CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-721

CHEMISTRY REVIEW(S)

NDA 21-721

LEVAQUIN® (levofloxacin) Oral Solution

Ortho McNeil Pharmaceutical, Inc.

Gene W. Holbert, Ph.D.

Division of Special Pathogen and Immunologic Drug Products

Table of Contents

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	19-DEC-2003
BC Amendment	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)

11. DOSAGE FORM: Solution CODE: 138

12. STRENGTH/POTENCY: 25 mg/mL

13. ROUTE OF ADMINISTRATION: Oral CODE: 001

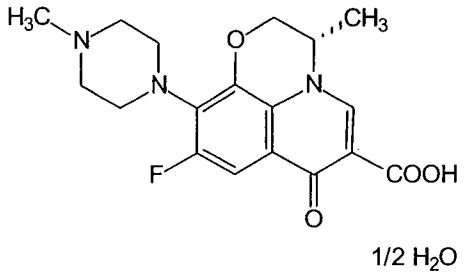
14. Rx/OTC DISPENSED: ✓Rx ___OTC

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-7*H*-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate



Molecular Formula: $C_{18}H_{20}FN_3O_4 \cdot 1/2\ H_2O$ Molecular Weight: 370.38
CAS: 138199-71-0

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF No.	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	IV			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

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 [redacted] 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

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

pplication	: NDA 21721/000	Sponsor:	ORTHO MCNEIL PHARM
Org Code	: 590		1000 RT 202
Priority	: 3S		RARITAN, NJ 08869
Stamp Date	: 22-DEC-2003	Brand Name :	LEVAQUIN(LEVOFLAXIN ORAL
PDUFA Date	: 22-OCT-2004		SOLUTION)25MG/M
Action Goal	:	Estab. Name:	
District Goal:	23-AUG-2004	Generic Name:	LEVOFLOXACIN ORAL SOLUTION
		Dosage Form:	(SOLUTION)
		Strength :	25 MG/ML

FDA Contacts:	S. PEACOCK	Project Manager (HFD-590)	301-827-2173
	G. HOLBERT	Review Chemist (HFD-590)	301-827-2396
	N. SCHMUFF	Team Leader (HFD-590)	301-827-2425

Overall Recommendation: ACCEPTABLE on 13-SEP-2004by J. D AMBROGIO(HFD-322) 301-827-9049

Establishment : CFN : 2650104 FEI : 3002942061

JANSSEN ORTHO LLC

STATE RD 933 KM 0.1 MAMEY WARD

GURABO, PR 00658

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

DRUG SUBSTANCE STERILITY TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 16-MAR-04

Decision : ACCEPTABLE

ason : DISTRICT RECOMMENDATION

Establishment : CFN : 2242843 FEI : 2242843

JANSSEN PHARMACEUTICA INC

1125 TRENTON HARBOURTON RD

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

sponsibilities: 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:

sponsibilities: 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: