting. The meeting is scheduled for:

Date: February 27, 2002

Time: 12:00 P.M. – 2:00 P.M.

Location: 9201 Corporate Blvd., Room S-300, Rockville, MD 20850

CDER participants:

Mark J. Goldberger, M.D., M.P.H., Acting Director, Office of Drug Evaluation IV
Renata Albrecht, M.D., Acting Director, Division of Special Pathogen and
Immunologic Drug Products
Edward Cox, M.D., Medical Reviewer
John H. Powers, M.D., Medical Reviewer
Regina Alivisatos, M.D., Medical Reviewer

NDA 21-158

NDA —

Page 2

Markham C. Luke, M.D., Medical Reviewer
Sary Beidas, M.D., Medical Reviewer
Kenneth Hastings, Dr.P.H., Pharmacology/Toxicology Team Leader
Stephen G. Hundley, Ph.D., DABT, Pharmacology/Toxicology Reviewer
Philip M. Colangelo, Pharm.D., Ph.D., Clinical Pharmacology/Biopharmaceutics
Reviewer
Karen M. Higgins, Sc.D., Statistics Team Leader
Cheryl A. Dixon, Ph.D., Statistical Reviewer
Nancy Silliman, Ph.D., Statistical Reviewer
Norman R. Schmuff, Ph.D., Chemistry Team Leader
Milton J. Sloan, Ph.D., Chemistry Reviewer
Shukal Bala, Ph.D., Microbiology Team Leader
Peter A. Dionne, Microbiology Reviewer
Ellen C. Frank, R.Ph., Chief, Project Management Staff
Michael Bourg, Pharm.D., Regulatory Project Manager
Rene Kimzey, R.N.C., M.Ed., Regulatory Project Manager

Provide the background information for this meeting at least two weeks prior to the meeting. If we do not receive it by February 13, 2002, we may need to reschedule the meeting.

If you have any questions, call me at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Michael Bourg, Pharm.D.
Regulatory Project Manager
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

nulldate
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-158

LG Life Sciences
C/o PAREXEL International
Attention: Gail Glifort, Regulatory Project Manager
195 West Street
Waltham, Massachusetts 02451-1163

**APPEARS THIS WAY
ON ORIGINAL**

Dear Ms. Glifort:

We acknowledge receipt on October 4, 2002 of your October 4, 2002 resubmission to your new drug application for Factive® (gemifloxacin mesylate) Tablets, 320 mg.

We consider this a complete, class 2 response to our December 15, 2000 action letter. Therefore, the user fee goal date is April 4, 2003.

If you have any question, call Michael Bourg, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Ellen Frank
11/15/02 11:50:26 AM
NDA 21-158

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: November 6, 2002

To: Gail Gilfort Regulatory Affairs Associate II	From: Matthew A. Bacho (for Michael Bourg) Regulatory Project Manager
Company: Parexel International	Division of Special Pathogen and Immunologic Drug Products (HFD-590)
Fax number: (919) 544-3170, Ext. 5099	Fax number: (301) 827-2475
Phone number: (919) 361-2956	Phone number: (301) 827-2127
Subject: A request for data (NDA 21-158)	

Total no. of pages including cover: 5

Reviewers: Edward Cox, M.D., Medical Team Leader/Maureen Tierney, M.D., Medical Officer

Document to be mailed: YES NO

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NDA 21-158

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Dear Ms. Gilfort:

Please refer to NDA 21-158 for Factive[®], your October 4, 2002 resubmission, and our conversation on October 31, 2002. We would like to request additional data and analyses that pertain to Studies 303, 333, and 287 as well as the CAP-IV Studies 106, 107, and 111. We are also providing additional details on the types of QT analyses we would like to see performed:

- Adverse events by body system similar to the data compiled in Safety Update Tables 5.2 and 5.3.
- Most frequently occurring AE's (Table 5.4).
- AE's associated with liver function abnormalities (Table 8.5).
- Liver chemistries outside of F3 and F2F3 ranges (Tables 10.19-10.26).
- F2F3 Flagged liver chemistries with history (Table 10.46).
- Any data on actual liver function values (how many 2-x nml, 4-6x nml, etc.) in a format that is similar to the attached tables.
- QT_C values such as in Tables 11.21-11.29.
- Please also perform the analyses in the item above (i.e. Tables 11.21-11.29) in the subsets of patients receiving concomitant agents known to prolong the QT interval and those not receiving concomitant QT prolonging agents by treatment arm.

