

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-721

CHEMISTRY REVIEW(S)



CHEMISTRY REVIEW



NDA 21-721

LEVAQUIN® (levofloxacin) Oral Solution

Ortho McNeil Pharmaceutical, Inc.

Gene W. Holbert, Ph.D.

**Division of Special Pathogen and
Immunologic Drug Products**



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**APPEARS THIS WAY
ON ORIGINAL**



Chemistry Review Data Sheet

1. NDA 21-721
2. REVIEW #: 1
3. REVIEW DATE: 29-SEP-2004
4. REVIEWER: Gene W. Holbert, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original
BC Amendment

19-DEC-2003
07-JUL-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Address: 920 U.S. Highway 202, P.O. Box 300
Raritan, NJ 08869
Representative: Manisha Padhye, Ph.D.
Telephone: (908) 218-7473

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: LEVAQUIN® Oral Solution
- b) Non-Proprietary Name (USAN): levofloxacin
- c) Code Name/# (ONDC only): RWJ-25213-097
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Antibacterial (Synthetic)



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11. DOSAGE FORM: Solution CODE: 138

12. STRENGTH/POTENCY: 25 mg/mL

13. ROUTE OF ADMINISTRATION: Oral CODE: 001

14. Rx/OTC DISPENSED: Rx OTC

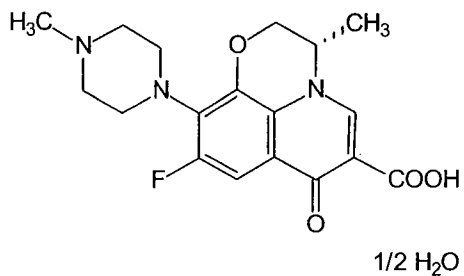
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOLECULAR WEIGHT:

(-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate



Molecular Formula: C₁₈H₂₀FN₃O₄ · 1/2 H₂O Molecular Weight: 370.38
CAS: 138199-71-0



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17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF No.	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
1	IV	[Redacted]	[Redacted]	1	Adequate	1/30/04	
	III			3, 4	Adequate	3/17/03	
	III			3, 4	Adequate	9/29/02	
	III			3, 4	Adequate	9/22/99	
	III			3, 4	Adequate	5/4/00	
	III			3, 4	Adequate	5/27/03	
	III			7			

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	36,627	Levofloxacin tablets
NDA	20-634	Levofloxacin tablets
IND	38,368	Levofloxacin IV
NDA	20-635	Levofloxacin IV



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18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	13-SEP-2004	D'Ambrogio
Pharm/Tox			
Biopharm			
LNC			
Methods Validation			
OPDRA			
EA	FONSI	06-MAY-2004	Zielinski
Microbiology			

**APPEARS THIS WAY
ON ORIGINAL**



Executive Summary Section

The Chemistry Review for NDA 21-721

The Executive Summary**I. Recommendations****A. Recommendation and Conclusion on Approvability**

From the chemistry, manufacturing and controls standpoint, APPROVAL of this application is recommended.

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)**

The drug substance, levofloxacin, is a synthetic broad-spectrum fluoroquinolone antibacterial agent that functions by inhibition of topoisomerase IV and DNA gyrase (type II bacterial topoisomerases). These enzymes are required for DNA replication, transcription, repair and recombination.

LEVAQUIN® (levofloxacin) Tablets (NDA 20-634) and LEVAQUIN® (levofloxacin) Injection are currently approved products for the treatment of complicated and uncomplicated urinary tract infections, acute pyelonephritis, chronic bacterial prostatitis, complicated and uncomplicated skin and skin structure infections, respiratory infections including community-acquired pneumonia (including infections due to penicillin-resistant *Streptococcus pneumoniae*), nosocomial pneumonia, acute maxillary sinusitis and acute bacterial exacerbation of chronic bronchitis. Levofloxacin has been approved for many of these applications in Canada, Mexico and in parts of Asia, Europe and Latin America. LEVAQUIN® (levofloxacin) Oral Solution was developed to provide an oral formulation for those patients for whom tablets or injection are not appropriate dosage forms.

The chemistry, manufacturing and controls information concerning the drug substance is incorporated by cross reference to NDA 20-634 (LEVAQUIN® Tablets) and DMF

The same drug substance is used for the injection, oral solution and tablet formulations, and the analytical methods and acceptance criteria remain the same.

LEVAQUIN® (levofloxacin) Oral Solution, 25 mg/mL, is a clear, yellow to greenish yellow aqueous solution with a pH ranging from 5.0-6.0. It contains the following

**Executive Summary Section**

inactive ingredients: sucrose, glycerin, sucralose, hydrochloric acid, purified water, propylene glycol, artificial and natural flavors, benzyl alcohol, ascorbic acid and caramel color. It may also contain sodium hydroxide for pH adjustment.

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

The usual dose of LEVAQUIN® Oral Solution is 250 (2 tsp), 500 (4 tsp) or 750 mg (6 tsp) administered orally every 24 hours, as indicated by the dosing chart in the Package Insert. The dosage may be adjusted in patients with impaired renal function.

Levofloxacin oral solution should be taken 1 hour before or 2 hours after a meal. Oral doses of levofloxacin should be administered at least two hours after antacids containing any of the following: magnesium, aluminum (includes sucralfate), metal cations such as iron, and multivitamin preparations with zinc or Videx® (didanosine) chewable/buffered tablets

The applicant has proposed an _____ expiration date for the product packaged in _____, and a 24 month expiry date for product supplied in 16-oz bottles when stored at controlled room temperature. The proposed expiration dating is acceptable.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments ultimately provided adequate information on the chemistry, manufacturing and controls for the production of LEVAQUIN® (levofloxacin) Oral Solution. The drug substance specification is identical to that for levofloxacin tablets and injection. For the drug product, the specification is comparable in terms of assay and impurities to the other levofloxacin formulations. Minor deficiencies were identified and the issues were satisfactorily resolved.

As amended, all methods and acceptance criteria were found acceptable for the drug product.

DDMAC has found the labeling to be generally acceptable.

III. Administrative**A. Reviewer's Signature**

Signed electronically

B. Endorsement Block

Gene W. Holbert /Date: 29-SEP-2004

Mark R. Seggel/Date

Susan Peacock/Date

C. CC Block

58 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

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

/s/

Gene Holbert
10/12/04 05:00:31 PM
CHEMIST

Mark Seggel
10/13/04 08:58:59 AM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Responsibilities: FINISHED DOSAGE STERILITY TESTER

Profile : CTL OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 08-JAN-04
 Decision : ACCEPTABLE
 Reason : DISTRICT RECOMMENDATION

 Establishment : CFN : 2650078 FEI : 2650078
 ORTHO PHARMACEUTICALS INC
 BO CAMPO ALEGRE RD NO 2KM 45.6
 MANATI, PR 00674

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER

Profile : LIQ OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 13-SEP-04
 Decision : ACCEPTABLE
 Reason : DISTRICT RECOMMENDATION

TITUSVILLE, NJ 08560

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 07-JAN-04
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 2211100 FEI : 2211100
ORTHO PHARMACEUTICAL CORP
1000 RTE 202
RARITAN, NJ 08869

DMF No:

AADA: