

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208251Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 208251-1

SUPPL #

HFD # 520

Trade Name Otovel Otic Solution

Generic Name ciprofloxacin 0.3% and fluocinolone acetonide 0.025%

Applicant Name Laboratorios Salvat, SA

Approval Date, If Known April 29, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

c) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21537	Ciprodex Otic Sol
NDA# 20805	Cipro HC Otic Sol
NDA# 21918	Cipro Otic Solution 0.2%
NDA# 207986	Otiprio Otic
NDA# 19857	Cipro (IV) Flexible Bag
NDA# 19847	Cipro IV Injection
NDA # 21473	Cipro XR
NDA# 21554	Cipro XR 1000 mg
NDA # 19537	Cipro Tablets
NDA # 20780	Cipro Oral Suspension
NDA # 12787	Fluocinolone Acetonide
NDA # 19950	Fluocinolone Acetonide
NDA # 201923	Fluocinolone Acetonide
NDA # 21737	Fluocinolone Acetonide
NDA # 19452	Fluocinolone Acetonide
NDA # 13960	Fluocinolone Acetonide
NDA # 20001	Fluocinolone Acetonide
NDA # 15296	Fluocinolone Acetonide
NDA # 21112	Fluocinolone Acetonide; hydroquinone; tretinoin
NDA # 19079	Fluocinolone Acetonide

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

N/A

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

N/A

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

N/A

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

CIFLOTHI/10IA02 - Multicenter randomized double-blind active controlled study in Pediatric Patients with AOMT
CIFLOTHI/10IA04- Multicenter randomized double-blind active controlled study in Pediatric Patients with AOMT

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved

application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

N/A

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

N/A

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

CIFLOTHI/10IA02 - Multicenter randomized double-blind active controlled study in Pediatric Patients with AOMT
CIFLOTHI/10IA04- Multicenter randomized double-blind active controlled study in Pediatric Patients with AOMT

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the

sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # 107809 YES ☒

Investigation #2
IND # 107809 YES ☒

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

N/A

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

N/A

=====

Name of person completing form: Carmen DeBellas, Regulatory Project Manager 4.29.16

Name of Office/Division Director signing form: Sumathi Nambiar, MD, MPH, Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

APPEARS THIS WAY ON ORIGINAL

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

/s/

CARMEN L DEBELLAS
04/29/2016

SUMATHI NAMBIAR
04/29/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208251-1	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Otovel Otic Solution Established/Proper Name: ciprofloxacin 0.3% and fluocinolone acetonide 0.025% Dosage Form: Otic Solution		Applicant: Laboratorios SALVAT, S.A. Agent for Applicant (if applicable): Premier Research
RPM: Carmen DeBellas		Division: Division of Anti-Infective Products
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> - Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. - Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☒ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>April 30, 2016</u>		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		N/A
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
 Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

- | | |
|---|---|
| ☐ Fast Track | ☐ Rx-to-OTC full switch |
| ☐ Rolling Review | ☐ Rx-to-OTC partial switch |
| ☐ Orphan drug designation | ☐ Direct-to-OTC |
| ☐ Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H

- ☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)

Subpart I

- ☐ Approval based on animal studies

- ☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- ☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)

Subpart H

- ☐ Approval based on animal studies

- REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	N/A
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	Approval 4/29/2016
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☒ Included
Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	☐ Medication Guide ☒ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	See Most Recent Draft Labeling Above
Original applicant-proposed labeling	See Original Label Above
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
Most-recent draft labeling	☒ Included
❖ Proprietary Name	Not Acceptable 12/30/2015
Acceptability/non-acceptability letter(s) (indicate date(s))	Acceptable 4/4/2016
Review(s) (indicate date(s))	Not Acceptable 12/28/15
	Acceptable 3/31/2016
❖ Labeling reviews (indicate dates of reviews)	RPM: 8/21/2015 DMEPA: 2/4/2016 & 4/22/2016 DMPP/PLT 3/25/16 OPDP: 4/1/2016 SEALD: None CSS: None Product Quality None Other: None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	8/24/2015
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	4/29/2015
❖ NDAs only: Exclusivity Summary (signed by Division Director)	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
Applicant is on the AIP	☐ Yes ☒ No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

- This application is on the AIP - If yes, Center Director's Exception for Review memo <i>(indicate date)</i> - If yes, OC clearance for approval <i>(indicate date of clearance communication)</i>	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics <i>(approvals only)</i> Date reviewed by PeRC <u>April 27, 2016</u> If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) <i>(include only the completed template(s) and not the meeting minutes)</i>	
CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) <i>(include only the completed template(s) and not the meeting minutes)</i> <i>(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)</i>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) <i>(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)</i>	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	N/A
❖ Minutes of Meetings	
If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	☒ N/A
Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	1/15/2015
EOP2 meeting <i>(indicate date of mtg)</i>	☒ No mtg
Mid-cycle Communication <i>(indicate date of mtg)</i>	☒ N/A
Late-cycle Meeting <i>(indicate date of mtg)</i>	☒ N/A
Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) <i>(indicate dates of mtgs)</i>	N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	☒ None
Division Director Summary Review <i>(indicate date for each review)</i>	4/29/2016
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	4/29/2016
PMR/PMC Development Templates	1 PMC
Clinical	

❖ Clinical Reviews	
• Clinical Team Leader Review(s) (indicate date for each review)	☒ No separate review
• Clinical review(s) (indicate date for each review)	3/15/16 (b) (4) 8/27/15
• Social scientist review(s) (if OTC drug) (indicate date for each review)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☒ and include a review/memo explaining why not (indicate date of review/memo)	See Medical Officer Review Page 13
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review) ⁵	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document (indicate date(s) of submission(s)) • REMS Memo(s) and letter(s) (indicate date(s)) • Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)	☒ None
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	Letter - 3/9/16 Summary 2/12/16
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	☒ No separate review
Clinical Microbiology Review(s) (indicate date for each review)	3/16/16
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (indicate date for each review)	☒ No separate review
Statistical Team Leader Review(s) (indicate date for each review)	☒ No separate review
Statistical Review(s) (indicate date for each review)	4/4/2016
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	☒ No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☒ No separate review
Clinical Pharmacology review(s) (indicate date for each review)	3/14/16
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	☒ None requested

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	☒ No separate review
• Supervisory Review(s) (indicate date for each review)	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	April 1, 2016
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	☒ None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (indicate date for each review)	☒ None
• Secondary review (e.g., Branch Chief) (indicate date for each review)	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (indicate date for each review)	April 1, 2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (indicate date of each review)	N/A
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	See page 120 of the Integrated Quality Assessment
☐ Review & FONSI (indicate date of review)	
☐ Review & Environmental Impact Statement (indicate date of each review)	
❖ Facilities Review/Inspection	
☐ Facilities inspections (action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity (<i>Notify CDER OND IO</i>)
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): <u>Flush List</u> • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☐ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☐ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☐ Done

PeRC Meeting Minutes
April 27, 2016

PeRC Members Attending:

Hari Cheryl Sachs (Acting Chairperson)

