CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-634/S-015, S-021, S-022
20-635/S-012, S-019, S-020

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

NDA 20-634/S-015,S-021,S-022
NDA 20-635/S-012,S-019,S-020

Labeling, Clinical, Pharmacology and Biopharmaceutics Review of Supplemental Labeling Revisions (SLRs):

Sponsor: RW Johnson

Products: Levaquin® (levofloxacin) Tablets, 250 mg, 500 mg, 750 mg
Levaquin® (levofloxacin) Injection, 5 mg/mL, 25 mg/mL

Materials Reviewed:

NDA 20-634 (Tablets):

SLR	Date submitted	Date received	Date completed
015	March 9, 2000	March 10, 2000	December 13, 2001
021/CBE	August 27, 2001	August 28, 2001	December 13, 2001
022/CBE	October 2, 2001	October 3 , 2001	December 13, 2001
Amendments			
015, 021, 022	December 11, 2001	December 12, 2001	December 13, 2001

NDA 20-635 (Injection):

SLR	Date submitted	Date received	Date completed
012	March 9, 2000	March 10, 2000	December 13, 2001
019/CBE	August 27, 2001	August 28, 2001	December 13, 2001
020/CBE	October 2, 2001	October 3, 2001	December 13, 2001
Amendments			
012, 019, 020	December 11, 2001	December 12, 2001	December 13, 2001

•Approved package insert for NDAs 20-634 and 20-635 dated September 8, 2000
•FDA fax to RW Johnson concerning photo-carcinogenicity and QTc wording dated November 30, 2001

Background:
NDA 20-634 (Levaquin Tablets) and NDA 20-635 (Levaquin Injection) were originally approved on December 20, 1996. The last labeling change occurred on September 8, 2000, when an efficacy supplement adding the skin indication was approved.

Supplement 015 (Tablets) and S-012 (Injection) were submitted for prior approval and provide for the addition of photo-carcinogenicity wording in the **PRECAUTIONS** section, **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection of the Levaquin package insert. Since Dr. Steve Hundley, Pharm/tox reviewer did not agree with the company's proposed wording, a brief telecon was held with the company on November 6, 2001, at which time they were advised that revised wording from FDA would be forthcoming. In an e-mail message dated November 14 , 2001, Dr. Ken Hastings, Pharm/tox Team Leader stated that he agreed with the following wording as proposed by Dr. Hundley:

> "Levofloxacin did not shorten the time to tumor development of UV-induced skin tumors in hairless albino (Skh-1) mice at any levofloxacin dose level and was therefore not photo-carcinogenic under conditions of this study. Dermal levofloxacin concentrations in the hairless mice ranged from 25 to 42 µg/g at the highest levofloxacin dose level (300 mg/kg/day) used in the photo-cocarcinogenicity study. By comparison, dermal levofloxacin concentrations in human subjects receiving 750 mg of levofloxacin (contained in Levaquin® tablets) averaged approximately 11.8 µg/g at Cmax."

The proposed wording noted above was faxed to RW Johnson on November 30, 2001.

Supplement 021 (Tablets) and S-019 (Injection) were submitted as Changes being Effected (CBE) and provide for revisions to the **PRECAUTIONS** and **CLINICAL PHARMACOLOGY** sections of the Levaquin package insert concerning QTc effects. In his intial review of this submission, Dr. Phil Colangelo, Biopharmaceutics Reviewer , disagreed with the company's proposed changes. In an e-mail message dated November 28, 2001, Dr. Colangelo stated the following:

> (1). The proposed wording for the **CLINICAL PHARMACOLOGY,** of the label should be removed because the wording is based on preliminary, not a final analysis, of the data and the study report is not yet final. In addition, the final study report for a second clinical pharmacology study has not been provided.
>
> (2). The proposed wording for the **PRECAUTIONS: General** section of the label is acceptable. That is, it does not diminish the QT prolongation potential for levofloxacin and actually provides greater details of post-marketing events.

Dr. Colangelo also requested that the company submit the finalized study reports as soon as they're ready. The comments noted above and the request for the finalized study reports were faxed to RW Johnson (along with the revised photo-carcinogenicity wording) on November 30, 2001.