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

Sincerely yours,

{See appended electronic signature page}

Matthew A. Bacho
Regulatory Project Manager
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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Attachments: Two Sample Tables

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Number of Patients with Maximum LFT Values from Beginning of Therapy to End of Therapy in the specified ranges, Gemifloxacin vs. Comparators

Functional Group/ Variable	Range	Treatment Group			
		Gemifloxacin		Comparators	
		n/N*	N (%)	n/N*	N (%)
ALT	<ULN				
	ULN-				
	<2xULN				
	2-<4xULN				
	4-<6xULN				
	6-<8xULN				
≥8xULN					
AST	<ULN				
	ULN-				
	<2xULN				
	2-<4xULN				
	4-<6xULN				
	6-<8xULN				
≥8xULN					
ALK-P	<ULN				
	ULN-				
	<2xULN				
	2-<4xULN				
	4-<6xULN				
	6-<8xULN				
≥8xULN					
Total Bilirubin	<ULN				
	ULN-				
	<2xULN				
	2-<4xULN				
	4-<6xULN				
	6-<8xULN				
≥8xULN					

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Number of Patients with Maximum LFT Values from End of Therapy to Latest Follow-up in the specified ranges, Gemifloxacin versus Comparators

Functional Group/ Variable	Range	Treatment Group			
		Gemifloxacin		Comparators	
		n/N*	N (%)	n/N*	N (%)
ALT	<ULN				
	ULN-<2xULN				
	2-<4xULN				
	4-<6xULN				
	6-<8xULN				
	≥8xULN				
AST	<ULN				
	ULN-<2xULN				
	2-<4xULN				
	4-<6xULN				
	6-<8xULN				
	≥8xULN				
ALK-P	<ULN				
	ULN-<2xULN				
	2-<4xULN				
	4-<6xULN				
	6-<8xULN				
	≥8xULN				
Total Bilirubin	<ULN				
	ULN-<2xULN				
	2-<4xULN				
	4-<6xULN				
	6-<8xULN				
	≥8xULN				

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/s/

Matthew Bacho
11/6/02 05:07:45 PM
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NDA 21-158 (October 4, 2002)

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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Division of Special Pathogen and Immunologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850
FACSIMILE TRANSMISSION

DATE: 12/16/02
TO: Gail Glifort, Regulatory Project Manager
COMPANY: Parexel International
FAX NUMBER: (919)-544-3410
RE: NDA 21,158

FROM: Yon Yu, Regulatory Project Manager
DSPIDP
TELEPHONE: (301) 827-2127
FAX NUMBER: (301) 827-2475
Number of Pages (including cover sheet): 2

MESSAGE: Please see the attached comments for Factive™. If you have questions regarding the comments and would like to schedule a teleconference for additional information, please contact Yon Yu, Project Manager at (301) 827-2127.

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

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NDA 21-158**Comments for the sponsor**

1. Since the changes in the granulation end point parameters are outside the previous parameter range used to manufacture the bio-batch (N99112) and presumably the clinical batches, please provide comparative dissolution profile data between the bio-batch/clinical batch and the batch manufactured after implementing the above mentioned manufacturing changes.
2. Please correct the tablet description and the punch description on page 1 of the submitted batch record PR-1 to reflect change from ' _____
3. We recognize that a _____ similarity factor value supports the claim that the dissolution profiles for the two products are comparable. However, please explain why a minor change in debossing resulted in significant change in the dissolution of the two products.
4. Please clarify if the tablet debossing from ' _____ will be done prior to commercialization of the product or at some later stage in which case the ' _____ debossed product will be commercial product. Please also explain what does _____ stand for?
5. Please confirm if the promotional samples will be in 1-count child-resistant package as requested by the agency earlier in their December 4, 2000 correspondence.
6. You have supplied the artwork and foils configuration for packages of three tablets (_____ unit of use commercial presentation. However, the "How Supplied" labeling section does not include ' _____ packaging presentation. Please indicate if _____ packaging presentation will be commercially available.
7. Please tighten the stability acceptance criterion for ' _____ _____ as requested by the agency in their correspondence dated December 4, 2000.

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/s/

Yon C. Yu
12/16/02 12:56:12 PM
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: January 13, 2003

To: Gail Glifort	From: Yon Yu, Regulatory Project Manager
Company: PAREXEL International	Division of Special Pathogen and Immunologic Drug Products.
Fax number: (919) 544-3410	Fax number: 301- 827-2326
Phone number: (919) 544-3170	Phone number: 301- 827-2127

Subject: Biopharmaceutics comments on NDA 21-158

Total no. of pages including cover: 2

Comments: Please review the following document before submitting the revised protocol.