Linda Lewis

Meshaun Payne

Dianne Murphy

George Greeley

Gil Burckart

Raquel Tapia

Greg Reaman

Tom Smith

Peter Starke

Raquel Tapia

Michelle Roth-Cline

Wiley Chambers

John Alexander

Kevin Krudys

Ruthie Davi

Gettie Audain

Lily Mulugeta

Shrikant Pagay

Maura O'Leary

Daiva Shetty

Shrikant Pagay

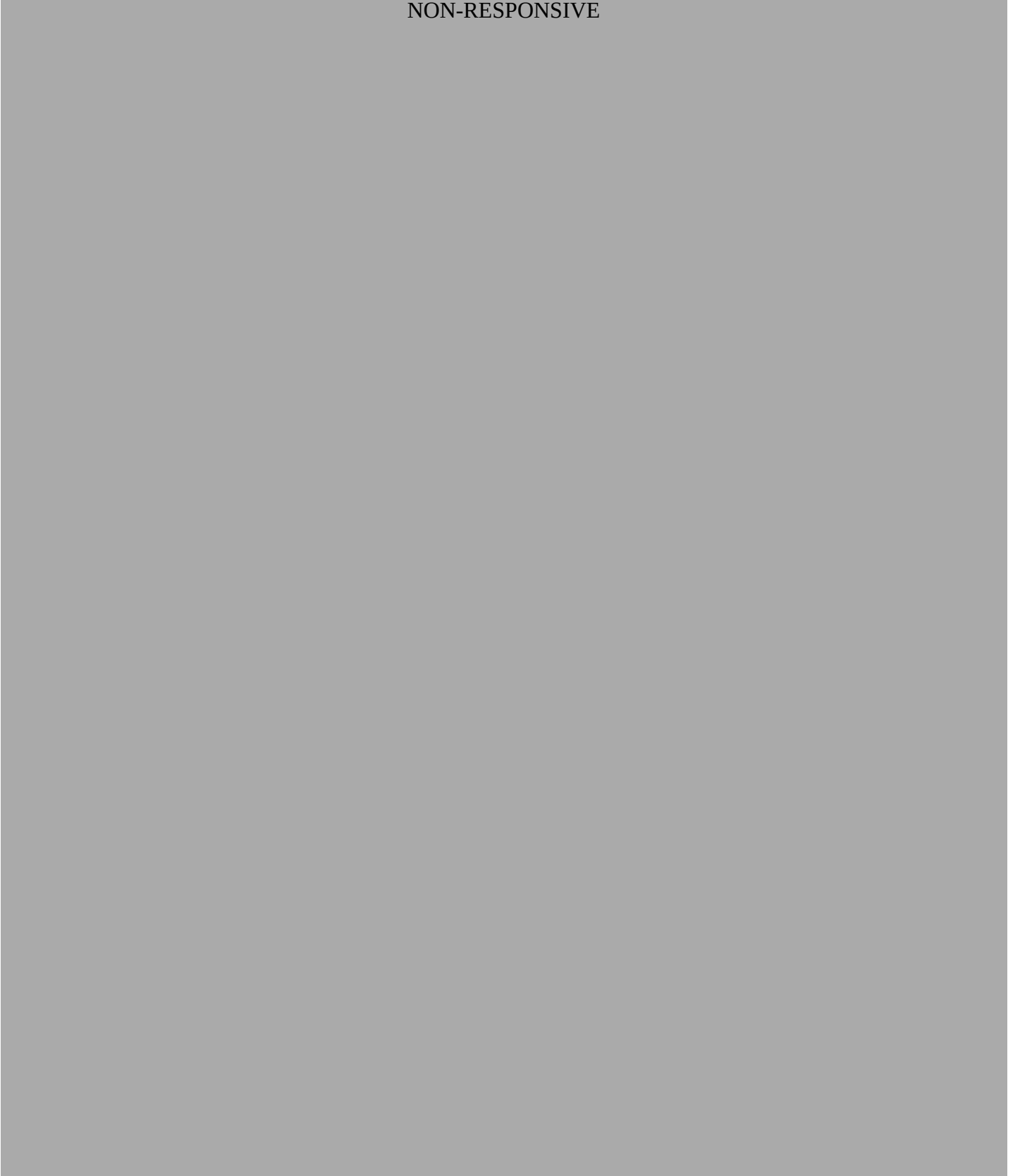
Lily Mulugeta

Maura O'Leary

NON-RESPONSIVE

Agenda

NON-RESPONSIVE



11:20	NDA 208251/01	Otovel (ciprofloxacin 0.3% and fluocinolone acetonide 0.025%) Otic Partial Waiver/Assessment with Agreed iPSP	DAIP	Carmen DeBellas	Treatment of Acute Otitis Media in patients with tympanostomy tubes
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NON-RESPONSIVE

4 Page(s) has been Withheld in Full as NON-RESPONSIVE
immediately following this page

NON-RESPONSIVE

Otovel (ciprofloxacin 0.3% and fluocinolone acetonide 0.025%) Otic Partial Waiver/Assessment with Agreed iPSP

- Proposed Indication: Treatment of Acute Otitis Media in patients with tympanostomy tubes.
- This product triggers PREA as a new indication, new dosage form and new dosing regimen. The PDUFA date is April 30, 2016
- *PeRC Recommendations:*
 - o The PeRC agreed with the division to grant a partial waiver in pediatric patients less than 6 months of age, which is consistent with the agreed iPSP because studies are impossible or highly impracticable
 - o The PeRC agrees with the divisions plan to label the product in patients 6 months and older and has reviewed the assessment.

NON-RESPONSIVE

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

/s/

MESHAUN L PAYNE
05/18/2016

NDA 208251 Information Request 472016.txt

From: Bhandari, Navi
Sent: Thursday, April 07, 2016 7:23 AM
To: Linda Hibbs
Cc: DeBellas, Carmen
Subject: NDA 208251 Information Request 4/7/2016

Good Morning Linda,

My team has the following comments and we ask that you confirm receipt. Please note that we are asking for your agreement on the date for the final report submission (the final agreement will need to be submitted officially to the NDA).

Please indicate (by April 8, 2016) if you agree to the proposed timetable for submission of the final report for the following postmarketing commitment:

POSTMARKETING COMMITMENT

Submit tabulated results from the validation batches of the drug product (ciprofloxacin and fluocinolone acetonide otic solution, 0.3% / 0.025%) including actual yields for all unit operations and batch records along with results from all in-process tests.

Final Report Submission: November 2016

Thank you,

LT Navi Bhandari, Pharm.D, USPHS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
CDER/FDA
240-402-3815

Carton and Container label IR.txt

From: DeBellas, Carmen
Sent: Wednesday, April 06, 2016 11:18 AM
To: Linda Hibbs (Linda.Hibbs@premier-research.com)
Subject: Carton and Container label IR

Hi Linda, Please find the following request

Can you please reach out to the Applicant and see if they can move the manufacture info to the back.

