

NDA 21-918

Cetraxal[®] Otic Suspension

Laboratorios SALVAT, S.A.

Milton J. Sloan, Ph. D.
Division of Anti-Infective and Ophthalmology Drug
Products

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CHEMISTRY REVIEW

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 21-918
2. REVIEW #: 1
3. REVIEW DATE: Sept 3, 2005
4. REVIEWER: Milton J. Sloan, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	09-JUN-2005
Amendment (BI)	13 JUL-2005
Amendment (BZ)	03-AUG-2005
Amendment (BZ)	25-AUG-2005
Amendment (BZ)	06-SEP-2005
Amendment (BL)	20-MAR-2006
Amendment (BC)	28-MAR-2006

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	09-JUN-2005
Amendment (BZ)	03-AUG-2005
Amendment (BZ)	25-AUG-2005
Amendment (BZ)	06-SEP-2005
Amendment (BL)	20-MAR-2006
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Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Laboratories SALVAT, S. A..
Gall, 30-36
Address: 08950 Espugues de Llobregat
Barcelona, SPAIN
PAREXEL International, PAREXEL Consulting
Representative: 195 West Street
Waltham, MA02451-1163
Telephone: (781) 487-9900

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Cetraxal
b) Non-Proprietary Name (USAN): Ciprofloxacin Otic Solution , 02%
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3 New Formulation
 - Submission Priority: S Standard Review, Substantially equivalent

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 0.2% w/v Ciprofloxacin hydrochloride monohydrate

13. ROUTE OF ADMINISTRATION: Topical otic

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product - Form Completed

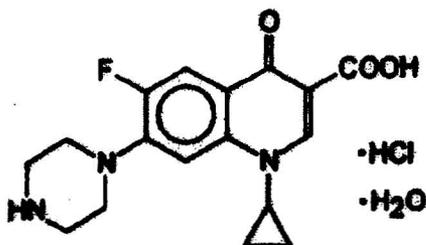
Not a SPOTS product

CHEMISTRY REVIEW

Chemistry Review Data Sheet

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

Ciprofloxacin Hydrochloride (1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperaziny)-3-quinolinecarboxylic acid, monohydrochloride, monohydrate)



Molecular Formula: C₁₇H₁₈FN₃O₃ xHCl xH₂O
Molecular Mass: 385.82

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
1	II	/	/	3	Adequate	March 2, 2006	N/A
	III			3	Adequate	19-Mar-2001	An Information Update was submitted (07-Feb-2006)
	III			3 and 4	Adequate	04-Feb-2000	N/A

b(4)

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")

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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 67,173		Annual Report for Ciprofloxacin Otic Solution

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Acceptable	07-April-2006	Christopher Khedouri
EES	Acceptable EER	09-Aug-2005	S. Adams
Pharm/Tox	Acceptable	07-April-2006	Amy L. Ellis
Biopharm	Acceptable	07-April-2006	Charles Bonapace
LNC	N/A; see ODS review	N/A	N/A
Methods Validation	N/A	N/A	N/A
ODS	See review for recommendations and concerns	10-Jan-2006	Todd Bridges
EA	Claim of Categorical Exclusion	N/A	N/A
Quality Microbiology	N/A	N/A	N/A

19. ORDER OF REVIEW (OGD Only) N/A

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-918

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for an approvable (AE) action from the Chemistry, Manufacturing and Control perspective.

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

II. Summary of Chemistry Assessments

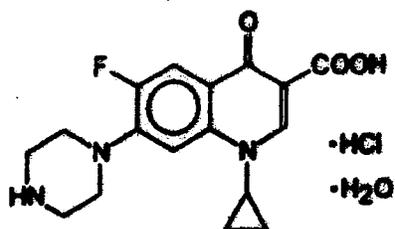
A. Description of the Drug Product(s) and Drug Substance(s)

Ciprofloxacin is a synthetic fluoroquinolone antibiotic with broad-spectrum antibacterial activity. It is a well-characterized compound that is used intravenously, orally, and topically to treat a variety of infections. The primary mode of action of the fluoroquinolones is inhibition of the bacterial gyrase enzyme. Thus, ciprofloxacin inhibits the synthesis of bacterial nucleic acids. The proposed drug product, Ciprofloxacin Otic Solution 0.2% is a sterile, preservative-free solution for otic use. Each single-dose vial of Ciprofloxacin Otic Solution 0.2% delivers 0.25 mL ciprofloxacin hydrochloride equivalent to 0.50 mg of ciprofloxacin in a sterile, preservative-free solution. The inactive ingredients are povidone, glycerin, and water for injection. Sodium hydroxide and/or lactic acid may be added to adjust pH. Ciprofloxacin is available as the monohydrochloride, monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is: $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$, molecular weight is 385.82.