Supplement 022 (Tablets) and S-020 (Injection) were submitted as CBE and provide for additional wording to the **WARNINGS** section of the Levaquin package insert concerning tendon rupture and the increased risk in patients receiving concomitant corticosteroids, especially in the elderly. In an e-mail message dated November 27, 2001, Dr. Leonard Sacks, Medical Officer stated that the proposed labeling changes were acceptable.

RW Johnson submitted a revised label including the proposed FDA revisions included in the November 30, 2001 fax on December 11, 2001.

Electronic Labeling Comparison:
The approved package insert dated September 8, 2000 was electronically compared to the proposed package insert dated December 11, 2001. The changes were as follows:

strike through=deleted
double underline=added

1. **WARNINGS**
•A sentence was added to the last paragraph regarding tendon rupture and is now the second sentence as follows:

> " Post-marketing surveillance reports indicate that this risk may be increased in patients receiving concomitant corticosteroids, especially in the elderly."

2. **PRECAUTIONS**
•In the **General** subsection, the following paragraph concerning QTc prolongation was revised to read:

> "Some quinolones, including levofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. During post-marketing surveillance, ~~extremely~~ very rare cases of torsades de pointes have been reported in patients taking levofloxacin. These reports generally involved patients ~~who had other~~ with concurrent medical conditions ~~and the relationship to levofloxacin has not been established. Among drugs known to cause prolongation of the QT interval, the~~ or concomitant medications that may have been contributory. The risk of arrhythmias may be reduced by avoiding ~~use in the presence of~~ concurrent use with other drugs that prolong the QT interval including ~~hypokalemia, significant bradycardia, or concurrent treatment with~~ class Ia or class III antiarrhythmic agents; in addition, use of levofloxacin in the presence of risk factors for torsades de pointes such as hypokalemia, significant bradycardia, and cardiomyopathy should be avoided."

REVIEWER NOTE: Dr. Renata, Albrecht, Acting Division Director requested that the word "very" be deleted before the word "rare" in the second sentence above in order to be consistent with other labeling.

•In the **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection, the following sentences were added to the first paragraph to read:

> "Levofloxacin did not shorten the time to tumor development of UV-induced skin tumors in hairless albino (Skh-1) mice at any levofloxacin dose level and was therefore not photo-carcinogenic under conditions of this study. Dermal levofloxacin concentrations in the hairless mice ranged from 25 to 42 µg/g at the highest levofloxacin dose level (300 mg/kg/day) used in the photo-carcinogenicity study. By comparison, dermal levofloxacin concentrations in human subjects receiving 750 mg of levofloxacin averaged approximately 11.8 µg/g at Cmax."

Conclusions/Recommendations:
These labeling changes are acceptable. An approval letter (with a minor editorial revision to delete the word "rare" in the **Precautions, General** subsection) should be sent advising the applicant that these supplemental NDA submissions are approved.

Robin Anderson, R.N., M.B.A.
Labeling Reviewer

Stephen Hundley, Ph. D.
Pharm/tox Reviewer

Philip Colangelo, Pharm.D., Ph.D.
Biopharmaceutics Reviewer

Leonard Sacks, M. D.
Medical Officer

cc:
HFD-590/MO/l. Sacks
HFD-590/MedicalTL/R. Roca
HFD-590/Pharm/tox/S. Hundley
HFD-590/Pharm/toxTL/K. Hastings
HFD-590/Biopharm/P. Colangelo
HFD-590/BiopharmTL/F. Ajayi
HFD-590/ActingDivDir/R. Albrecht
HFD-590/Y. Kong

Concurrence:
HFD-590/MO/L. Sacks 12/14/01
HFD-590/MedicalTL/R. Roca 12/13/01
HFD-590/Pharm/tox/S. Hundley 12/13/01
HFD-590/Pharm/toxTL/K. Hastings
HFD-590/Biopharm/P. Colangelo 12/17/01
HFD-590/BiopharmTL/F. Ajayi 12/13/01
HFD-590/ActingDivDir/R. Albrecht 12/18/01

DFS keywords:
admin review
class, quinolone
indic bronchitis, ABECB
indic sinusitis
indic UTI, comp
indic UTI, uncomp
indic pneumonia, CAP
indic SSSI, uncomp

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/s/

Robin Anderson
12/18/01 03:52:53 PM
INTERDISCIPLINARY

Renata Albrecht concurred with this review on 12/18/01.