Thus have as follow:

1. Front panel:

Otovel Otic solution
Ciprofloxacin 0.3% &
Fluocinolone 0.025%

2. Back panel:

Lot number

Expiration date

Dist. by Arbor

Thank you, Carmen



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208251

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Laboratorios SALVAT, S.A.
c/o Premier Research
One Park Drive, STE 150
Durham, NC 27709

ATTENTION: Linda Hibbs
Associate Director, Global Regulatory Affairs and Operations

Dear Ms. Hibbs:

Please refer to your New Drug Application (NDA) dated June 30, 2015, received June 30, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ciprofloxacin and Fluocinolone Acetonide Otic Solution, 0.3 %/ 0.025%.

We also refer to your January 29, 2016, correspondence, received January 29, 2016, requesting review of your proposed proprietary name, Otovel.

We have completed our review of the proposed proprietary name, Otovel and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your January 29, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Higgins, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-0330. For any other information regarding this application, contact Carmen DeBellas, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1203.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES

04/04/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208251

INFORMATION REQUEST

Laboratorios SALVAT, S.A.

Attention: Linda Hibbs, Associate Director, Global Regulatory Affairs and Operations, Premier Research
1500 Market Street
STE 3500 West
Philadelphia, PA 19102

Dear Ms. Hibbs:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b)(4) (ciprofloxacin 0.3% and fluocinolone acetonide 0.025%) Otic Solution.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comment:

We acknowledge your batch size for the exhibit (b)(4) and commercial batches (b)(4) are the same. In addition, the following batches were partially filled: exhibit batches G10098, G10099, G10100, Lot 1N95, Lot 2M07 and Lot 3M83. Only one batch was completely filled, 3C30. It was noted the filling yield for batch 3C30 is low and not adequately supported. Further, you have not demonstrated that your manufacturing process is robust. In order to demonstrate the manufacturing process is robust, provide tabulated results from your validation batches including actual yields for all unit operations (e.g., compounding, filtration, filling, packaging, and rejection yields). Include also batch records along with results from all in-process tests. To facilitate first-cycle approval of the NDA, the Agency would consider a proposal to provide this information under a Post-Marketing Commitment (PMC) within a defined time period (assuming the NDA is approved this cycle). Further details and timelines for the PMC proposal will need to be mutually agreed upon in a follow up communication.

We request a prompt written response to the above comment indicating agreement by March 31, 2016, in order to continue our evaluation of your NDA.

In addition, we are providing below the responses to your questions submitted to the Agency via email dated January 19, 2016:

Question1:

1. We would appreciate the opinion of the FDA on the acceptability of the proposed manufacturing strategy of partial filling of the batches for validation and stability.

Agency Response:

Please refer to the comment above regarding the proposed drug product manufacturing process referencing a proposal for a Post-Marketing Commitment (PMC).

Questions 2 and 3:

Additionally, we are considering applying some other changes in the manufacture in the new site; we would appreciate the FDA confirmation of their feasibility and/or acceptability:

2. Batch size: The currently proposed batch size in (b)(4) and the intended batch size in the new manufacturing site will be in a range of (b)(4). We believe this will not be an issue if all the supporting documentation for the new site is submitted with batches of the proposed size, but we would also appreciate confirmation from the FDA on this.
3. Vial labels: The currently proposed labeling of the vial (b)(4) as shown in Figure 1 below. We are considering replacing the (b)(4). We would like to confirm the following:
 - a. Is it acceptable for a prescription product to have the (b)(4) (b)(4)?
 - b. The intention of the sponsor is to launch with product manufactured at (b)(4) but to manufacture always in the new site as soon as it is approved. (b)(4) would be kept as back-up, and product manufactured at both sites would be only on the market for a limited time period. Would it be acceptable to have different label formats approved for the vials manufactured in the different sites?
 - c. The vials are packaged in an aluminum pouch to protect the product from light. Would it be acceptable to replace the (b)(4) in the product manufactured at the currently proposed site (b)(4) without the need to conduct additional stability studies?

Agency Response to Questions 2 and 3:

Please note that the above proposals lack sufficient details to enable an adequate and complete response. We recommend that you consult the Guidance for Industry: Changes to an Approved NDA or ANDA and other applicable guidances available on the FDA website. In addition, once your plans are finalized, you have an option to discuss your proposals with the Agency via a post-NDA action communication (e.g., a Type C meeting request).

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 - 3815.

Sincerely,

Navdeep
Bhandari -S

Digitally signed by Navdeep Bhandari -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2001220182,
cn=Navdeep Bhandari -S
Date: 2016.03.30 11:44:55 -0400

LT Navi Bhandari, Pharm.D, USPHS
Regulatory Health Project Manager
Office of Office of New Drug Quality Assessment
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208251

INFORMATION REQUEST

Laboratorios SALVAT, S.A.

Attention: Linda Hibbs, Associate Director, Global Regulatory Affairs and Operations, Premier Research
1500 Market Street
STE 3500 West
Philadelphia, PA 19102

Dear Ms. Hibbs:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ciprofloxacin 0.3% and fluocinolone acetonide 0.025% otic solution.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by March 29, 2016, in order to continue our evaluation of your NDA.

We note the following errors in the drug product specification (P.5.1) and in the Analytical Procedure (P.5.2) sections. Please revise and submit all relevant sections of the NDA with the correct information:

1. The identity test method for spectrophotometry, USP (b)(4) is incorrect. The correct reference is USP <851>.
2. The RSD of NMT (b)(4)% for sample processing in the Assay of fluocinolone acetonide related substances is likely an error. Please provide the correct value.

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 - 3815.

Sincerely,

Navdeep
Bhandari -S

Digitally signed by Navdeep
Bhandari -S
DN: cn=US, o=U.S. Government,
ou=FDA, ou=FDA, ou=People,
0.9.23.42.19200300.100.1.1=2001220
182, cn=Navdeep Bhandari -S
Date: 2016.03.25 11:39:30 -0400

LT Navi Bhandari, Pharm.D, USPHS
Regulatory Health Project Manager
Office of Office of New Drug Quality Assessment
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208251

INFORMATION REQUEST

Laboratorios SALVAT, S.A.

Attention: Linda Hibbs, Associate Director, Global Regulatory Affairs and Operations, Premier Research
1500 Market Street
STE 3500 West
Philadelphia, PA 19102

Dear Ms. Hibbs:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b)(4) (ciprofloxacin 0.3% and fluocinolone acetonide 0.025%) Otic Solution.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by March 7, 2016, in order to continue our evaluation of your NDA.

1. In regard to the container closure integrity test by (b)(4), please provide the actual results of validation studies (i.e., the total number of vials tested and the results for each vial as well as results for the positive and negative controls).
2. In regard to the environmental monitoring, we acknowledge that the (b)(4) bioburden action limit has been reduced to NMT (b)(4) CFU/mL. The action limit (b)(4) bioburden bulk drug solution (NMT (b)(4) CFU/mL) is excessive. This level of contamination may allow for product contamination (b)(4).
Additionally, bioburden contamination nearing this level (b)(4). We recommend decreasing the (b)(4) bioburden action limit to NMT (b)(4) CFU/mL.