The chemical structure of ciprofloxacin hydrochloride is:

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Executive Summary Section



Ciprofloxacin Otic Solution 0.2% is a sterile, aqueous-based solution manufactured and packaged via _____ manufacturing technology. The drug product is packaged in a low-density polyethylene (LDPE) single-dose vial with a deliverable volume of 0.25 mL. b(4)

All raw materials used to manufacture Ciprofloxacin Otic Solution 0.2% are in accord with USP monographs. Therefore, both the drug substance and the excipients follow the specifications and test methods as outlined in the compendium. The drug product is not compendial; however, some of the same drug substance test methods can be utilized for the drug product.

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

Ciprofloxacin Otic Solution 0.2% is indicated for treatment of acute diffuse otitis externa in adult and pediatric. Ciprofloxacin Otic Solution 0.2% is a sterile otic solution in single unit dose vials proposed for the twice daily treatment of otitis externa (OE). Ciprofloxacin is light-sensitive and the immediate container is _____ of which seven are contained in an aluminum foil overwrap pouch for protection; two pouches are then placed into a carton for distribution _____ 14 for the whole dosage regimen). Each vial delivers one dose of 0.25 mL or approximately 0.50 mg of ciprofloxacin. b(4)

C. Basis for Approvability or Not-Approval Recommendation

Topical formulations containing ciprofloxacin in combination with hydrocortisone and dexamethasone have been approved for the treatment of OE. Otic formulations containing ciprofloxacin alone have been approved outside the U.S. PAREXEL International (PAREXEL) has submitted this NDA for Ciprofloxacin Otic Solution 0.2% on behalf of Laboratorios SALVAT, S.A. in accordance with Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. PAREXEL is acting as the US Agent on behalf of Laboratorios SALVAT, S.A. The NDA uses Cipro[®] HC (ciprofloxacin hydrochloride and hydrocortisone otic suspension) 0.2% as the reference listed drug (RLD). In contrast to the RLD, the proposed drug product consists of a single active ingredient, ciprofloxacin hydrochloride, devoid of any corticosteroid component. The NDA utilizes substantial ciprofloxacin data from published data sources, and a

CHEMISTRY REVIEW

Executive Summary Section

reference to the Agency's determination of the safety and efficacy of ciprofloxacin. SALVAT has completed one clinical study essential to approval to demonstrate safety and efficacy of the proposed drug product. The NDA is presented in the Common Technical Document (CTD) format.

The applicant has demonstrated via CMC data submitted in the application that this new formulation is stable throughout the proposed two year shelf life of the drug product. The manufacturing sites have all been found acceptable with the Office of Compliance. The proposed specifications have been found adequate and suitable for a quality drug product. However, concern over the newly proposed container/closure system exists. The Office of Drug Safety's Division of Medication Errors and Technical Support (DMETS) recommended against the use of the proposed LDPE container. Their concern was that this container would be mistaken for those used for oral inhalation or eye drops. DMETS noted that a number of such errors have already occurred with other products. The review team met to discuss this and a consensus was reached that this is a serious safety concern. The safety concern was communicated to the Sponsor via teleconference on March 7th 2006. Subsequently, PAREXEL International (PAREXEL) on behalf of Laboratorios SALVAT, S.A. has notified the FDA of their intent to alter the container/closure system of their pending NDA. The sponsor acknowledges that the current proposed drug product packaging does not distinguish itself from similar vials used for alternate routes of administration i.e. nebulizer/inhalation dispensers. SALVAT wishes to propose a unique configuration designated for otic vials; however, they have not withdrawn the initial proposed drug product packaging. Given the safety concerns noted, which could result in serious medication errors, an approvable action is recommended.

b(4)

b(4)

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist: Milton J. Sloan, Ph.D.

Date: April 6, 2005

Chemistry Branch Chief: Norman R. Schmuff, Ph.D.

Date:

Project Manager: Susmita Samanta, M.D.

Date:

C. CC:

SamantaS/PM

MoledinaN/MO

SchmuffN/ChmBC

SloanM/Chm

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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

/s/

Milton Sloan

4/6/2006 12:04:51 PM

CHEMIST

Comments have been communicated to sponsor.

Norman Schmuff

4/6/2006 03:50:55 PM

CHEMIST