CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208251Orig1s000

CHEMISTRY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: Approval

NDA 208251

Drug Name/Dosage Form	OTOVEL Otic Solution (ciprofloxacin and fluocinolone acetonide otic solution)
Strength	0.3%/0.025%
Route of Administration	Otic
Rx/OTC Dispensed	Rx
Applicant	Laboratorios SALVAT S.A.
US agent, if applicable	Linda Hibbs

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	June 30, 2015	All
Quality Amendment	November 10, 2015	All
Quality Amendment	December 17, 2015	Process, Microbiology
Quality Amendment	March 3, 2016	Process
Quality Amendment	March 28, 2016	Drug Product
Quality Amendment	March 31, 2016	Process

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Haripada Sarker	ONDP/NDB1/DNDAPI
Drug Product	Milton Sloan	ONDP/DNDP I/Branch III
Process	Dhana Kasi	OPF/DPA III/Branch VII
Microbiology	Julie Nemecek	OPF/DMA/Branch III
Facility	Vidya Pai	OPF/DIA/Branch III
Biopharmaceutics	Banu Zolnik	ONDP/DBP/Branch I
Environmental Assessment (EA)	Milton Sloan	ONDP/DNDP I/Branch III
Regulatory Business Process Manager	Navi Bhandari	OPRO
Laboratory (OTR)	N/A	N/A
ORA Lead	N/A	N/A
Application Technical Lead	Dorota Matecka	ONDP/DNDP I/Branch III

Table of Contents

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b)(4)	Type II	(b)(4)	API: Ciprofloxacin hydrochloride	Adequate	Last rev dt August 17, 2012 adequate. No further amend.	LoA provided Dt.: 10/6/2014
	Type II		API: Fluocinolone acetonide	Adequate	Last rev dt 05/28/2015 adequate. No further amend	LoA provided Dt.: 10/13/2014
	Type III		(b)(4)	N/A		
	Type III			N/A		

[1] *Adequate, Adequate with Information Request, Deficient, or N/A (there is enough data in the application, therefore the DMF did not need to be reviewed)*

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	107809	

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA, as amended, has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product, ciprofloxacin and fluocinolone acetonide otic solution. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "approve" recommendation was entered into Panorama by the Office of Process and Facilities on March 18, 2016.

Therefore, NDA 208251 is recommended for approval by the Office of Pharmaceutical Quality. Based on the overall stability information submitted in the NDA, 24 months of expiration dating may be granted for the proposed drug product stored at 20°- 25°C (68° - 77°F) excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

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

The following post-marketing commitment (PMC) has been established (the final text and timelines to be finalized and included in the action letter):

Laboratorios SALVAT, S.A., with business address in c/ Gall 30-36, 08950 Esplugues de Llobregat, Barcelona, Spain, will provide tabulated results from the validation batches of Ciprofloxacin 0.3% and Fluocinolone acetonide 0.025% Otic Solution to include actual yields for all unit operations and batch records along with results from all in-process tests.

II. Summary of Quality Assessments

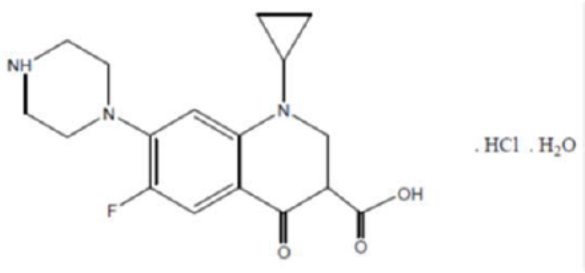
A. Drug Substance Quality Summary

The proposed drug product contains two drug substances, ciprofloxacin hydrochloride and fluocinolone acetonide. The ciprofloxacin hydrochloride drug substance will be supplied by [redacted] (b)(4) (a holder of DMF [redacted] (b)(4), whereas the fluocinolone acetonide will be supplied by [redacted] (b)(4) (a holder of DMF [redacted] (b)(4). Both DMFs were previously reviewed and found to be adequate.

