APPLICATION NUMBER:
21-158

CHEMISTRY REVIEW(S)
NDA 21-158

Factive (gemifloxacin mesylate) tablets

LG Life Sciences

Ramesh Sood, Ph. D.
Division of Special Pathogen and Immunologic Drug Products, HFD-590.
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Chemistry Review Data Sheet

1. NDA 21-158

2. REVIEW #: 3

3. REVIEW DATE: 16-Jan-2003

4. REVIEWER: Ramesh Sood

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7. NAME & ADDRESS OF APPLICANT:

Name: LG Life Sciences, Ltd.
25th Floor, LG Twin Tower East
20, Yoido-dong, Youngdungpo-gu
Seoul 150-721, Korea.

Representative: Alberto Grignolo
PAREXEL International
195 West Street
Waltham, MA 02451

Telephone: 781-487-9900
8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Factive
   b) Non-Proprietary Name (USAN): gemifloxacin mesylate
   c) Code Name/# (ONDC only): (SB-265805-S, EF03, LB20304a)
   d) Chem. Type/Submission Priority (ONDC only):
      • Chem. Type: 1
      • Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION:

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 320 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note24]:
   _____SPOTS product – Form Completed
   _x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
   (R,S)-7-(3-aminomethyl-4-Z-methoxyimino-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-
   dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid methanesulfonate. C_{14}H_{20}FN_3O_{18}
   CH_3O_2S. 1.5 H_2O; MW: 485.49 (mesylate salt), 389.39 (free base);
   CAS NUMBER: 204519-65-3

---

\[
\text{COOH} \\
\text{H_2CO} \\
\text{N} \\
\text{N} \\
\text{H_2N} \\
\text{N}  \\
\text{CH_3SOH} \\
\text{1.5 H_2O}
\]
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[ ] b(4) TS
[ ] b(5) Deliberative Process; Attorney Client and Attorney Work Product Privilege
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The Chemistry Review for NDA 21-158

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
From the chemistry, manufacturing and controls (CMC) point of view this application is recommended for approval as there are no CMC related issues pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Factive is oral tablets that are formulated in 320 mg strength. The inactive ingredients include crospovidone, hydroxypropyl methyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone and titanium dioxide. The clinical formulation used for the phase III studies is the same as the proposed commercial formulation. The drug is packaged in child-resistant (CR) blisters containing 5 or 7 tablets that will be dispensed to patients.

The CMC comments that included a request to set a _________ limit for the DS and tightening of the _________ in the drug product were sent to the applicant after review #1. The applicant did not address all the comments from this communication in their resubmission. These unaddressed issues and some new issues regarding the comparative dissolution profile of the new batches manufactured after incorporating some
manufacturing changes in their resubmission were sent to the firm after the second cycle. These issues were satisfactorily addressed by the applicant in their final amendment and they have been reviewed in this cycle. The firm and the FDA also agreed on a final

B. Description of How the Drug Product is Intended to be Used

Factive is indicated for the treatment of acute bacterial exacerbation of chronic bronchitis (ABECB) and for community acquired pneumonia (CAP) caused by susceptible strains of designated microorganisms. The daily dose is one tablet a day containing 320 mg equivalent of gemifloxacin present in each tablet. The prescribed treatment is either for 5 or 7 days and, accordingly, the drug is packaged in either a 5-tablet or 7-tablet CR blister pack. The 5 and 7-tablet package is consistent with the dosage duration and is part of the risk management to control the extended use of the drug. A hospital pack of three blister cards each card containing ten tablets will also be supplied for hospital use only. In addition, the professional samples will be packaged as 1 tablet in unit carton. The requested and granted expiration period for the drug is 36-months and this expiration period is supported with adequate real time stability data. The storage conditions on the labels are “Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). See USP Controlled Room Temperature”.

C. Basis for Approvability or Not-Approval Recommendation

The drug product specification negotiation with the firm that resulted in the final acceptance and CMC approval have been summarized in section IIA above. The drug substance and drug product manufacturing facilities LG Chemical Ltd, Ilsan City, Korea, and SB Pharmco Puerto Rico Inc., Puerto Rico, respectively, were found acceptable by the Office of Compliance (OC). The final overall acceptable recommendation was granted by OC on 25th Aug, 2000.

III. Administrative

A. Reviewer’s Signature

B. Endorsement Block

Review Chemist/Ramesh Sood, Ph.D./ ChemistryTeamLeader/ Norman Schmuff, Ph.D./
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REASON:

_____ b(2) 'low'

x b(4) CCI

x b(4) TS

b(5) Deliberative Process; Attorney Client and Attorney Work Product Privilege

_____ b(6) Personal Privacy

_____ b(7) Law Enforcement Records
DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS, HFD 590
Review of Chemistry, Manufacturing and Controls

NDA #: 21-158  CHEM.REVIEW #: 2  REVIEW DATE: 6-Nov-2002
12-Dec-2002

SUBMISSION/TYPEDOCUMENT DATE CDER DATE ASSIGNED DATE
BC 26-JUN-00 27-JUN-00 28-JUN-00
BL 19-OCT-00 20-OCT-00 23-OCT-00
Resubmission1 4-OCT-02 4-OCT-02 10-OCT-02

1Subject of current review.