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 - 3815.

Sincerely,

LT Navi Bhandari, Pharm.D, USPHS
Regulatory Health Project Manager
Office of Office of New Drug Quality Assessment
Center for Drug Evaluation and Research



NDA 208251

INFORMATION REQUEST

Laboratorios SALVAT, S.A.

Attention: Linda Hibbs, Associate Director, Global Regulatory Affairs and Operations, Premier Research

1500 Market Street

STE 3500 West

Philadelphia, PA 19102

Dear Ms. Hibbs:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ciprofloxacin 0.3% and fluocinolone acetonide 0.025% otic solution.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by March 10, 2016, in order to continue our evaluation of your NDA.

1. We acknowledge that you have provided test results for appearance, clarity, pH, osmolality, viscosity, ciprofloxacin assay, fluocinolone assay, and related substances to show that the contact equipment is not additive, reactive and/or absorptive. Your study report doesn't contain any information about potential additives from the contact equipment (i.e., extractables, leachables and (b)(4) impurities). Provide supporting information addressing potential extractables, leachables and (b)(4) impurity analysis for your bulk solution contact materials.
2. You have partially filled exhibit batches G10098, G10099, G10100, Lot 1N95, Lot 2M07, Lot 3M83 and completely filled batch 3C30. Your filling yield for batch (3C30) is (b)(4). Provide a detailed rejection yield report for batch number 3C30. Also include the rejection rate for your partially filled batches. Furthermore, include how this relates to your proposed commercial scale process including your anticipated yield during routine commercial manufacturing.
3. You have mentioned that the stirring time of (b)(4) is sufficient for dissolution of fluocinolone acetonide in the (b)(4) medium. This was further supported by the stirring times reported in your executed submission batch records. In order to avoid batch to batch variation please include upper and lower limits for the stirring time of fluocinolone acetonide in (b)(4).

4. You have not included a properly designed stability protocol for your proposed drug product in section P.8.2. Please provide a detailed stability plan including batch size, time points, storage conditions, specification, container storage orientation, sampling plan, etc., to confirm/support the expiration dating period for your proposed drug product.

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 -3815.

Sincerely,

**Navdeep
Bhandari -S**

Digitally signed by Navdeep Bhandari -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2001220182,
cn=Navdeep Bhandari -S
Date: 2016.03.03 14:22:03 -05'00'

LT Navi Bhandari, Pharm.D, USPHS
Regulatory Health Project Manager
Office of Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

From: DeBellas, Carmen
Sent: Friday, February 05, 2016 1:36 PM
To: Linda Hibbs (Linda.Hibbs@premier-research.com)
Subject: NDA 208251 Carton and Container Labeling Recommendations

Hi Linda, Please find Carton and Containing labeling Recommendations.

Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

Reference ID: 3883536

file:///C:/.../DEBELLASC/Downloads/Desktop/NDA%20208251%20Carton%20and%20Container%20Labeling%20Recommendations%20.txt[2/5/2016 1:37:33 PM]

A. Carton labeling

1. On front and back panels, replace the images with large and clearer ear image for clarity of route of administration.
2. On the back panel, remove the duplicative route of statement “For Use in the Ear Only” that appears below the contents statement to reduce clutter since this statement already appears under the figure of the ear.
2. To clarify that each carton has one pouch and to prevent partial dispensing and individual sale of each vial, revise all statements on the back panel appearing after the dosage form statement from  (b) (4) to read “Contents: one foil pouch containing 14 vials, 0.25 mL each (deliverable volume). Vials not for individual sale. Dispense entire carton.”
4. On the front panel, revise the contents statements from “ (b) (4)  (b) (4)” to read “Contents:  (b) (4) 14 vials, 0.25 mL each (deliverable volume)”.
5. Submit NDC numbers assigned for this product.

B. Foil Pouch labeling

1. To clarify that each pouch has 14 vials and to prevent partial dispensing and individual sale of each vial, revise the contents statement to read “Contents: 14 vials, 0.25 mL each (deliverable volume). Vials  (b) (4) not for individual sale.”
2. Add clarifying statement “Date of first opening __/__/__. Discard unused portion 7 days after first opening the pouch.” to prevent the use of the product 7 days after opening the pouch.
3. Replace the images with large and clearer ear image for clarity of route of administration.

C. Container label (vial)

1. Add the established name to the vial label. To accommodate, revise the label according to 21 CFR 201.10(i)(A drug packaged in a container too small or otherwise unable to accommodate a label with sufficient space to bear the information required for compliance with section 502(e)(1) (A)(ii) and (B) of the act shall be exempt from compliance with those clauses: Provided, That: (1) The label bears: (i) The proprietary name of the drug; (ii) The established name, if such there be, of the drug; (iii) An identifying lot or control number; and (iv) The name of the manufacturer, packer, or distributor of the drug; and (2) All the information required to appear on the label by the act and the regulations in this chapter appears on the carton or other outer container or wrapper if such carton, outer container, or wrapper has sufficient space to bear such information, or such complete label information appears on a leaflet with the package). Your proposed container vials has the Proprietary name, dosage form, strength, (b) (4) name, Lot number and expiration date.
2. Clarify the Name of manufacturer. The (b) (4) has the Name of manufacturer noted as (b) (4), however, the labeling on the foil pouch and carton states "Salvat".

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/s/

CARMEN L DEBELLAS
02/05/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208251

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Laboratorios SALVAT, S.A.
c/o Premier Research
One Park Drive
Suite 150
Durham, NC 27709

ATTENTION: Linda Hibbs
Associate Director, Global Regulatory Affairs and Operations

Dear Ms. Hibbs :

Please refer to your New Drug Application (NDA), dated and received, June 30, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ciprofloxacin and Fluocinolone Acetonide Otic Solution , 0.3 %/0.025 %.

We also refer to your correspondence, dated and received, October 14, 2015, requesting review of your proposed proprietary name, (b)(4).

We have completed our review of the proposed proprietary name, (b)(4), and have concluded that this name is unacceptable for the following reasons:

(b)(4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)

¹ Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names, Feb 2010, Available at:

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075068.pdf>

² Institute for Safe Medication Practices. Safety briefs: Ranexa and Prenexa too similar. ISMP Med Saf Alert Community/Ambulatory Care. 2012;11(3):1-4.

³ Institute for Safe Medication Practices. Errors and near misses prompt warning to practitioners and a call to rename CELEBREX. ISMP Med Saf Alert Acute Care. 1999; (7):1.

⁴ Institute for Safe Medication Practices. Safety briefs: Include purpose on Rx. ISMP Med Saf Alert Acute Care. 2011; 16(17):1-2.

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend , Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-5413. For any other information regarding this application, contact Carmen DeBellas, Regulatory Project Manager in the Office of New Drugs, at 301-796-1203.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

IRENE Z CHAN on behalf of TODD D BRIDGES
12/30/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208251

INFORMATION REQUEST

Laboratorios SALVAT, S.A.