Ciprofloxacin hydrochloride

Chemical Name: 1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid, monohydrochloride, monohydrate

Structure:



Properties:

Physical Description	Appearance: pale yellow to light yellow crystals.
Physical Form	Polymorphism: Ciprofloxacin Hydrochloride does not exist in different polymorphic forms.
Solubility	Water: Sparingly soluble Acetic Acid, Methanol: Slightly soluble Dehydrated alcohol: Very slightly Acetone, Acetonitrile, Ethyl Acetate, Hexane, Methylene chloride: Practically insoluble
Function of pH Variation	pH 3 to 4.5: (b)(4) (Solubility (mg/mL) (b)(4) (Solubility (mg/mL)

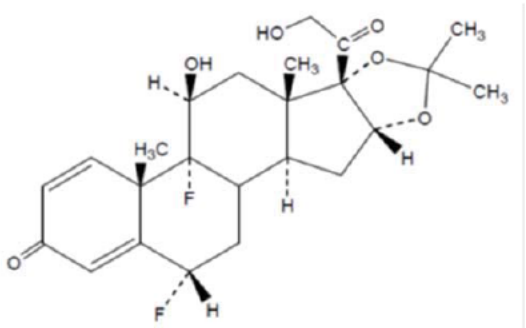
Stability/expiration period:

Ciprofloxacin hydrochloride drug substance has been assigned a retest period of (b)(4) when stored under (b) (4) (b)(4)

Fluocinolone acetonide

Chemical name: Pregna-1,4-diene-3,20-dione,6,9-difluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-(6α,11β,16α)-.

Structure:



General properties:

Physical Description	White to off-white, odorless, crystalline powder.
Physical Form	(b)(4) [redacted]
Solubility	Water: Insoluble Methanol: soluble Ether, chloroform: slightly

Stability/expiration period:

Fluocinolone acetonide drug substance has been assigned a retest period of (b)(4) [redacted], when packaged (b)(4) [redacted]

B. Drug Product [ciprofloxacin and fluocinolone acetonide otic solution] Quality Summary

The drug product proposed via this NDA is an aqueous-based otic solution containing two drug substances, ciprofloxacin hydrochloride and fluocinolone acetonide. (b)(4) [redacted] The drug product container closure system is a low-density polyethylene (LDPE) translucent blue single-dose vial with a deliverable volume of approximately 0.25 mL. The vials (14-count) are contained in an aluminum foil overwrap pouch and a carton box for protection. Each vial contains one dose (0.25 mL solution) of approximately 0.75 mg of ciprofloxacin and 0.0625 mg of fluocinolone acetonide.

The excipients in the proposed formulation include: polysorbate 80, glycerin, povidone K90F, and water for injection. All excipients used in the drug product manufacture are compendial (USP/NF).

The proposed manufacturing process includes the following unit operations:

(b)(4) [redacted]

(b)(4) Several issues with respect to the manufacturing process were identified and communicated to the Applicant via several information requests during the review cycle. While most of the comments were addressed adequately, the issues relating to the low yield of the filling and overall manufacturing process have not been completely addressed. To further demonstrate the robustness of the commercial process, the Applicant has agreed to provide, via a post marketing commitment, the results from the drug product validation batches that will include actual yields for all unit operations and batch records, along with results from all in-process tests.

The application includes comparability protocols for the following proposed changes: (b) (4) Following several revisions to the proposed protocols, the comparability protocols have been found acceptable (as described in the Product Quality Microbiology Assessment section of this review).

The proposed drug product specification includes all quality attributes required for an otic solution such as: appearance, clarity, pH, osmolality, viscosity, assay, identification, impurities/degradation products (ciprofloxacin and fluocinolone acetonide related substances), particulate matter, weight loss, endotoxins, sterility, and uniformity of dosage units. Following recommendations from the Agency, several revisions were made to the analytical procedures, and the proposed drug product specification (tests, acceptance criteria and analytical procedures), as revised, has been found acceptable.

The proposed container closure system (LDPE vial) was evaluated for potential leachables. Leachables were tested on the drug product samples stored under long term and accelerated conditions over time to demonstrate that throughout the proposed expiration period of the drug product, no leachables from the container itself and no inks from the pouch migrate into the drug product solution at levels above the specification limits.

All manufacturing and testing facilities for both drug substances and the drug product were found acceptable in support of this NDA.