You may call us for further clarification.

Document to be mailed: YES NO

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Memorandum

TELEPHONE FACSIMILE

Date: January 13, 2003

From: Yon Yu, Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products (HFD-590)

To: Gail Glifort
Senior Regulatory Associate
PAREXEL International

NDA: 21-158 (FACTIVE)

Subject: Comments on NDA 21-158

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The following comments are from our Clinical Pharmacology and Biopharmaceutics reviewers on NDA 21-158.

We would like to request that you please conduct a different data analysis to clarify the relationship between systemic exposure of Gemifloxacin and N-acetyl Gemifloxacin and rash incidence. We would appreciate your prompt response to this request.

According to your study report, rash severity can be categorized as mild (62%), moderate (31%) and severe (7%). You compared systemic exposure of gemifloxacin and its metabolite between rash and no-rash groups. However, an alternative comparison of systemic exposure as a function of the severity of rash may help to understand if the rash incidence is related with the systemic exposure of drug and/or its metabolite. Therefore, please (a) re-group the patients who had rashes according to the severity of rashes, i.e., mild, moderate, and severe; (b) compare the systemic exposure, including AUC and Cmax of gemifloxacin and N-acetyl gemifloxacin in each group; and (c) present re-analyzed data as shown in Tables 39, 40, 41 and Figures 11, 12, and 13 of your submission, e.g., AUC of gemifloxacin in no rash, mild, moderate and severe rash groups.

If you have any questions, please contact Yon Yu, Regulatory Project Manager, at (301) 827-2195.

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/s/

Yon C. Yu
1/13/03 04:14:21 PM
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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Division of Special Pathogen and Immunologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: 1/27/03
TO: Gail Glifort, Senior Regulatory Associate
COMPANY: Parexel International
FAX NUMBER: (919) 544-3410
RE: NDA 21-158

FROM: Yon Yu, Regulatory Project Manager
DSPIDP
TELEPHONE: (301) 827-2127
FAX NUMBER: (301) 827-2326
Number of Pages (including cover sheet): 2

MESSAGE: Please see the attached request of information regarding NDA 21-158 (Factive™). If you have questions, please contact Yon Yu, Project Manager at (301) 827-2127.

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

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NDA 21-158

Request to the Sponsor:

1. To follow up on the discussion of histopathology slides from the teleconference on January 22, 2003, the Agency requests the following histopathology slides of participants from study 344.

Patient #:

344.025.01471

344.030.01420

344.020.00844

344.007.00355

344.016.00756

In addition, please provide the slide of the histopathology report that describes linear basement membrane IgM.

2. There are a number of elevated CPK values in the combined clinical population. We would be interested in seeing the CRFs of these cases. Please provide CRFs of all the patients in Table 10.48 (pp. 273-276) of Safety Update for both gemifloxacin and comparator. In addition, please provide CRFs of the of 2 QT prolongation cases in the clinical pharmacology studies. One is patient # 344.025.01144. The other is a NDA clinical pharmacology subject with a QTc > 500 msec whose patient # is unknown.
3. Please tabulate the number of patients in the combined clinical population with Bilirubin levels > 3.0 mg/dl and ALT > 2xULN and those with Bilirubin > 1.5 mg/dl and ALT > 2xULN for both the gemifloxacin and all com[parator groups.

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this page is the manifestation of the electronic signature.**

/s/

Yon C. Yu
1/27/03 02:05:04 PM
CSO

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**APPEARS THIS WAY
ON ORIGINAL**

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Division of Special Pathogen and Immunologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850
FACSIMILE TRANSMISSION

DATE: 1/27/03
TO: Gail Glifort, Senior Regulatory Associate
COMPANY: Parexel International
FAX NUMBER: (919) 544-3410
RE: NDA 21-158

FROM: Yon Yu, Regulatory Project Manager
DSPIDP
TELEPHONE: (301) 827-2127
FAX NUMBER: (301) 827-2326
Number of Pages (including cover sheet): 3

**APPEARS THIS WAY
ON ORIGINAL**

MESSAGE: Please see the attached comments for NDA 21-158 (Factive™). If you have questions regarding the comments, please contact Yon Yu, Project Manager at (301) 827-2127.

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you

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Changes to the AC Background Package – AECB sections

In section 7.4.2 Eradication of *H. influenzae* (page 63) of the Advisory Committee Background Package there is a discussion of a “prospectively defined analysis” in a subset of patients with *H. influenzae* in study 068. It states:

For each patient the time to bacterial eradication was defined as the time in days to the first day on which there was an outcome of eradication. Eradication was defined as elimination of *H. influenzae* from the repeat sputum culture... The results are shown in Table 22 and Figure 6.