Attention: Linda Hibbs, Associate Director, Global Regulatory Affairs and Operations, Premier Research
1500 Market Street
STE 3500 West
Philadelphia, PA 19102

Dear Ms. Hibbs:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b)(4) (ciprofloxacin 0.3% and fluocinolone acetonide 0.025%) Otic Solution.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by December 22, 2015, in order to continue our evaluation of your NDA.

1. (b)(4)
Comment on the stability of the drug product (b)(4) and provide data to show that the drug product is stable at that temperature.
2. According to the Pharmaceutical Development Report 3.2.P.2, Table 5, fluocinolone acetonide (b)(4)
(b)(4) Provide information regarding the container closure and storage conditions used for this study. Also, provide supporting information to explain the (b)(4)
3. Provide compatibility study results to show your bulk solution contact equipment i.e., (b)(4)
(b)(4) used in the manufacturing process is not additive, reactive and/or adsorptive.
4. Provide hold time study results for your exhibit batches and provide the proposed hold time limits for manufacture of your commercial product.
5. Provide actual yield, reconciliation yield, rejection rate for all your manufacturing steps like compounding, filtration, filling and packaging for all the exhibit batches and include yield limit in your commercial batch record.
6. Table 1 for in process tests and control provided on page number 1/2 section P.3.4 includes only fill weight range. Provide target fill weight in addition to the fill weight range. Also provide justification that the volume is sufficient to permit administration of the labeled volume.
7. Your target fill weight provided for the exhibit batches (IN95 : (b)(4) 2M07 : (b)(4)
(b)(4) 3C30 : (b)(4) 3M83 : (b)(4) G10098 : (b)(4)

G10099 : (b)(4) and the commercial batch (fill volume: 0.25 mL) (b)(4)
Provide reason for the (b)(4) for your submission batches.

8. (b)(4) preparation is considered a critical process parameter. You have defined the lower limit (b)(4) as NLT (b)(4) min. Based on your submission batch experience, also provide the upper limit (b)(4)

9. According to the manufacturing process development, (b)(4)
(b)(4)
(b)(4) Please clarify.

10. In regard to the container closure integrity test by (b)(4), please provide the results of validation studies.

11. In regard to the environmental monitoring, we acknowledge that bulk bioburden testing will be performed for the bulk drug product (b)(4)
(b)(4) The action limit for (b)(4) bioburden bulk drug solution (NMT (b)(4) CFU/mL) is excessive. We recommend decreasing the (b)(4) bioburden action limit to a level closer to that (b)(4)
(b)(4) bioburden levels of (b)(4) cfu/mL may allow for product contamination (b)(4)
Additionally, bioburden contamination at this level (b)(4)

Additionally, please confirm that the bulk bioburden testing of the bulk drug product (b)(4)

12. It is stated that the maximum holding period (b)(4) is NMT (b)(4)
The maximum holding periods provided (b)(4)
(b)(4) and the duration of filling (b)(4)
however, exceed the stated (b)(4) limit for the total process. Please clarify the maximum holding period for the following: (b)(4)
(b)(4)

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 - 3815.

Sincerely,

Navdeep
Bhandari -S

Digitally signed by Navdeep Bhandari -S
DN: cn=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2001220182,
cn=Navdeep Bhandari -S
Date: 2015.12.03 10:41:44 -0500

LT Navi Bhandari, Pharm.D, USPHS
Regulatory Health Project Manager
Office of Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

From: [DeBellas, Carmen](#)
To: ["Linda Hibbs \(Linda.Hibbs@premier-research.com\)"](#)
Subject: NDA 208251 Information request
Date: Tuesday, November 17, 2015 7:40:00 AM

Hi Linda,

Please find additional information response.

We have received your response to our IR on November 13, 2015. We note that the following subjects received antibacterials as concomitant, prohibited and rescue medications in the AOMT trials. We assume that concomitant antibacterials would be the sum of prohibited and rescue medications. Please explain the discrepant numbers. Please also clarify if all the subjects who received concomitant antibacterials were counted as failures in the efficacy analysis.

Ciprofloxacin + Fluocinolone N=224 Ciprofloxacin

N=220 Fluocinolone

N=213

Concomitant antibacterials	42 (18.75%)	42 (19.09%)	63 (29.58%)
Prohibited antibacterials	15 (6.7%)	14 (6.4%)	19 (8.9%)
Rescue antibacterials	20 (8.9%)	21 (9.5%)	41 (19.2%)

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
11/17/2015

From: DeBellas, Carmen
Sent: Monday, November 09, 2015 12:03 PM
To: 'Linda Hibbs (Linda.Hibbs@premier-research.com)'
Subject: NDA 208251 Carton and Container request

Hello Linda,

Please provide samples for the vial, foil and carton for (b)(4) Otic Solution. Send them directly to me and not to the document room.

Address

FDA/CDER/OND/OAP/DAIP
Carmen DeBellas
10903 New Hampshire Ave.
Building #22 Room 6232
Silver Spring, MD 20903.

Thanks,
Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
11/09/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208251

INFORMATION REQUEST

Laboratorios SALVAT, S.A.

Attention: Linda Hibbs, Associate Director, Global Regulatory Affairs and Operations, Premier Research
1500 Market Street
STE 3500 West
Philadelphia, PA 19102

Dear Ms. Hibbs:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b)(4) (ciprofloxacin 0.03% plus fluocinolone acetonide 0.025%) otic solution.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by November 10, 2015, in order to continue our evaluation of your NDA.

1. In regard to the container closure integrity validation test, please provide a description of the integrity test method (type of study, controls used, detection method, sensitivity, etc.) and results of testing. Please confirm that the identical container closure system proposed for use in commercial production of the drug product is also used in the container closure integrity validation tests.
2. In regard to the environmental monitoring:
 - a) For the monitoring of surfaces, please clarify the action level for the ISO^{(b)(4)} filling environment.
 - b) For the monitoring of personnel, please clarify the action level and frequency of sampling.
 - c) For the monitoring of WFI, please clarify the action level, frequency of sampling, and sampling sites.
 - d) The bioburden action limit for the bulk drug solution (NMT (b)(4) CFU/mL) is excessive. (b)(4) level of contamination may allow for product contamination (b)(4). Additionally, bioburden contamination nearing this level (b)(4). Please review the bioburden action limit, keeping in mind that the level should be based on historical knowledge of the manufacturing process.
 - e) Provide a commitment to conduct bulk drug solution bioburden testing prior to bulk product (b)(4).

- f) Provide details of the monitoring methods used for yeast, molds and anaerobic microorganisms, if applicable.

3.

(b) (4)

4. Provide the proposed maximum holding periods for routine production for the following:

(b) (4)

(b) (4) sterile bulk hold times should be supported by (b) (4) data.

(b) (4)

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 - 3815.

Sincerely,

Navi Bhandari, Pharm.D
Regulatory Health Project Manager
Office of Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

From: DeBellas, Carmen
Sent: Monday, October 26, 2015 3:50 PM
To: 'Linda Hibbs (Linda.Hibbs@premier-research.com)'
Subject: NDA 208251 Information Request

Hi Linda,

I have the following information request.

