

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-158

CHEMISTRY REVIEW(S)

CHEMISTRY REVIEW

Chemistry Review Data Sheet

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ON ORIGINAL

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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ON ORIGINAL



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CHEMISTRY REVIEW



Chemistry Review Data Sheet

VIII. List of chemistry comments..... 17

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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
5. PREVIOUS DOCUMENTS:

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ON ORIGINAL

Previous Documents

Document Date

| | |
|--------------|-------------|
| Original | 15-Dec-1999 |
| BC | 26-Jun-2000 |
| BL | 19-Oct-2000 |
| Resubmission | 4-Oct-2002 |
| IR request | 16-Dec-2002 |

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

| | |
|-----------|-------------|
| Amendment | 30-Dec-2002 |
|-----------|-------------|

7. 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.

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

Telephone: 781-487-9900

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CHEMISTRY REVIEW

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

APPEARS THIS WAY
ON ORIGINAL

- 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

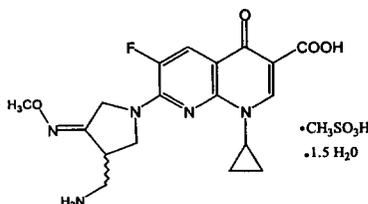
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ON ORIGINAL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note24]: SPOTS product – Form Completed 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. $C_{18}H_{20}FN_5O_{18}$. $CH_4O_3S \cdot 1.5 H_2O$; MW: 485.49 (mesylate salt), 389.39 (free base); CAS NUMBER: 204519-65-3

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ON ORIGINAL

2

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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



CHEMISTRY REVIEW



Chemistry Review Data Sheet

| | | | |
|--------------|-----------------------|------------|--|
| | acceptable | | |
| DMETS | Acceptable | 12/27/2002 | |
| EA | Categorical exclusion | | |
| Microbiology | N/A | | |

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ON ORIGINAL



The Chemistry Review for NDA 21-158

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

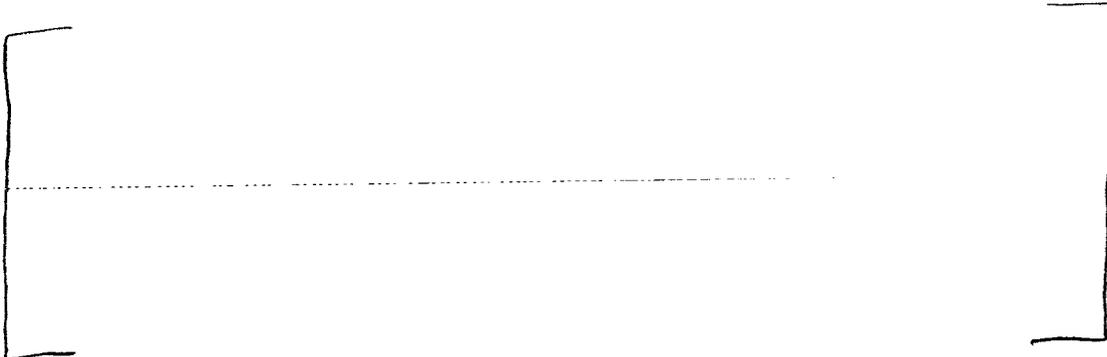
From the chemistry, manufacturing and controls (CMC) point of view this application is recommended for approval as there are no CMC related issues pending.

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



CHEMISTRY REVIEW



Executive Summary Section

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, Iksan 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

**APPEARS THIS WAY
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B. Endorsement Block

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

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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

**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**

| <u>SUBMISSION/TYPE</u> | <u>DOCUMENT DATE</u> | <u>CDER DATE</u> | <u>ASSIGNED DATE</u> |
|---------------------------|----------------------|------------------|----------------------|
| ORIGINAL | 15-DEC-99 | 16-DEC-99 | 20-DEC-99 |
| BC | 26-JUN-00 | 27-JUN-00 | 28-JUN-00 |
| BL | 19-OCT-00 | 20-OCT-00 | 23-OCT-00 |
| Resubmission ¹ | 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.