However, table 22 and figure 6 report the rates of persistence over time. This is not the same as the number of eradicated. Since many patients had an observation of unable to determine the results differ greatly.

The following table shows number eradicated and percent eradicated.

Corrected Table 22

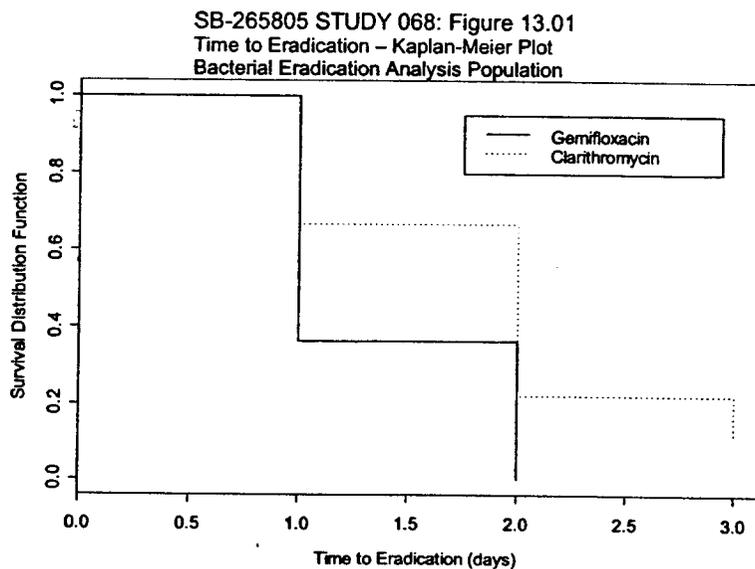
	Gemifloxacin 320 mg PO x 5 days N = 12	Clarithromycin 500 mg bid x 7 days N = 12
Number Eradicated		
Day 1	7 (58%)	3 (25%)
Day 2	11 (92%)	7 (58%)
Day 3	11 (92%)	8 (67%)

1 subject was censored on day 0

1 subject was censored on day 0
1 subject was censored on day 3
2 subjects were censored on day 4

The following figure shows the Kaplan-Meier plot for the time to eradication. It is a copy of figure 13.01 from the original NDA submission.

Corrected Figure 6



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Two analyses were proposed for the *H. Influenzae* eradication data, a comparison of the Day 1 eradication rates and a survival analysis of time to eradication. Note that the comparison of the Day 1 eradication rates did not lead to a statistically significant result ($p=0.21$).

On page 65 of the background package it states that in Study 069 gemifloxacin was studied versus Trovan, "but at twice the dose of trovafloxacin indicated in the U.S. product insert." In the NDA submission it was phrased as

"however, the comparator trovafloxacin dose regimen of 200 mg OD for 5 days was not the same as the approved dose (100 mg OD for 7-10 days) in the US."

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/s/

Yon C. Yu
1/27/03 02:13:45 PM
CSO

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NDA 21-158

**APPEARS THIS WAY
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FACTIVE[®] (gemifloxacin mesylate) 320mg Tablets

Action Date: December 15, 2000

TL: Leissa

MO: Powers, Alivisatos, Cox

CHM: M. Sloan

PCL: Ellis

MIC: Dionne

**APPEARS THIS WAY
ON ORIGINAL**

BPH: Colangelo

STT: Higgins, Dixon, Silliman

RPM: Kimzey

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DEPARTMENT OF HEALTH & HUMAN SERVICES

21-158

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE

Date: December 10, 1999

To: Edward Yuhas, Ph.D.
Associate Director, U.S. Regulatory Affairs
SmithKline Beecham
Phone (215) 751-3836
Fax (215) 751-4926

From: Rene Kimzey *rk*
Regulatory Project Manager, DSPIDP
Phone (301) 827-2196
Fax (301) 827-2326

Subject: Establishment Evaluation Request Summary Report (EES)
NDA 21-158 - Factive (gemifloxacin mesylate) 320 mg tablets

**APPEARS THIS WAY
ON ORIGINAL**

Attached is the inspection request filed for NDA 21-158. Please confirm in writing the following:

- 1) The listed facilities are involved in this application.
- 2) No additional facilities are involved
- 3) The listed responsibilities for each facility are correct.
- 4) The facilities are ready for inspection.