NAME & ADDRESS OF APPLICANT
Name: LG Life Sciences, Ltd.
25th Floor, LG Twin Tower East
Address: 20, Yoido-dong, Youngdungpo-gu
Seoul 150-721, Korea.

Alberto Grignolo
Representative: PAREXEL International
195 West Street
Waltham, MA 02451

Telephone: 781-487-9900

DRUG PRODUCT NAME
Proprietary: Factive™
Established: gemifloxacin mesylate
Laboratory Code Name: (SB-265805-S, EF03, LB20304a)
Chemical type: 1P

PHARMACOLOGICAL CATEGORY/INDICATION: Antibacterial. Treatment of
infections caused by susceptible strains of designated organisms in acute exacerbation of
chronic bronchitis (AECB) and community acquired pneumonia (CAP).

DOSAGE FORM: Tablets
STRENGTHS: 320 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XX Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOLECULAR WEIGHT
(R,S)-7-(3-aminomethyl-4-Z-methoxyimino-1-pyrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-
1,8-naphthyridine-3-carboxylic acid methanesulfonate
C_{18}H_{20}FN_3O_5CH_4O_3S; 485.49 (mesylate salt) free base;
CAS NUMBER: 204519-65-3

SUPPORTING DOCUMENTS
N/A

RELATED DOCUMENTS
N/A

CONSULTS
N/A

REMARKS/COMMENTS:
This review deals with the resubmission of the original NDA with minor changes. The drug product comments following first review of the original NDA were sent to the sponsor on 12/4/2000. The applicant has addressed some of these comments satisfactorily in this submission. The remaining comments that were not addressed by the applicant in this submission are again being communicated to the applicant with some new comments. The sections that are not dealt in this review were found to be adequate in CMC review #1 by Dr. M. Sloan.

CONCLUSIONS & RECOMMENDATIONS:
Approvable

Some pending CMC issues remain to be resolved. However, there are no outstanding approvability issues. From the CMC viewpoint the application is recommended for approval following satisfactory resolution of the communicated CMC issues.

Ramesh Sood, Ph. D. Review Chemist

Concurrence: Norman Schmuff, Ph.D. Team Leader:

C:\Data\NDA Reviews\Factive_gemifloxacin_21158\21158RV2A.doc
# TABLE OF CONTENTS

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A. **DRUG SUBSTANCE**

The _______ was updated on February 22, 2002. The applicant has included the Index to Revisions and an addendum to the Index to Revisions. The DMF including the 2/22/2002 revision was reviewed by Dr. M. Sloan on April 4, 2002 and found to be adequate for the support of the NDA 21-158 and _______ Any updated information provided in the resubmitted NDA 21-158 is provided in the appropriate sections below. For all other relevant drug substance information please refer to the _______ review dated 4/4/2002.

2. **MANUFACTURER:**

The commercial site of manufacture of gemifloxacin mesylate (sesquihydrate) is:

LG Life Sciences, Ltd. (Formerly known as LG Chem Investment, Ltd.)
Ikseon Factory
601 Yongjei-dong, Ikseon City
Chunbuk-do 570-350
Korea.

**APPEARS THIS WAY ON ORIGINAL**

B. **DRUG PRODUCT**

3. **SPECIFICATIONS & METHODS FOR DRUG PRODUCT COMPONENTS**

   A. **ACTIVE INGREDIENT:**

The received drug substance is tested at the commercial drug product site [SB Pharmco, Puerto Rico, Inc.]. The revised specification given below is to comply with the specification changes made by LG Chem Investment, Ltd. in the DMF. The revised DMF _______ has been found to be adequate by M. Sloan. The specification and methods used for acceptance of the drug substance, gemifloxacin mesylate at SB Pharmco, PR, have been included as SB document number: SB-265805/RSD-100Z85/2 (issue date 1/16/02). If the DS manufacturer states that a particular test is performed periodically, that test shall be done by GSK, Cidra.

**APPEARS THIS WAY ON ORIGINAL**
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REASON:

_____ b(2) 'low'

____ X b(4) CCI

____ X b(4) TS

_____ b(5) Deliberative Process; Attorney Client and Attorney Work Product Privilege

_____ b(6) Personal Privacy

_____ b(7) Law Enforcement Records
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ramesh Sood
12/12/02 10:21:00 AM
CHEMIST

NS has looked at the review and the suggested changes have been made.