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

Telephone: 781-487-9900

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

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

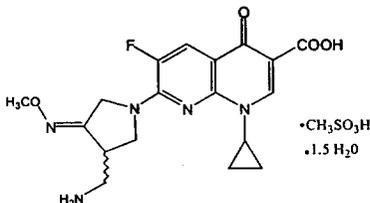
ROUTE OF ADMINISTRATION: Oral

DISPENSED: XX R_x ___ 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

**APPEARS THIS WAY
ON ORIGINAL**



C₁₈H₂₀FN₅O₁₈CH₄O₃S; 485.49 (mesylate salt) free base);
CAS NUMBER: 204519-65-3

SUPPORTING DOCUMENTS

N/A

RELATED DOCUMENTS

N/A

**APPEARS THIS WAY
ON ORIGINAL**

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

**APPEARS THIS WAY
ON ORIGINAL**

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| 3. SYNTHESIS / METHOD OF MANUFACTURE | n/a |
| 4. PROCESS CONTROLS | n/a |
| 5. REFERENCE STANDARD | n/a |
| 6. REGULATORY SPECIFICATIONS / ANALYTICAL METHODS | n/a |
| 7. CONTAINER/CLOSURE SYSTEM FOR DRUG SUBSTANCE STORAGE | n/a |
| 8. DRUG SUBSTANCE STABILITY | n/a |
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| C. INVESTIGATIONAL FORMULATIONS | n/a |
| D. ENVIRONMENTAL ASSESSMENT | n/a |
| E. METHODS VALIDATION | n/a |
| F. LABELING | n/a |
| G. ESTABLISHMENT INSPECTION | n/a |
| H. LIST OF COMMENTS | 10 |

**APPEARS THIS WAY
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A. DRUG SUBSTANCE

Adequate

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:

Adequate

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

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

**APPEARS THIS WAY
ON ORIGINAL**

B. DRUG PRODUCT

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

Adequate

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.

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ON ORIGINAL**

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REASON:

b(2) 'low'

b(4) CCI

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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

**APPEARS THIS WAY
ON ORIGINAL**

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

**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-158

FACTIVE[®] (gemifloxacin mesylate) 320mg Tablets

Action Date: December 15, 2000

TL: Leissa

MO: Powers, Alivisatos, Cox

CHM: M. Sloan

PCL: Ellis

MIC: Dionne

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ON ORIGINAL**

BPH: Colangelo

STT: Higgins, Dixon, Silliman

RPM: Kimzey

**APPEARS THIS WAY
ON ORIGINAL**

**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

| <u>SUBMISSION/TYPE</u> | <u>DOCUMENT DATE</u> | <u>CDER DATE</u> | <u>ASSIGNED DATE</u> |
|------------------------|----------------------|------------------|----------------------|
| ORIGINAL | 15-DEC-99 | 16-DEC-99 | 20-DEC-99 |
| BC ¹ | 26-JUN-00 | 27-JUN-00 | 28-JUN-00 |
| BL ² | 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

DRAFT

CONTACT

Edward M. Yuhas, Ph. D.,
Associate Director,
U.S. Regulatory Affairs
(215) 751-3868

or

Sharon Maglennon,
Assistant Director
U.S. Regulatory Affairs
(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

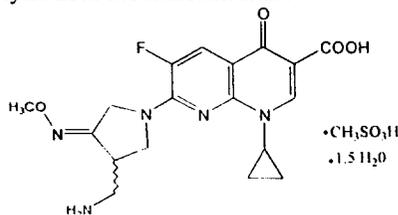
STRENGTHS: 320 mg

ROUTE OF ADMINISTRATION: Oral

DISPENSED: XX R_x ___ 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



C₁₈H₂₀FN₅O₁₈CH₄O₃S; 485.49 (mesylate salt) free base);
CAS NUMBER: 204519-65-3

SUPPORTING DOCUMENTS

| DMF# | Type | Holder | Item/Component | Review Date | LOA | Status |
|------|------|--------|----------------|-------------|-----|--------|
| | | | | | | |

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. **Complete**
- 3) A trademark, packaging and labeling consults were submitted for suitability to OPDRA (Appendix). **Complete**
- 4) A microbiology sterility consult of the CMC was not requested. **N/A**
- 5) The applicant claims categorical exclusion, and Environmental Assessment was not prepared and no consult requested. **N/A**

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.

/S/

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

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

_____ b(6) Personal Privacy

_____ b(7) Law Enforcement Records

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

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
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: 17-AUG-2000

FDA Contacts: L. KIMZEY (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

Establishment: _____
LG CHEMICAL LTD
IKSAN CITY, , KS

DMF No: _____
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 25-AUG-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: []

Establishment: _____
SB PHARMCO PUERTO RICO INC
RD 172 KM 9.1 BO CERTENEJAS
CIDRA, PR 007391975

DMF No: _____
AADA No:

Profile: TCM OAI Status: POTENTIAL OAI
Last Milestone: OC RECOMMENDATION
Milestone Date: 13-MAR-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: []

**APPEARS THIS WAY
ON ORIGINAL**