**APPEARS THIS WAY
ON ORIGINAL**

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 21158/000
Stamp: 16-DEC-1999 Regulatory Due: 16-OCT-2000
Applicant: SKB PHARMS
1 FRANKLIN PLAZA
PHILADELPHIA, PA 191017929

Priority: 1S
Action Goal:
Brand Name: FACTIVE(GEMIFLOXACIN MESYLATE)320MG TAB
Established Name:
Generic Name: GEMIFLOXACIN MESYLATE
Dosage Form: TAB (TABLET)
Strength: 320 MG

Org Code: 590
District Goal:

FDA Contacts: L. KIMZEY (HFD-590) 301-827-2196 , Project Manager
M. SLOAN (HFD-520) 301-827-2182 , Review Chemist
N. SCHMUFF (HFD-590) 301-827-2425 , Team Leader

Overall Recommendation:

Establishment:

DMF No:

AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: DRAFT
Milestone Date: 06-JAN-2000

Responsibilities:

Profile: CTL OAI Status: NONE
Last Milestone: DRAFT
Milestone Date: 06-JAN-2000

Establishment:

DMF No:

AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: DRAFT
Milestone Date: 04-JAN-2000

Responsibilities:

Profile: TCM OAI Status: NONE
Last Milestone: DRAFT
Milestone Date: 04-JAN-2000

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: 9614352
SMITHKLINE BEECHAM PHARMACI
THIRD AVENUE
HARLOW, ESSEX, UK CM19 5AW

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: DRAFT
Milestone Date: 04-JAN-2000

Responsibilities: FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE STABILITY
TESTER

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DEC 27 1999

NDA 21-158

SmithKline Beecham Pharmaceuticals
Attention: Edward M. Yuhas, Ph.D.
Associate Director, U.S. Regulatory Affairs
P.O. Box 7929
Philadelphia, PA 19101

APPEARS THIS WAY
ON ORIGINAL

Dear Dr. Yuhas:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Factive (gemifloxacin mesylate) tablet

Therapeutic Classification: Standard (S)

Date of Application: December 15, 1999

Date of Receipt: December 16, 1999

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Our Reference Number: NDA 21-158

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 14, 2000, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 16, 2000, and the secondary user fee goal date will be December 16, 2000.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you

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within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Division Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

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NDA 21-158
Page 3

**APPEARS THIS WAY
ON ORIGINAL**

If you have any questions, please contact Rene Kimzey, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

/S/

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and Immunologic Drug
Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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DEPARTMENT OF HEALTH & HUMAN SERVICES

DIV FIG
21-158

Food and Drug Administration
Rockville MD 20857

JAN 21 2000

NDA 21-158

SmithKline Beecham Pharmaceuticals
Attention: Edward M. Yuhas, Ph.D.
Associate Director, Regulatory Affairs
One Franklin Plaza
Philadelphia, PA 19101

**APPEARS THIS WAY
ON ORIGINAL**

Dear Dr. Yuhas:

Please refer to your new drug application NDA 21-158 for Factive (gemifloxacin mesylate), 320 mg tablet.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you submit an 8-month safety update of your NDA in August, 2000. In light of this submission, the Agency will waive the requirement for a 4-month safety update. Please provide updated information as listed below.

The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

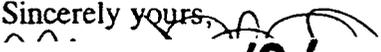
1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.
2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.
3. Details of any significant changes or findings.
4. Summary of worldwide experience on the safety of this drug.
5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.
6. English translations of any approved foreign labeling not previously submitted.
7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

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NDA 21-158
January 18, 2000
Page 2

If you have any questions, please call Rene Kimzey, Regulatory Project Manager, at
(301)827-2127.

Sincerely yours,


/S/

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

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Date: February 8, 2000

To: Edward M. Yuhas, Ph.D.
Associate Director, U. S. Regulatory Affairs
SmithKline Beecham
Phone (215) 751-3868
Fax (215) 751-4926

From: Rene Kimzey *pk*
Regulatory Project Manager
Phone (301) 827-2127

Subject: Fileability of NDA 21-158

**APPEARS THIS WAY
ON ORIGINAL**

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Factive (gemifloxacin mesylate) tablet

Therapeutic Classification: Standard (S)

Date of Application: December 15, 1999

Date of Receipt: December 16, 1999

We have found this application sufficiently complete to permit a substantive review and it will be filed under section 505(b) of the Act on February 14, 2000, in accordance with 21CFR 314.101(a).

If you have any questions, please feel free to contact me at the above numbers.