Please send us an updated table listing subjects who received antibacterials for systemic use as concomitant medications for the AOMT trials only. Please confirm that the subjects who received prohibited and rescue medications were counted once for the purpose of concomitant antibacterials use. Please clarify the difference between prohibited and rescue medications. It is our understanding that the prohibited medication group includes subjects who started antibacterials by themselves and rescue medications were initiated by the investigators. Please confirm that subjects who were receiving systemic antibacterials were not enrolled in the studies.

Thanks,
Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS

10/26/2015

MEMORANDUM (b) (4)

NDA	NDA 208251
Product	(b) (4) (Ciprofloxacin 0.3% plus Fluocinolone acetonide 0.025% Otic Solution)
Indication	(b) (4)
Sponsor	Laboratorios SALVAT SA
Review completed	August 21, 2015
Reviewer	Mayurika Ghosh MD, DAIP

(b) (4)

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MAYURIKA GHOSH
08/27/2015

DMITRI IARIKOV
08/27/2015

SUMATHI NAMBIAR
08/27/2015



NDA 208251/Original-1

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Laboratorios SALVAT, SA
c/o Premier Research
Attention: Linda Hibbs
Associate Director, Global Regulatory Affairs and Operations
1500 Market Street, Suite 3500 West
Philadelphia, PA 19102

Dear Ms. Hibbs:

Please refer to your New Drug Application (NDA) dated June 30, 2015, received June 30, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for (b)(4) (ciprofloxacin 0.3% plus fluocinolone acetonide 0.025%) Otic Solution.

We also refer to your amendments dated July 24 and August 6, 2015.

NDA 208251 provides for the use of (b)(4) (ciprofloxacin 0.3% plus fluocinolone acetonide 0.025%) Otic Solution for the following indications (b)(4)

- NDA 208251/Original-1 – Acute Otitis Media in Patients with Tympanostomy Tubes (AOMT)
- (b)(4)

We have completed our filing review and have determined that NDA 208251/Original-1 is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), NDA 208251/Original-1 is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the user fee goal date is April 30, 2016.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

Clinical Microbiology

The microbiology dataset ADEF includes multiple variables under columns “PARAM” and “AVALC”. Please provide an analysis dataset for the Phase 3 clinical trials CIFLOTIII/10IA02 and CIFLOTIII/10IA04 such that there is one record per patient and contains the following variables:

- Patient ID (USUBJID)
- Study ID (STUDYID)
- MITT flag (MITTFL)
- MPP flag (MPPFL)
- Treatment Group
- Clinical response at Visit 3 (Clinical success or Clinical failure)
- Clinical outcome at Visit 4 (Clinical success or Clinical failure)
- Microbiological outcome at Visit 3 (Eradication, Presumed Eradication, Persistence, Indeterminate, Superinfection)
- Microbiological outcome at Visit 4 (Eradication, Presumed Eradication, Indeterminate, Persistence, Superinfection, Recurrence, Re-infection)
- Sustained microbiological cure flag at Visit 3
- Sustained microbiological cure flag at Visit 4
- Baseline isolate ID
- Isolate ID at Visit 3
- Isolate ID at Visit 4
- Baseline pathogen flag (analysis value containing only pathogen or non-pathogen)

Statistics

We have the following comments pertaining to the Summary of Clinical Efficacy:

1. Table 1 has misaligned rows of numbers and is also missing the Median (95% CI) row; please submit a corrected table.
2. Tables 2 and 4 are based on observed data only; please submit the corresponding tables with missing data imputed as ‘No’ (i.e. No Sustained Microbiological Cure).
3. Provide the “Analysis Data Reviewer’s Guide” for Protocol CIFLOTII/10IA04

Clinical

Please submit the integrated summary of safety (ISS) and the ISS datasets for AOMT trials alone.

Labeling

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified labeling issues and have attached to this letter an example of the format for the **HIGHLIGHTS OF PRESCRIBING INFORMATION**.

In addition, we have the following labeling comments:

1. Currently, Section 8.1 does not contain an adequate risk summary regarding pregnancy, lactation, and reproductive potential. Because there are no adequate human pregnancy data to include in this section, the animal data from developmental toxicity and peri/postnatal studies should be included in 8.1 and not in Section 13. We will work with you regarding compliance with the Pregnancy and Lactation Labeling Rule. In addition to the labeling resources noted above, we advise you to consult the draft guidance document “Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products —Content and Format”
2. (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).
3. Please change the title (b) (4) “to “**PATIENT INFORMATION/INSTRUCTIONS FOR USE**”

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by October 15, 2015. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the waiver request is acceptable.

If you have any questions, call Carmen DeBellas, Regulatory Project Manager, at (301) 796-1203.

Sincerely

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Format Example

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

SUMATHI NAMBIAR
08/28/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208251 (b) (4)

(b) (4)

Laboratorios SALVAT, SA
c/o Premier Research
Attention: Linda Hibbs
Associate Director, Global Regulatory Affairs and Operations
1500 Market Street, Suite 3500 West
Philadelphia, PA 19102

Dear Ms. Hibbs:

Please refer to your June 30, 2015 New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (ciprofloxacin 0.3% plus fluocinolone acetonide 0.025%) Otic Solution.

(b) (4)

A meeting request. To file this NDA 208251/ (b) (4)
(b) (4)

(b) (4)
All future submissions to your NDA should specify the NDA number and all original numbers to which each submission pertains.

If you have any questions, call Carmen DeBellas, PharmD, Regulatory Project Manager, at (301) 796-1203.

Sincerely yours,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SUMATHI NAMBIAR

08/28/2015

From:DeBellas, Carmen
Sent:Thursday, July 30, 2015 10:09 AM
To:'Linda Hibbs (Linda.Hibbs@premier-research.com)'
Subject:NDA 208251 Information request

Hello Linda,

Please find information request below.

" 1. Please submit a rationale for assuming the applicability of foreign data in the submission to the U.S. population/practice of medicine.

2. Please submit the EPOCH variable for the Adverse event domain for studies CIFLOT III -101A 02, CIFLOT III -101A 04 and (b)(4)

Thank you,
Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
07/30/2015

From: DeBellas, Carmen
Sent: Monday, July 13, 2015 7:28 AM
To: 'Linda Hibbs (Linda.Hibbs@premier-research.com)'
Subject: NDA 208251 additional information request

Good morning Linda,

Please see request below.

Please ask the Sponsor to clarify the specific SAS file with clinical site ID , list of investigators, protocol deviations etc.

Thanks,
Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
07/13/2015

From: DeBellas, Carmen
Sent: Friday, July 10, 2015 1:50 PM
To: 'Linda Hibbs (Linda.Hibbs@premier-research.com)'
Subject: NDA 208251 Douxal Information Request

Hi Linda,

We have an information request, please see below.

“ Please clarify the location of the clinical site datasets for the Phase 3 AOMT (b)(4) .”

