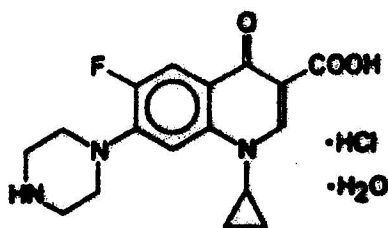


NDA 21-918

**CETRAXAL[®] (ciprofloxacin otic solution),
0.2%**



Laboratorios SALVAT, S.A.

**Division of Anti-Infective and Ophthalmology Drug
Products**

**Milton J. Sloan, Ph. D.
ONDQA Pre-Marketing Assessment Division II Branch IV**

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**CHEMISTRY REVIEW****Chemistry Review Data Sheet**

Chemistry Review Data Sheet

1. NDA 21-918
2. REVIEW #: 2
3. REVIEW DATE: March 17, 2009
4. REVIEWER: Milton J. Sloan, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents**Document Date**

Original	09-JUN-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:**Submission(s) Reviewed****Document Date**

Amendment (AZ)	31-OCT-2008
Amendment (BZ)	10-DEC-2008
Amendment (BZ)	15-JAN-2009
Amendment (BC)	29-JAN-2009
Amendment (BC)	02-MAR-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Laboratories SALVAT, S. A..
	Gall, 30-36
Address:	08950 Esplugues de Llobregat
	Barcelona, SPAIN
	ANSON Group
Representative:	11460 N. Meridian Street, Suite 150
	Carmel, IN 46032
Telephone:	(317) 569-9500

CHEMISTRY REVIEW

Chemistry Review Data Sheet

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

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

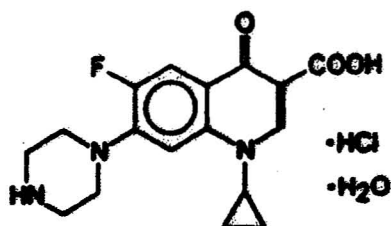
Ciprofloxacin Hydrochloride (1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperaziny)-3-quinolinecarboxylic acid, monohydrochloride, monohydrate)



CHEMISTRY REVIEW



Chemistry Review Data Sheet



Molecular Formula: C₁₇H₁₉FN₃O₃•HCl•H₂O
Molecular Mass: 385.82

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
I	II			3	Adequate	3-Mar-2008	N/A
	III			3	Adequate	24-April-2008	
	III			3 and 4	Adequate		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")

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

**CHEMISTRY REVIEW****Chemistry Review Data Sheet****18. STATUS:****ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Acceptable	07-April-2006	Christopher Khedouri
EES (Resubmitted)	Acceptable EER Pending EER	09-Aug-2005 16-Jan-2008	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	Acceptable Proprietary Name	10-Jan-2006 16-Mar-2009	Todd Bridges Denise Baugh
EA	Claim of Categorical Exclusion- Acceptable	03-Sep-2005 17-Mar-2009	Milton J. Sloan
Quality Microbiology	Pending	20-Nov-2008	Denise Miller

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

The Chemistry Review for NDA 21-918

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is not recommended for an approval action from the Chemistry, Manufacturing and Control perspective. Satisfactory overall acceptable recommendation from Office of Compliance is still pending. Although an overall acceptable recommendation was given on 09-Aug-2005, an updated request for the sites was submitted and completion pending. Response to comments and Quality Micro review is also pending.

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

II. Summary of Chemistry Assessments

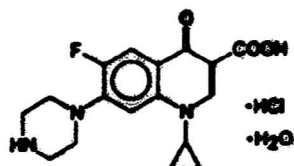
A. Description of the Drug Product(s) and Drug Substance(s)

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 molecular 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:

CHEMISTRY REVIEW

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. The drug product is _____ filtered with a _____ into a _____ system to attain sterility. The packaging is in single-dose units. A preservative is not added to the formulation.