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ON ORIGINAL**

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MEMORANDUM OF TELEPHONE FACSIMILE

Food and Drug Administration
Rockville MD 20857

Date: February 17, 2000

To: Edward Yuhas, Ph.D.
Associate Director, U.S. Regulatory Affairs
SmithKline Beecham
Phone (215) 751-3836
Fax (215) 751-4926

From: Rene Kimzey *pk*
Regulatory Project Manager, DSPIDP
Phone (301) 827-2196
Fax (301) 827-2326

**APPEARS THIS WAY
ON ORIGINAL**

Subject: NDA 21-158 – Factive (gemifloxacin mesylate) Tablets
Study Report 074 (RSD-100VS9/1): A Meta-Analysis to Investigate the
Effect of Gemifloxacin on QTc Interval in Healthy Volunteers

The Agency is providing the following request for additional analysis from the biopharmaceutics reviewer:

In addition to evaluation of the effect of escalating doses on the QTc interval in the clinical pharmacology studies used for the meta-analysis, please evaluate the effect of the plasma concentrations resulting from escalating doses of gemifloxacin on the QTc interval. More specifically, we request that you perform regression analyses to explore any potential relationship between the plasma concentration of gemifloxacin and the corresponding change in the QTc interval, i.e., both determined at the same time postdose.

We recommend that two regression analyses be performed as follows.

Regression 1: Relationship between Maximum Plasma Concentration (C_{max}) and the Corresponding Change in QTc

In this case, gemifloxacin concentrations (i.e., x-axis) would be either the actual observed C_{max} for each subject or those levels determined at the time closest to the occurrence of the actual C_{max} (i.e., T_{max} generally between 1 and 3 hours). The change in manually read QTc (i.e., y-axis) would be the change from placebo and/or baseline for each subject determined at or nearest to the time of C_{max}.

Regression 2: Relationship between Plasma Concentration Corresponding to the Time of Maximal Change in QTc

In this case, the maximum change in manually read QTc from placebo and/or baseline for each subject determined over the first 12 hours postdose would be regressed against the corresponding

NDA 21-158
February 18, 2000
Page 2

plasma concentration (i.e., x-axis) determined at or nearest to the time of the maximal change in QTc.

NOTE: Regressions 1 and 2 may be the same if the time of maximal change in QTc corresponds to the same time of Cmax.

For each regression analyses, separate regression plots should be constructed for the single and repeat dose studies and the regression results should be displayed/reported (i.e., fitted regression line, regression equation, correlation coefficient, other pertinent statistics). Also, please include the concentration-QTc data resulting from administration of all doses given in these studies, i.e., from 160 mg to 640 mg gemifloxacin. In addition, the plots should distinguish between the concentration-QTc data that are associated with the respective doses, and if possible, there should also be some delineation made to be able to distinguish between the data from the elderly (i.e., from Study 005) and young subjects.

Please feel free to contact me at the above numbers for any questions or concerns.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE

Date: March 7, 2000

To: Edward Yuhas, Ph.D.
Associate Director, U.S. Regulatory Affairs
SmithKline Beecham
Phone (215) 751-3836
Fax (215) 751-4926

From: Rene Kimzey
Regulatory Project Manager, DSPIDP
Phone (301) 827-2196
Fax (301) 827-2326

Subject: NDA 21-158- Factive (gemifloxacin mesylate) Tablet
Chemist's Preliminary Comments on Packaging

**APPEARS THIS WAY
ON ORIGINAL**

Per your request of February 24, 2000, we are providing provisional guidance from the review chemist on packaging for NDA 21-158:

There are no storage condition statements on the Blister. Once it is removed, the storage condition statements contained on the carton may not assure safe and effective use of the product. It would be advisable to add the statements

Please feel free to contact me at the above numbers for any questions.

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1-21-00 F. 1E

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE

Date: April 27, 2000

To: Edward Yuhas, Ph.D.
Associate Director, U.S. Regulatory Affairs
SmithKline Beecham
Phone (215) 751-3836
Fax (215) 751-4926

From: Rene Kimzey *RKC*
Regulatory Project Manager, DSPIDP
Phone (301) 827-2196
Fax (301) 827-2326

**APPEARS THIS WAY
ON ORIGINAL**

Subject: _____
NDA 21-158 (gemifloxacin mesylate) IV

This memorandum is to inform you that following our review of SKB's proposed _____

1) The _____ population studied represents a subset of the larger complicated urinary tract infection (CUTI) population. The Division is concerned that it is difficult to appropriately pre-select _____ patients in an empirically treated disease. Of specific concern, a group of _____

2) Gemifloxacin was not shown to be statistically non-inferior relative to _____

_____ In addition, gemifloxacin pharmacokinetics may explain the inferior efficacy as attributed to its relatively low excretion rate into the urinary tract (30 - 40%) compared to other antimicrobials.