Based on the overall stability information provided in the NDA for the drug product, the proposed shelf life of 24 months has been found acceptable. The initially proposed storage conditions statement (b)(4) has been revised to the following recommended statement: "Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature]." In addition, the proposed storage time of 7 days after opening the pouch has also been found acceptable.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	OTOVEL
Non Proprietary Name of the Drug Product	Ciprofloxacin and Fluocinolone Acetonide Otic Solution
Non Proprietary Name of the Drug Substance	Ciprofloxacin and Fluocinolone Acetonide
Proposed Indication(s) including Intended Patient Population	Acute Otitis Media with Tympanostomy Tubes (AOMT) in 6 months and older
Duration of Treatment	7 days
Maximum Daily Dose	0.25 mL solution (0.75 mg ciprofloxacin and 0.0625 mg fluocinolone acetonide) instilled into the affected ear canal twice daily
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Classification:
   - Drug Substance and Drug Product: Not Applicable
2. Biowaivers/Biostudies
   - Biowaiver Requests: Not Applicable
   - PK studies
     The Applicant provided PK sub-study results from clinical studies CIFLOTIII/10IA02 and CIFLOTIII/10I04. The blood samples for PK assessment were collected before the administration of the first dose, on day 1, and within 1 to 2 hours after the last dose on Day 7. The submitted PK data were evaluated by the Office of Clinical Pharmacology.
   - IVIVC: Not Applicable

E. Novel Approaches N/A

F. Any Special Product Quality Labeling Recommendations N/A

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:
This NDA is recommended for approval from the Product Quality perspective.

Dorota Matecka, Ph.D., CMC Lead; Branch III; Division of New Drug Products I

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ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

This 505 (b)(2) NDA submission is for ciprofloxacin, 0.03% and fluocinolone acetonide, 0.025% indicated for the treatment of acute otitis media in patients with tympanostomy tubes (AOMT) [redacted] (b)(4) The proposed drug product is an otic solution. The Applicant conducted [redacted] (b)(4) two phase III trials (CIFLOTIII/10IA02, and CIFLOTIII/10IA04) to assess the efficacy and safety in the treatment of AOMT in pediatric patients aged 6 months and older.

The Applicant provided PK sub-study results from clinical studies CIFLOTIII/10IA02 and CIFLOTIII/10I04. The blood samples for PK assessment were collected before the administration of the first dose, on day 1, and within 1 to 2 hours after the last dose on Day 7. As per the "Memorandum of Understanding between the Division of Biopharmaceutics and the Office of Clinical Pharmacology", the PK data were evaluated by Dr. Dakshina Chilukuri, Clinical Pharmacology Reviewer. For detail information, refer to Dr. Chilukuri's ClinPharm review dated 3/14/16 in DARRTS.

Since the NDA does not include Biopharmaceutics information, this NDA submission does not require further assessment from the OPQ's Division of Biopharmaceutics team.

BIOPHARMACEUTICS OVERALL ASSESSMENT AND SIGNATURES:

Reviewer's Recommendation and Signature:
This 505 (b)(2) NDA submission does not require further assessment from the OPQ's ONDP-Biopharmaceutics team because the proposed drug product is a solution. It is noted that the submitted PK sub-study information was evaluated by OCP.

From a Biopharmaceutics perspective, NDA 208251 for ciprofloxacin, 0.3% and fluocinolone acetonide, 0.025% otic solution is recommended for **APPROVAL**

Banu S. Zolnik, Ph.D. **3/29/2016**
Biopharmaceutics Reviewer
Division of Biopharmaceutics

Secondary/Tertiary Concurrence and Signature:
I concur with Dr. Zolnik's assessment and recommendation.

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Lead (acting)
Division of Biopharmaceutics

Angelica Dorantes, Ph.D. **3/30/2016**
Biopharmaceutics Branch Chief (acting)
Division of Biopharmaceutics

ASSESSMENT OF MICROBIOLOGY

16. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)
MODULE 3.2: BODY OF DATA

P DRUG PRODUCT
P.1 Description of the Composition of the Drug Product
Description of drug product –

Aqueous-based solution, light-sensitive.

Drug product composition –

Ingredient	Content per mL
Ciprofloxacin hydrochloride, USP	(b)(4)
Fluocinolone acetonide, USP	
Polysorbate 80 NF	
Glycerin, USP	
Povidone K90F, USP	
Water for injection, USP	

Description of container closure system –

Component	Description	Manufacturer
Container body/seal	(b)(4)	
Foil		

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Acceptable

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)
MODULE 1

A. PACKAGE INSERT
(b)(4) draft labeling text.pdf)

Storage temperature: (b)(4) °C; Route of administration: otic solution; Container: Single dose

The drug product is not diluted or reconstituted.

Acceptable

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

ANDA: 208251 APPLICANT: Laboratorios SALVAT, S.A

DRUG PRODUCT: (b)(4)

The Division of Microbiology has no additional comments at this time.

Applicant's Response:

Reviewer's Assessment: Acceptable. Julie Nemecek 3/8/2016

2.3.P.7 Container/Closure System

17. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

See response to Question #25.