Mark Seggel
12/12/02 01:18:27 PM
CHEMIST
for N. Schmuff
NDA 21-158

FACTIVE® (gemifloxacin mesylate) 320mg Tablets

Action Date: December 15, 2000

TL: Leissa
MO: Powers, Alvisatos, Cox
CHM: M. Sloan
PCL: Ellis
MIC: Dionne
BPH: Colangelo
STT: Higgins, Dixon, Silliman
RPM: Kimzey
DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

NDA #: 21-158  CHEM.REVIEW #: 1  REVIEW DATE: 28-AUG-2000

SUBMISSION/TYPEDOCUMENT DATECDER DATEASSIGNED DATE
BC1 26-JUN-00 27-JUN-00 28-JUN-00
BL2 19-OCT-00 20-OCT-00 23-OCT-00

1Amendment to correct Analytical Method No. D-RM G-12B.
2Amendment to revise packaging presentations.

NAME & ADDRESS OF APPLICANT
SmithKline Beecham Pharmaceuticals
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101-7929
(215) 751-3868

CONTACT
Edward M. Yuhas, Ph. D., or Sharon Maglennon,
Associate Director,
U.S. Regulatory Affairs Assistant Director
U.S. Regulatory Affairs
(215) 751-3868 (610) 971-5856

DRUG PRODUCT NAME
Proprietary: Factive
Established: gemifloxacin mesylate
Laboratory Code Name: (SB-265805-S, EF03, LB20304a)
Chemical type: 1 S

PHARMACOLOGICAL CATEGORY/INDICATION:

DOSAGE FORM: Tablets
STRENGTHS: 320 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: ___ XX ___ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT
(R,S)-7-(3-aminomethyl-4-Z-methoxyimino-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid methanesulfonate

\[ \text{C}_{18}\text{H}_{20}\text{FN}_{3}\text{O}_{8}\text{S} \]

CAS NUMBER: 204519-65-3
**SUPPORTING DOCUMENTS**

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**RELATED DOCUMENTS**

IND Information Amendment to include updated stability data (see Comments in Review).

**CONSULTS**

1) The establishment inspections have received an overall acceptable recommendation. A current inspection report is included in the Appendix A. Complete
2) Methods Validations consult have been presented to Philadelphia (transferred to Los Angeles) and San Juan District Laboratories. Results from San Juan are complete and discussed in review.

3) A trademark, packaging and labeling consults were submitted for suitability to OPDRA (Appendix).

4) A microbiology sterility consult of the CMC was not requested.

5) The applicant claims categorical exclusion, and Environmental Assessment was not prepared and no consult requested.

REMARKS/COMMENTS:

The Applicant has submitted data to assure high quality CMC of drug product. However, additional information is requested. The CMC details regarding the drug substance were referenced to the supporting DMF (see Review). The Applicant and DMF Holder have jointly developed the drug substance, therefore pertinent information about the drug substance has been included in this review.

CONCLUSIONS & RECOMMENDATIONS: Approvable

Some pending CMC issues remain to be resolved. However, there are no outstanding approvability issues. From the CMC viewpoint the application is recommended for approval.

Milton J. Sloan, Ph. D. Review Chemist

cc: Org. NDA 21-158
HFD-590/Division File
HFD-590/NSchmuff/Team Leader
HFD-520/Sloan/Chem
HFD-520/Ellis/Pharm
HFD-590/Dionne/Micro
HFD-590/Powers/MO
HFD-590/Dixon/Stat
HFD-590/Colangelo/Biopharm
HFD-590/Kimzey/CSO
HFD-830/C-wChen/ONDCIII/Div.Dir.
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REASON:

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X b(4) CCI

X b(4) TS

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_____ b(6) Personal Privacy

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**Application:** NDA 21158/000
**Stamp:** 16-DEC-1999  Regulatory Due: 04-APR-2003
**Applicant:** LG LIFE
LG TWIN TOWER
150 721
SEOUL, , KS

**Priority:** 1S  
**Org Code:** 590
**Action Goal:**  
**District Goal:** 17-AUG-2000
**Brand Name:** FACTIVE(GEMIFLOXACIN MESYLATE)320MG TAB

**Established Name:**  
**Generic Name:** GEMIFLOXACIN MESYLATE
**Dosage Form:** TAB (TABLET)
**Strength:** 320 MG

**FDA Contacts:**
- L. KIMZEF (HFD-104) 301-827-2350, Project Manager
- M. SLOAN (HFD-520) 301-827-2174, Review Chemist
- N. SCHMUFF (HFD-590) 301-827-2425, Team Leader

---

**Overall Recommendation:**

**ACCEPTABLE on 25-AUG-2000 by EGASM**

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**APPEARS THIS WAY ON ORIGINAL**