3)

└

_____ In all analyses, _____ demonstrated statistical non-inferiority to the two approved comparators.

4) 

5) The _____, population studied was primarily composed of female subjects, < 65 years of age. Few males were studied. Additionally in a gender analysis of the total CUTI population, _____

If you have any questions, please feel free to contact me at the above numbers.

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NDA 21-158
April 27, 2000
Page 3

CC:

Division file
NDA 21-158
HFD-590/Leissa - *revised 4/28*
HFD-590/Alivisatos - *email 4/27*
HFD-590/Powers
HFD-590/Cox
HFD-590/Sloan
HFD-590/Ellis
HFD-590/Dionne
HFD-725/Dixon
HFD-725/Elashoff
HFD-880/Colangelo
HFD-880/Ajayi
Kumler - Email 4/28
DFS Keywords
Admin-memo

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faxed to sponsor 4/28/00 MC

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ON ORIGINAL**



Date: July 6, 2000

To: Edward M. Yuhas, Ph.D.
Associate Director, U. S. Regulatory Affairs
SmithKline Beecham
Phone (215) 751-3868
Fax (215) 751-4926

From: Rene Kimzey
Regulatory Project Manager
Phone (301) 827-2127

Subject: NDA 21-158 - Results of OPDRA Consults

**APPEARS THIS WAY
ON ORIGINAL**

The Division is providing to the sponsor the following results based on OPDRA's consult:

This OPDRA consult was in response to an April 13, 2000 request, by the Division of Special Pathogen and Immunologic Drug Products, to review the proposed proprietary drug name, Factive, regarding potential name confusion with other proprietary/generic drug names. The container label, the carton labeling, and the package insert were reviewed for possible interventions in minimizing medication errors.

PLEASE NOTE THAT FOR NDAs WITH ACTION DATES BEYOND 90 DAYS OF THIS REVIEW, this name will be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDAs.

LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container label, carton and insert labeling of Factive, OPDRA attempted to focus on safety issues relating to possible medication errors. OPDRA reviewed the current container label, carton labeling, and the package insert and has identified several areas of possible improvement, which might minimize potential user error.

CONTAINER LABEL:

We believe that the established name should be revised to be reflective of the strength of the product. This would be consistent with current USP nomenclature practices. That is, if the tablets contain 320 mg of gemifloxacin freebase then, the established

**APPEARS THIS WAY
ON ORIGINAL**

name should not contain "mesylate." Only if the tablets contain 320 mg of gemifloxacin mesylate should the established name be gemifloxacin mesylate tablets.

Assuming the former to be the case, we recommend the following presentation for the established name:



Note: The "Each tablet contains..." statement will reflect that the product contains the mesylate salt of gemifloxacin.

We recommend relocating the statement, "Rx Only", from the side to the front of the label.

It is unnecessary to state, _____ We recommend deleting this statement and including the following information:

On pages 000009-10, we recommend relocating the strength so that it is not situated immediately above the NDC number. We believe that the location of the strength is best positioned below the established name.

We recommend revising the statement, _____ to read, _____

The strength of the product is missing on the container labels for the bottles containing 30 and 50 tablets. Revise accordingly.

Blister Label (p 000016)

On page 000016, we recommend including the _____ statement, if space permits.

SAMPLE CARTON LABELING (p 000011-4):

We recommend that the established name be printed in letters that are at least half as large as the letters comprising the proprietary name to be in accordance with 21 CFR 201.10 (g) (2).

See comments under CONTAINER LABEL.

CARTON LABELING (p 000005-8):

**APPEARS THIS WAY
ON ORIGINAL**

We recommend revising the statement, " _____ " to read, " _____ "

See comments under CONTAINER LABEL.

RECOMMENDATIONS:

OPDRA does not object to the use of the proprietary name, Factive.

OPDRA recommends the above labeling revisions that might lead to safer use of the product.

For any questions, please feel free to contact me at the above numbers.