Applicant's Response:

Reviewer's Assessment: Acceptable. Julie Nemecek 3/8/2016

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

18. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

See response to Question #25.

Applicant's Response:

Reviewer's Assessment: Acceptable. Julie Nemecek 3/8/2016

19. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

See response to Question #25.

Applicant's Response:

Reviewer's Assessment: Acceptable. Julie Nemecek 3/8/2016

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Acceptable. Julie Nemecek, 3/4/2016

Secondary Review Comments and Concurrence:
I concur with Dr. Nemecek's assessment. The NDA is recommended for approval from the perspective of product quality microbiology. John W. Metcalfe, 3/4/2016

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

ENVIRONMENTAL ASSESSMENT

Pursuant to 21 CFR 25.15(d) and 21 CFR 25.31(b), Laboratorios SALVAT, S.A., (SALVAT) hereby requests a categorical exclusion from the requirements of an Environmental Assessment for its product, (b)(4) (ciprofloxacin 0.3% plus fluocinolone acetonide 0.025%) Otic solution. Under 21CFR 25.31(b) a categorical exclusion exists for:

"Action on an NDA, abbreviated application, or a supplement to such applications, or action on an OTC monograph, if the action increases the use of active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1part per billion."

The Agency's approval of the application increases the use of the active moieties (ciprofloxacin and fluocinolone acetonide), but the estimated concentration of the substances at the point of entry into the aquatic environment will be below 1 part per billion (ppb).

The estimated concentration of ciprofloxacin plus fluocinolone acetonide at the point of entry into the aquatic environment has been calculated using the formula provided in the FDA "Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications" dated July 1998. SALVAT certifies that the maximum Expected Introduction Concentration (EIC) from patient use of (b)(4) Otic solution entering into the aquatic environment is less than 1 ppb and is unlikely to have a significant effect on the environment.

The expected introduction concentration of the active moieties into the aquatic environment is provided in Table A-1.

Table A-1 EIC – Aquatic (ppb) = A x B x C x D

where	A = kg/year produced for direct use (as active moiety) B = 1/liters per day entering POTWs* C = year/365 days D = 109 µg/kg (conversion factor)	
* 1.214 x 1011 liters per day entering publicly owned treatment works (POTWs). (*1996 Needs Survey, Report to Congress*)		
PRODUCT	(b)(4)	
# treatments/year	(b) (4)	
#	(b) (4)	
Volume monodose	0.25	
Ciprofloxacin	Monodose Concentration	3
	API (kg/year)	(b) (4)
	EIC (ppb)	
Fluocinolone acetonide	Monodose Concentration	0.25
	API (kg/year)	(b) (4)
	EIC (ppb)	

Applicant's Response:

Reviewer's Assessment:

The applicant requests a categorical exclusion from the requirements of an Environmental Assessment for its product under 21CFR 25.31(b) and has provided an estimated introduction concentration (EIC) calculation of the actives into the environment to show the maximum expected substances will less than 1 ppb. The categorical exclusion is acceptable.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:
The categorical exclusion is acceptable.
Milton J. Sloan, Ph.D.
Branch 3, Division of New Drug Products I
March 29, 2016

Secondary Review Comments and Concurrence: I concur.
Balajee Shanmugam, Ph.D.
Branch Chief (Acting), Branch 3, DNDP 1
3/31/2016

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

For NDA only

Package Insert

(a) "Highlights" Section (21CFR 201.57(a))
(Attach proposed text)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [redacted] safely and effectively. See full prescribing information for [redacted] (ciprofloxacin [redacted] fluocinolone acetonide [redacted] otic solution)

Initial U.S. Approval: <<Insert 4-digit year>>

INDICATIONS AND USAGE

[redacted] a fluoroquinolone [redacted] indicated for the treatment of acute otitis media [redacted] with tympanostomy tubes (AOMT) due to *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa* [redacted] (1)

DOSAGE AND ADMINISTRATION

[redacted] for patients aged 6 months [redacted] (2)

DOSAGE FORMS AND STRENGTHS

[redacted]

CONTRAINDICATIONS

[redacted] is contraindicated in patients with known hypersensitivity to fluocinolone acetonide or other corticosteroids, ciprofloxacin or other quinolones, or to any [redacted] viral infections of the external ear canal, including varicella and herpes simplex infections and fungal otic infections. (4)

WARNINGS AND PRECAUTIONS

- [redacted]
- Hypersensitivity: discontinue at the first appearance of a skin rash or any other sign of hypersensitivity.
- Overgrowth of non-susceptible [redacted] and fungi. (5)

ADVERSE REACTIONS

The most common adverse reaction [redacted]

To report SUSPECTED ADVERSE REACTIONS contact <xxx> at <<number>> or FDA at 1-800-FDA-1088 or ***www.fda.gov/medwatch***.