Thank you,

Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
07/10/2015



IND 107809

MEETING MINUTES

Laboratories SALVAT
c/o Premier Research
Attention: Linda Hibbs
Associate Director, Global Regulatory Affairs and Operations
1500 Market Street, STE 3500 West
Philadelphia, PA 19102

Dear Ms. Hibbs:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (b)(4) (ciprofloxacin 0.3% plus fluocinolone acetonide 0.025%) Otic Solution.

We also refer to the meeting between representatives of your firm and the FDA on December 15, 2014. The purpose of the meeting was to discuss plans for the submission of an NDA.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Carmen DeBellas, at 301-796-1203.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
Preliminary Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: A
Meeting Category: Pre-NDA

Meeting Date December 15, 2014

Application Number: 107809
Product Name: (b)(4) (ciprofloxacin 0.3% plus fluocinolone acetonide 0.025%) Otic Solution.

Indication: Acute Otitis Media in pediatric patients with tympanostomy tubes (AOMT) due to *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa*.
(b)(4)

Applicant Name: Laboratories SALVAT with Premier Research as US representative

FDA ATTENDEES

Division of Anti-Infective Products

Dr. Sumathi Nambiar	Director
Dr. Katherine Laessig	Deputy Director
Dr. Christopher Kadoorie	Statistics Reviewer
Dr. Thamban Valappil	Statistics Team Leader
Dr. Mayurika Ghosh	Clinical Reviewer
Dr. Dmitri Iarikov	Acting Clinical Team Leader
Dr. Amy Ellis	Pharmacology/Toxicology Reviewer
Dr. Wendelyn Schmidt	Pharmacology/Toxicology Team Leader
Dr. Carmen DeBellas	Project Manager
Dr. Kristine Park	Project Manager
Dr. Joseph Toerner	Acting Deputy Director for Safety
Kerry Snow	Clinical Microbiology Team Leader
Dr. Kalavati Suvarna	Clinical Microbiology Reviewer
Dr. Dorota Matecka	CMC Lead

SPONSOR ATTENDEES

Laboratories Salvat

Mr. Alberto Bueno
Dr. Enrique Jimenez
Dr. Gemma Casadevall
Dr. Patricia Lois
Dr. Sofia Moreno

Chief Executive Officer
Medical Director
Pharmaceutical Technology Director
Clinical Trial Manager and Project Leader
Head of Regulatory Affairs

Premier Research

Ms. Jennifer Nezzar
Patrick Loebis
Mr. Thomas Loage
Dr. Charlene G. Sanders

Director, Biostatistics
Senior Project Manager, Global Regulatory Affairs
Director Regulatory Medical Writing
Vice President, Global Regulatory Affairs, Compliance and
Pediatric Strategic Consulting
Associate Director, Global Regulatory Affairs and Operations

BACKGROUND

Laboratories SALVAT requested a Type B (Pre-NDA) meeting in preparation for the planned NDA for (b)(4) to be filed via a 505(b)(2) pathway. Summary results from two Phase 3 clinical trials (CIFLOTIII/10IA02, CIFLOTIII/10IA04) (b)(4) and the proposed content of the NDA were discussed at the meeting. The Sponsor received the Agency responses to the meeting background package before the meeting. The Sponsor informed the Division that they would like to discuss responses to questions 2, 3, 5, 6, 8, 16, and 17 at the meeting. The minutes contain the discussion of those responses.

DISCUSSION

During the Special Protocol Assessment (SPA) review, the Division requested that SALVAT conduct pre-clinical microbiology studies in order to understand the spectrum of activity of ciprofloxacin against recent clinical isolates taken from sources similar to those sought in the proposed indication, and to provide data from studies designed to investigate the *in vitro* activity of ciprofloxacin against recent clinical isolates of bacteria associated with (b)(4) otitis media.

Since ciprofloxacin is already used for the same proposed indications, SALVAT has elected not to perform preclinical microbiologic studies prior to the investigations in human subjects. However, SALVAT considers that the microbiology studies conducted during the clinical trials will help to understand the spectrum of activity against recent clinical isolates. In these studies, samples from patients were taken at visits 1, 3 and 4 if otorrhea was present, and microbiology testing was performed. Identification of pathogens in the clinical samples by Maldi-TOF as well as susceptibility testing by MIC determination was performed. The target pathogens and non-target pathogens identified are listed below:

Target pathogens: *Haemophilus influenzae*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pneumoniae*

Non-target pathogens: *Achromobacter denitrificans*, *Achromobacter xylosoxidans*, *Citrobacter freundii*, *Enterobacter cloacae*, *Enterobacter cloacae* complex, *Enterococcus faecalis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Morganella morganii*, *Proteus mirabilis*, *Serratia liquefaciens*, *Serratia marcescens*, *Stenotrophomonas maltophilia*, *Streptococcus dysgalactiae*, *Streptococcus* Group C, *Streptococcus pyogenes*, *Turicella otitidis*

Antibiotic susceptibility testing to ciprofloxacin and other antibacterial drugs has been performed in both target and non-target pathogens as shown below:

Fluoroquinolones: Ciprofloxacin, Levofloxacin, Ofloxacin

Macrolides: Azithromycin

β -lactams: Amoxicillin, Amoxicillin-Clavulanic acid, Oxacillin and Penicillin

Cephalosporin: Cefuroxime

Aminoglycoside: Gentamicin

Since the isolates are taken from clinical samples of AOMT patients, from a representative cross-section of geographic regions in the US and other countries, SALVAT believes that the results will constitute recent and representative data about the efficacy of ciprofloxacin against recent clinical isolates of bacteria which are commonly associated with (b)(4) otitis media. The results of the above mentioned studies will be included in the final report of the clinical trials.

Question 2: Does the Agency concur with SALVAT's position?

FDA Response: *We agree with the inclusion of microbiology data from clinical studies. Laboratory reports should include complete descriptions of all methods employed for susceptibility testing, identification of isolates, viral testing, serologic techniques, genotyping (e.g. PVL testing), quality control procedures, and any other pertinent methodology. Quality control testing results should be included in the laboratory report. In addition to the summary microbiology data, please provide the following information in the NDA:*

- (a) *A microbiology analysis dataset for Phase 3 clinical trials CIFLOTIII/10IA02 and CIFLOTIII/10IA04 containing the following information:*
Patient ID, MITT, MPP, visit, clinical outcome, microbiological outcome, isolate ID, pathogen flag (target or non-target pathogen), MIC value against antimicrobials and study drugs tested, serotyping, and PVL status.

Meeting Discussion:

The Sponsor asked for clarification on how the Division would like the information submitted. The Division responded that (b)(4)

(b)(4)

Meeting Discussion:

No discussion necessary.

(c) *A summary of studies evaluating development of resistance to ciprofloxacin by micro-organisms associated with AOMT* (b)(4)

Meeting Discussion:

The Sponsor stated that they could look at patients who failed the study for MIC changes. The Division also suggested providing any literature that may concern resistant patterns in target organisms.

(d) *The microbiology study report entitled* (b)(4)

Meeting Discussion:

No discussion necessary

(e) *The final report (containing protocol and data) for the study evaluating the activity of ciprofloxacin against Pseudomonas aeruginosa in Cynomolgus monkeys.*

Meeting Discussion:

The Sponsor will provide the publication in the NDA submission.