**APPEARS THIS WAY
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**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-158
July 6, 2000
Page 4

CC:

Concurrence:

Division Files
NDA 21-158
HFD-590/Leissa
HFD-590/Kimzey
HFD-590/Powers
HFD-590/Alivisatos
HFD-590/Cox
HFD-590/Sloan
HFD-590/Schmuff (for Sloan)

E-mail 7/6/00

E-mail 7/6/00

E-mail 7/6/00

Verbal 7/6/00

DFS Keywords
Admin-memo

Faxed to sponsor 7/6/00

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12 Pages have been redacted in full
from this document

Reason:

_____ b(2) 'low'

_____ b(4) CCI

_____ b(4) TS

_____ b(5) Deliberative Process:

Attorney Client and Attorney Work
Product Privilege

_____ b(6) Personal Privacy

_____ b(7) Law Enforcement Records



DEPARTMENT OF HEALTH & HUMAN SERVICES

D.V. File

Food and Drug Administration
Rockville MD 20857

Date: August 15, 2000

To: Edward M. Yuhas, Ph.D.
Associate Director, U. S. Regulatory Affairs
SmithKline Beecham
Phone (215) 751-3868
Fax (215) 751-4926

From: Rene Kimzey
Regulatory Project Manager
Phone (301) 827-2127

NDA: 21-158 - Factive (gemifloxacin)

Subject: Request for information

References: Telephone Facsimile February 17, 2000
SKB Report of March 7, 2000

**APPEARS THIS WAY
ON ORIGINAL**

Please provide the following data electronically (CD or diskette) for the biopharmaceutics review:

Two additional QTc analyses: (1) Change in QTc vs. Cmax and (2) Maximum Change in QTc vs. Plasma Concentration. Specifically, Appendix B, Listings 1a, 1b, 2a, and 2b from the report dated March 7, 2000 (NDA Amendment BB). The preferred format is EXCEL files or flat ASCII files.

Should you have any question or concerns, please feel free to contact me at the above numbers.

**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-158
August 15, 2000
Page 2

CC:

NDA 21-158
Division Files
HFD-590/Leissa
HFD-590/Kimzey
HFD-880/Colangelo

DFS Keywords
Admin-memo

Faxed to sponsor 8/16

Concurrence:

E-mail 8/16

E-mail 8/16

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ON ORIGINAL**

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

**APPEARS THIS WAY
ON ORIGINAL**

Date: October 4, 2000

To: Edward M. Yuhas, Ph.D.
Associate Director, U. S. Regulatory Affairs
SmithKline Beecham
Phone (215) 751-3868
Fax (215) 751-4926

From: Rene Kimzey
Regulatory Project Manager
Phone (301) 827-2127

NDA: 21-158 - Factive (gemifloxacin) tablet

Subject: Package Label

**APPEARS THIS WAY
ON ORIGINAL**

The Agency has reviewed the submitted packaging and has the following comments:

UNIT of USE CARTONS _____ and OUTER CARTONS (3 Unit of Use Cartons)

1. The agreed proprietary name of this product is Factive not _____ is the most prominent name on the labeling. We discourage the use of a number in conjunction with a proprietary name or in this case the packaging nomenclature because numbers can often be misinterpreted for the strength of the product or total number of tablets to be administered on a prescription or inpatient order.

We note that the "ASHP Guidelines on Preventing Medication Errors in Hospitals", Am J Hosp. Pharm, Vol. 50, Feb 1993, notes that important information such as drug name and strength should have the greatest prominence. Factive should be relocated to appear at the top of the carton and its prominence should be increased. _____ should be relocated and the font size should be reduced to appear less prominent than the proprietary name or deleted altogether.

2. The _____ statement should be revised to include the number of tablets to be administered each day in addition to total number of days of therapy. For example: ? _____

3. A statement should be included to indicate that the unit-dose package is child-resistant.

4. We question the rational of the proposal to market a _____
_____ We are concerned that this proposed packaging configuration may
not be reasonable since _____

CONTAINER (30s)

We recommend the net quantity statement be relocated and unboxed. The location and boxing gives more prominence to this amount than the product strength. Post-marketing experience has demonstrated confusion due to this same approach. The Agency received several medication error reports due to confusion of the net quantity statement and strength.

UNIT DOSE BLISTER

The unit dose tablet is technically misbranded because the product _____

UNIT DOSE CARTON _____

1. See comment 1 under CONTAINER.

2. A statement should be included as to whether or not the unit-dose package is child-resistant. If it is not child-resistant we encourage the inclusion of a statement that if dispensed outpatient, it should be with a child-resistant container. For example:

**APPEARS THIS WAY
ON ORIGINAL**

CC:

Concurrence:

Division File
NDA 21-158
HFD-5990/Leissa
HFD-590/Kimzey
HFD-830/Sloan
HFD-830/Schmuff
HFD-590/Cox
HFD-590/Powers
HFD-590/Alivisatos

10/3 E-mail

10/4 E-mail
10/3 E-mail
10/4 E-mail
10/3 E-mail
10/3 E-mail

DFS Keywords
Admin-Memo

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