See 17 for PATIENT COUNSELING INFORMATION

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Yes	Pending revised proprietary name acceptance of Otovel
Dosage form, route of administration	Yes	Acceptable
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	No	Recommend revising see conclusion

Conclusion:

The applicant has proposed several proprietary names, [redacted], and currently Otovel. Otovel has been found acceptable upon review.

The Dosage Forms And Strengths section is recommended for revising:

Otic Solution: Each single-dose vial of OTOVEL (ciprofloxacin 0.3 % and fluocinolone acetonide 0.025 %) delivers 0.25 mL of solution equivalent to ciprofloxacin 0.75 mg and fluocinolone acetonide 0.0625 mg. (3)

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Yes	Otic solution
Strengths: in metric system	Yes	Acceptable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	N/A	Revision recommended; Only dosage form and strength information

Conclusion:
The current nomenclature format provide for the strength to be outside of the established name. For clarity the revised section is consistent with previous labels and regulations.

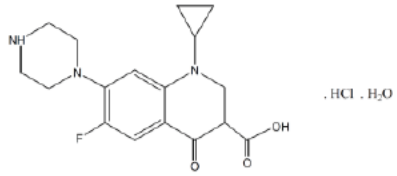
Otic Solution: Each single-dose vial of OTOVEL (ciprofloxacin 0.3 % and fluocinolone acetonide 0.025 %) delivers 0.25 mL of solution equivalent to ciprofloxacin 0.75 mg and fluocinolone acetonide 0.0625 mg.

#11: Description (21CFR 201.57(c)(12))
(Attach proposed text)

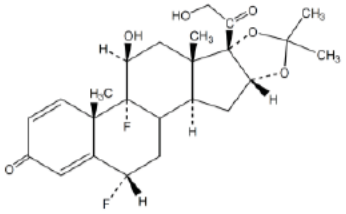
11. DESCRIPTION

(b)(4) (ciprofloxacin (b) (4) fluocinolone acetonide (b) (4) otic solution) is a sterile, preservative-free otic solution containing the (b)(4) antibacterial (b) (4), ciprofloxacin hydrochloride, combined with the anti-inflammatory corticosteroid, fluocinolone acetonide. (b) (4) The inactive ingredients are polysorbate 80, glycerin, povidone K90F and water for injection.

Ciprofloxacin, [redacted] (b) (4) 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 $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$.
The chemical structure of ciprofloxacin hydrochloride is:



[redacted] (b) (4) The chemical name of fluocinolone acetonide is (6α,11β,16α)-6,9-difluoro-11,21-dihydroxy- 16,17[(1-methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione, cyclic 16,17 acetal with acetone[67-73-2]. Its molecular formula is $C_{24}H_{30}F_2O_6$.
The chemical structure of fluocinolone acetonide is:



Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Yes	Acceptable Pending review
Dosage form and route of administration	Yes	Acceptable
Active moiety expression of strength with equivalence statement for salt (if applicable)	Yes	Acceptable
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Yes	Acceptable
Statement of being sterile (if applicable)	Yes	Acceptable
Pharmacological/ therapeutic class	Yes	Revision needed
Chemical name, structural formula, molecular weight	Yes	Acceptable
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	No	Revised statement added

Conclusion:

OTOVEL (ciprofloxacin and fluocinolone acetonide) otic solution, 0.3% / 0.025% is a sterile, preservative-free, clear otic solution containing the fluoroquinolone antimicrobial, ciprofloxacin hydrochloride, combined with the corticosteroid, fluocinolone acetonide.

Each single-dose vial contains a deliverable volume of 0.25 mL solution of ciprofloxacin hydrochloride equivalent 0.75 mg ciprofloxacin and 0.0625 mg fluocinolone acetonide. The pH of the solution ranges from 3.5 to 5.0. The inactive ingredients are polysorbate 80, glycerin, povidone K90F and water for injection.
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 $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$.