Renata Albrecht
12/18/01 05:34:11 PM
MEDICAL OFFICER

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:	11/30/01	Number of Pages (including cover sheet): 2
TO:	Trish Treichler	
COMPANY:	RW Johnson	
FAX NUMBER:	(908) 429-2783	
MESSAGE:	NDA 20-634/S-015, S-021, S-022	
	NDA 20-635/S-012, S-019, S-020	

Please see reviewer comments attached for the Photo-cocarcinogenicity statement and the QTc wording proposed for the Levaquin package insert.

Please also amend the labeling supplement for tendon rupture, and this will be acted on at the same time. This CBE is acceptable as currently proposed.

If you would like to schedule a teleconference to discuss these comments, please call Yoon Kong, Project Manager.

A revised label (including an electronic copy in WORD and PDF) incorporating these revisions should be submitted to the NDA supplements noted above. We will take action on all of these supplements as soon as the revised label is received by the Agency. Thank you.

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.

FROM: Robin Anderson, R.N., M.B.A.
TITLE: Regulatory Review Officer

THROUGH: Rigo Roca, M.D. 11/30/01
TITLE: Medical Team Leader

TELEPHONE: (302) 537-4340 FAX NUMBER:(302) 537-2208

FDA Labeling Comments
November 30, 2001

Photo-cocarcinogenicity Statement
NDA 20-634/S-015 and NDA 20-635/S-012

RW Johnson Proposed Language:

[redacted]

FDA Recommended Language:
Levofloxacin did not shorten the time to tumor development of UV-induced skin tumors in hairless albino (Skh-1) mice at any levofloxacin dose level and was therefore not photo-carcinogenic under conditions of this study. Dermal levofloxacin concentrations in the hairless mice ranged from 25 to 42 µg/g at the highest levofloxacin dose level (300 mg/kg/day) used in the photo-cocarcinogenicity study. By comparison, dermal levofloxacin concentrations in human subjects receiving 750 mg of levofloxacin (contained in Levaquin® tablets) averaged approximately 11.8 µg/g at Cmax.

QTc Labeling
NDA 20-634/S-020 and NDA 20-635/S-019

1. The proposed wording for the **CLINICAL PHARMACOLOGY,** [redacted] f the label should be removed because the wording is based on preliminary, not a final analysis, of the data and the study report is not yet final. In addition, the final study report for a second clinical pharmacology study has not been provided.

2. The proposed wording for the **PRECAUTIONS: General** section of the label is acceptable.

3. Please submit the following reports to the Levaquin NDAs:

   - The finalized study reports for the 2 Clinical Pharmacology studies that the Agency requested - Study LOFBO-PHI-111 and Study LOFBO-PHI-112. Implicit with saying "the finalized study reports" is the finalized data and the final analyses of the data (No Preliminary Analyses / Data).

   - The "Special Report" that you stated was sent to the Agency on October 6, 2000 entitled "Effects of Levofloxacin on Cardiac Electrical Conduction."

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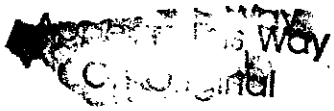
/s/

Robin Anderson
12/5/01 04:43:54 PM
INTERDISCIPLINARY

Rigo Roca concurred with this fax on 11/30/01.

Rigoberto Roca
12/6/01 09:50:00 AM
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-634/S-021
NDA 20-635/S-019

CBE-0 SUPPLEMENT

R.W. Johnson Pharmaceutical Research Institute
Attention: Heather Jordan, MBA
Director, Regulatory Affairs
Route 202, PO Box 300
Raritan, NJ 08869-0602

Dear Ms. Jordan:

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

Name of Drug Product	Levaquin Tablets (levofloxacin tablets), 250 mg and 500 mg	Levaquin Injection (levofloxacin injection), 5 mg/ml and 25 mg/ml
NDA Number	20-634	20-635
Supplement Number	S-021	S-019

Date of Supplements: August 27, 2001

Date of Receipt: August 28, 2001

This supplemental application, submitted as a "Supplement - Changes Being Effected" supplement, proposes:

Strengthening the Precautions section regarding QT_c intervals.

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 October 26, 2001, in accordance with 21 CFR 314.101(a).

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application 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

If you have any questions, call Yoon Kong, Pharm.D., 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

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

/s/

Ellen Frank
9/18/01 10:08:25 AM
NDA 20-634/S-021 and NDA 20-635/S-019