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 14 vials are contained in an aluminum foil overwrap pouch (2 X 7 per pouch = 14 vials for the whole dosage regimen) for protection then placed into a carton for distribution. 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

Laboratorios SALVAT, S.A. (SALVAT) has submitted this NDA for Ciprofloxacin Otic Solution 0.2% in accordance with Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The Anson Group is acting as the US Agent on behalf of Laboratorios SALVAT, S.A. Although the NDA uses Cipro[®] HC (ciprofloxacin hydrochloride and hydrocortisone otic suspension) 0.2% as the reference listed drug (RLD), the proposed drug product consists of a single active ingredient, ciprofloxacin hydrochloride, without a corticosteroid component. The NDA utilizes substantial ciprofloxacin data from published data sources, and a 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.

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Executive Summary Section

On April 6, 2006, FDA issued an approvable letter for this product. The agency requested that the vial configuration be changed to prevent the potential for this product to be mistaken for another drug. Additionally, the sponsor agreed that the _____ be changed to 14-count pouches, because one complete treatment corresponds to 7 days (14 vials). SALVAT now proposes a unique configuration designated for otic vials. Several new batches of product were manufactured and placed on stability in a new vial configuration and package size (14-count), including a physician sample package (2-count pouch). The _____ for both the LDPE vial primary package and the foil over-wrap pouch remains the same as the materials used for the original submission batches. The sponsor states the modified size _____

b(4)

_____ The decreased overall size of the vial parameters, in particular the _____

b(4)

However, the foil pouch has been _____ to accommodate the added vials. The minutes of the September 13, 2006 meeting with SALVAT reflects the discussion of the new vial configuration. The responses provided to sponsor's questions were based on satisfactory stability results for the proposed 24-month drug product shelf life and unrevised labeling as previously submitted. The sponsor at the time, _____

_____ submitted an incomplete resubmission of this NDA (December 18, 2007) with updated stability data to support the proposed shelf life of the new vial drug product package. A transfer of ownership of the NDA back to SALVAT was corresponded to Agency in Oct 10, 2008. SALVAT, provided in this latest resubmission (31-Oct-2008) stability data on three studies (S batches, G batches and, F batches) of the container closure system. The long-term data for each batch submitted extends up to 36, 12, and 3 months respectively. Stability test results contained in two previous submissions for the S batches, G batches have been corrected by the sponsor. These corrections involve the use of a _____

b(4)

_____ Apparently, the previous studies did not take into account the water content of the reference standard and were recalculated using an inaccurate correction factor. Although the sponsor states the corrections to the original calculations do not change the stability conclusions, several comments were recommended to the sponsor. Recommendation for the drug product specification to include water loss, with an acceptance criterion for weight loss of nmt _____ was communicated to the sponsor. SALVAT agreed to include the test but with acceptance criterion at nmt _____. This was found acceptable with adequate justification. SALVAT was also requested to continue the extractable/leachables testing (_____

b(4)

_____ on the finished drug product to the end of expiry at the long-term stability condition for the new package and labeling configuration to confirm that routine monitoring is not necessary. The stability updates that were submitted as requested did not include any monitoring for the new batches. The new revised labeling contains a substantial increase printing. Minimum annual monitoring continues to be recommended to expiry. The sponsor proposes an extended shelf life of 36-months and wider storage conditions (15°C-25°C) for the product based on 36



CHEMISTRY REVIEW



Executive Summary Section

months long-term and 6 months accelerated stability for S batches / _____
18 months long-term and 6 months accelerated stability updated for the G batches (14-
vial per pouch), and 6 months long-term and 6 months accelerated stability updated for
the F batches (14-vial per pouch). A 24-month expiry dating is proposed for the
physician sample configuration package (2-vial per pouch), based on 12 month long-
term and 6 months accelerated stability data for physician sample package
configuration.

b(4)

The manufacturing sites have not all been found acceptable with the Office of
Compliance. Inspection of two sites is ongoing with anticipated satisfactory results.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist: Milton J. Sloan, Ph.D.

Date: March 23, 2009

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

27 Page(s) Withheld

☒ 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
3/23/2009 12:39:12 PM
CHEMIST
Comments for Sponsor

Norman Schmuff
3/26/2009 12:55:25 PM
CHEMIST