The chemical structure of ciprofloxacin hydrochloride is:

Same as provided in PI

The chemical name of fluocinolone acetonide is (6α,11β,16α)-6,9-difluoro-11,21-dihydroxy- 16,17[(1-methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione, cyclic 16,17 acetal with acetone[67-73-2]. Its molecular formula is $C_{24}H_{30}F_2O_6$.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))
(Attach proposed text)

16. HOW SUPPLIED/STORAGE AND HANDLING

(b)(4) is a sterile, preservative-free otic solution supplied in blue translucent (b) (4)-(b) (4) 0.25 mL vials. Fourteen (b) (4) vials are packaged in a protective foil pouch contained in a carton (NDC <<xxx>>).

Do not store (b)(4) Protect from light; store unused vials in pouch and discard 7 days after opening the pouch. Do not open until ready to use.

Discard vials (b)(4) after (b)(4).

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Yes	See comment
Available units (e.g., bottles of 100 tablets)	Yes	Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes	Acceptable
Special handling (e.g., protect from light, do not freeze)	Yes	Acceptable
Storage conditions	Yes	Acceptable

Manufacturer/distributor name listed at the end of PI, following Section #17

(b)(4) is:
Distributed by:

<<xxx>>
<<xxx>>

(b)(4)

(b)(4) is a registered trademark of Laboratorios SALVAT, S.A.

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Yes	Acceptable

Conclusion:

How supplied

OTOVEL (ciprofloxacin and flocinolone acetonide) Otic Solution, 0.3 %/0.025 %, is a sterile, preservative-free, clear otic solution supplied in blue translucent single-dose 0.25 mL vials. Fourteen single-dose vials are packaged in a protective foil pouch contained in a carton (NDC <<xxx>>).

Storage

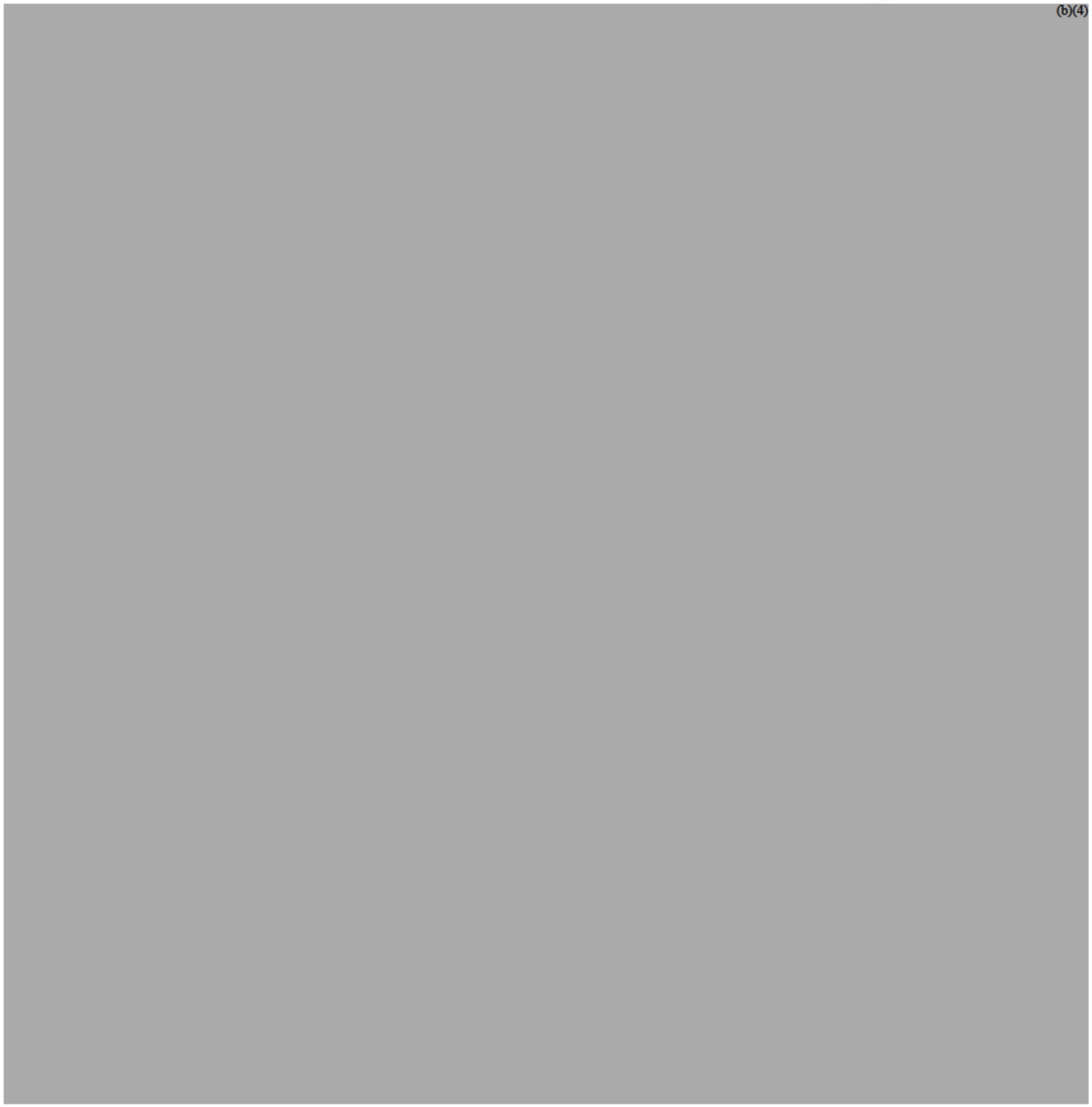
Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature]. Protect from light; store unused vials in pouch and discard 7 days after opening the pouch. Do not open until ready to use.

Discard vial after use.

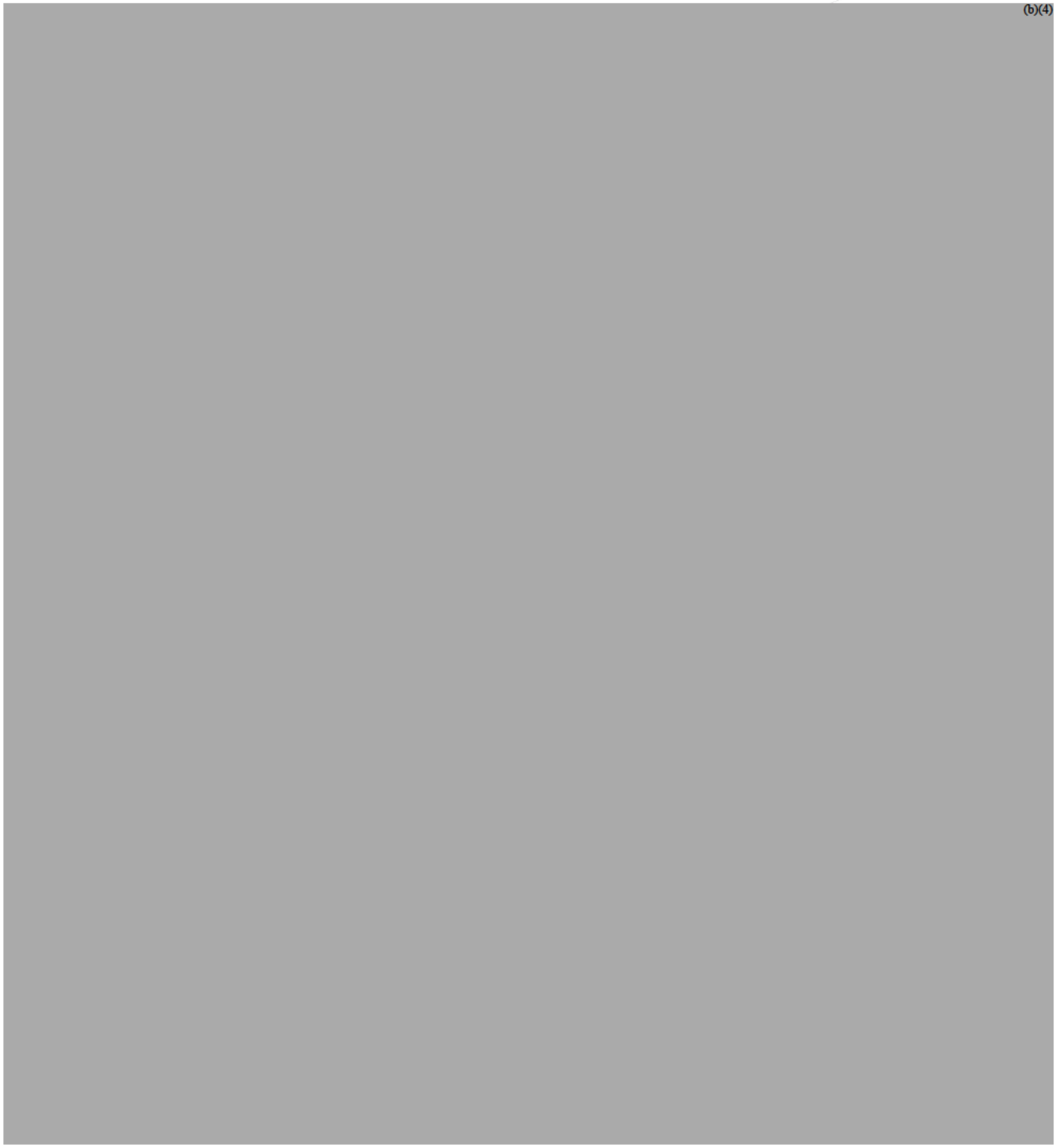
Container and Carton Labeling

Immediate Container Label

(b)(4)



(b)(4)



Carton Label

Reviewer's Assessment:

Ciprofloxacin ~~0.3%~~ and Fluocinolone acetonide ~~0.025%.~~ Otic Solution (b) (4)

14 (b) (4) vials, 0.25 mL each (deliverable volume)

NDC xxxxx-xxx-xx
Sterile **For use in ears only**
Preservative-free
OTOVEL (b)(4)
Ciprofloxacin ~~0.3%~~ and Fluocinolone acetonide ~~0.025%~~ (b) (4)
Otic Solution
FOR USE IN THE EAR ONLY
Ingredients: Each 0.25 mL contains ciprofloxacin hydrochloride equivalent to 0.75 mg of ciprofloxacin and fluocinolone acetonide 0.0625 mg. The inactive ingredients are polysorbate, povidone, glycerin and water for injection.
Instructions for use: See accompanying prescribing information

Store at 20°-25°C (68°-77°F).
Store vials in pouch to protect from light.
Discard vial after use.

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))		Please refer to DMEPA Review
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Yes	
Route of administration 21.CFR 201.100(b)(3))	Yes	
Net contents* (21 CFR 201.51(a))		
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Yes	
Lot number per 21 CFR 201.18	Yes	
Expiration date per 21 CFR 201.17	Yes	
"Rx only" statement per 21 CFR 201.100(b)(1)	Yes	
Storage (not required)	Yes	

NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Yes	
Bar Code per 21 CFR 201.25(c)(2)***	Yes	
Name of manufacturer/distributor (21 CFR 201.1)	Yes	
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion:
Please refer to DMEPA Review of Sevan Kolejian, Pharm. D.

Carton Labeling
(Attach the proposed carton labeling here)

(b)(4)

(b)(4)

FOIL POUCH LAYOUT:

(b)(4)

[redacted]

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))		
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	Yes	

Net contents (21 CFR 201.51(a))	Yes	
Lot number per 21 CFR 201.18	Yes	
Expiration date per 21 CFR 201.17	Yes	
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Yes	
Sterility Information (if applicable)	Yes	
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Yes	
Storage Conditions	Yes	
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	N/A	
Bar Code per 21 CFR 201.25(c)(2)**	Yes	
Name of manufacturer/distributor	Yes	
"See package insert for dosage information" (21 CFR 201.55)	Yes	
"Keep out of reach of children" (optional for Rx, required for OTC)	Yes	
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))		

Conclusion:
Labeling comments have been provided to review team and drafted in SharePoint location. Please refer to DMEPA Review of Sevan Kolejian, Pharm. D.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:
The information is adequate to support approval from drug product perspective. Minor labeling changes/revisions are ongoing.

Milton J. Sloan, Ph.D.
Branch 3, Division of New Drug Products I
March 25,2016

Secondary Review Comments and Concurrence: I concur.
Balajee Shanmugam, Ph.D.
Branch Chief (Acting), Branch 3, DNDP 1
3/31/2016

II. List of Deficiencies To Be Communicated

N/A

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
		H, M, or L		Acceptable or Not Acceptable	
Assay, stability	Formulation, Process parameters Raw materials Container closure	M	Minimum shelf life recommendation based on data provided	Acceptable	Possible out of specification near end of expiry.
Impurities (degradation products)	Adverse Storage conditions	M	Minimum shelf life recommendation based on data provided	Acceptable	Possible out of specification near end of expiry.

Leachables	Changes to container closure (levels may be significant)	L	Study conducted throughout shelf life.	Acceptable	Firm intend to change label. Further study will be needed for acceptability
Sterility	(b) (4)	H	Simulations and interventions conducted during (b) (4) environmental monitoring	Acceptable	
Potency	Manufacturing Process - Filling	M	PMC provided by the Firm	Acceptable	Firm will provide data to support that their manufacturing process is robust.