Chemistry, Manufacturing and Controls (CMC)

The controls for finished product testing include analyses for appearance, clarity, pH, osmolality, viscosity, identification, assay, related substances, dosage uniformity, sterility, bacterial endotoxin and particulate matter. The stability protocol has incorporated a similar analytical plan with the exception of identification and dosage uniformity and the addition of testing for weight loss and leachables.

Question 3: Does the Agency concur that these controls for finished product and stability testing are adequate to demonstrate quality with respect to identity, purity, strength and microbiological attributes to be presented in the marketing application?

FDA response: Yes, we concur. The proposed finished drug product specification appears to include the quality attributes generally critical for the sterile solution dosage form.

The release and shelf life specifications provided in Table 11 include testing for sterility per USP <71> and bacterial endotoxins per USP <85>. The appropriateness of each of these acceptance criteria and their respective assay methods is a review issue that will be assessed following submission of the NDA.

Additional information on weight loss and droplet size is expected.

The drug product is a sterile solution packaged in single dose units (b) (4) technology. The release and shelf life specifications provided in Table 11 include testing for sterility per USP <71> and bacterial endotoxins per USP <85>. The appropriateness of each of these acceptance criteria and their respective assay methods is a review issue that will be assessed following submission of the NDA.

Meeting Discussion:

The Sponsor explained that the droplet size determination does not apply to single-dose containers since the full content of the vial will be administered in one dose. The Division asked that the Sponsor submit a justification in the NDA submission.

Question 5: Does the Agency agree with this approach?

FDA response: We do not agree with this approach. Since you have proposed a 24-month shelf life, evaluation should be performed at the expiry.

Although water loss stability results from the G10098, G10099 and G10100 batches during the proposed shelf life of 24 months are considered acceptable for small containers by the ICH Q1A (R2) (all the physical and chemical parameters are within specifications), some inconsistencies were observed. After an investigation, it was concluded that the inconsistencies were due to the water loss method used. As a result, SALVAT decided to start a new stability and water loss study with batch 2M07. In this new stability study, the water loss was determined by two methods. The water loss results obtained with this batch were consistent and within specifications at all climatic conditions, independently of the method, thus confirming the acceptability of water loss for the drug product.

Meeting Discussion:

The Sponsor informed the Division that data has been generated for the 36-month time point which proved adequate. They felt this was acceptable since they are asking for 24 months shelf life. The Division agreed that this would be acceptable.

Question 6: Is this approach acceptable to the Agency?

FDA response: The comparative approach taken to provide consistent and accurate results for the primary stability batches and the additional supporting batch for the NDA submission is acceptable. The study should incorporate a comparative weight loss study using the two methods. The additional batch 2M07 may then be evaluated as supporting primary batches.

Meeting Discussion:

The Sponsor explained that water loss results were acceptable according to ICH guidelines but inconsistencies were found in the methods used to determine the water loss. The Sponsor developed four new methods each one improving on the previous one with the fourth one being best. The Sponsor then obtained data for up to 24 months on the last batch; this data will be submitted in the NDA. The Division stated that the Sponsor should submit a description and comparative data for all four methods and a justification for the changes in the NDA. The Division also recommended that the weight loss test be included in the drug product specification with a justification for the proposed acceptance criteria submitted in the NDA.

Clinical

(b)(4)



Some sites participated in both AOMT studies, however, sites were never simultaneously active in both trials and no patient participated in both studies. Since SALVAT followed FDA recommendations and avoided the transfer of sites that enrolled a large proportion of subjects in the CIFLOTIII/10IA04, the Sponsor considers that it is not necessary to investigate the potential influence of site sharing on the individual study results either in the ISS or ISE (July 23, 2013 FDA Letter).

(b)(4)



(b)(4)

Regulatory

In accordance with FDA's Draft Guidance for Industry, *Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document*, SALVAT proposes to place the text portions of the ISE and ISS (i.e., for the two phase 3 studies combined) in support of the AOMT indication, (b) (4)

(b) (4) within Module 2, as the Summary of Clinical Efficacy and Summary of Clinical Safety, (b) (4)

As suggested per CTD guidance, (*Registration of Pharmaceuticals for Human Use: Efficacy, M4E(R1), Clinical Overview and Clinical Summary of Module 2, Module 5: CSRs, 12SEPT2002*), (b) (4)

(b) (4)

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
Regulations and related guidance documents
A sample tool illustrating the format for Highlights and Contents, and
The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify in a single location, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities

associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry Applications Covered by Section 505(b)(2) (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the

proposed drug product that represent modifications to the listed drug(s). You should establish a “bridge” (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency’s finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA’s finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency’s regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the “listed drug for which FDA has made a finding of safety and effectiveness,” and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA’s finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA’s consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA’s finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA’s finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature

Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
1. Example: Published literature	Nonclinical toxicology
2. Example: NDA XXXXXX “TRADENAME”	Previous finding of effectiveness for indication X
3. Example: NDA YYYYYYY “TRADENAME”	Previous finding of safety for Carcinogenicity, labeling section XXX
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

1. FINAL LIST OF QUESTIONS

1.1. Pharmacology/Toxicology

Question 1: Does the Agency agree that all nonclinical toxicology studies undertaken with Ciprofloxacin plus Fluocinolone Acetonide are adequate and that no additional studies are required to support the NDA?

FDA Response: *We do not anticipate that additional nonclinical testing will be needed to support an NDA for your product.*

During the Special Protocol Assessment (SPA) review, the Division requested that SALVAT conduct pre-clinical microbiology studies in order to understand the spectrum of activity that Ciprofloxacin has against recent clinical isolates taken from sources similar to those sought in the proposed indication, and to provide data from studies designed to investigate the *in vitro* activity of Ciprofloxacin against recent clinical isolates of bacteria associated with (b)(4) otitis media.

Since Ciprofloxacin is already used for the same proposed indications, SALVAT has elected not to perform preclinical microbiologic studies prior to the investigations in human subjects. However SALVAT considers that the microbiology studies conducted during the clinical trials will help to understand the spectrum of activity against recent clinical isolates. In these studies, samples from patients included in the study were taken at visits 1, 3 and 4 if otorrhea was present, and microbiology testing was performed. Identification of pathogens in the clinical samples by Maldi-TOF as well as susceptibility testing by MIC determination was performed. The target pathogens and non-target pathogens identified are listed below:

- Target pathogens: *Haemophilus influenzae*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pneumoniae*
- Non-target pathogens: *Achromobacter denitrificans*, *Achromobacter xylosoxidans*, *Citrobacter freundii*, *Enterobacter cloacae*, *Enterobacter cloacae complex*, *Enterococcus faecalis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Morganella morganii*, *Proteus mirabilis*, *Serratia liquefaciens*, *Serratia marcescens*, *Stenotrophomonas maltophilia*, *Streptococcus dysgalactiae*, *Streptococcus Group C*, *Streptococcus pyogenes*, *Turicella otitidis*

Antibiotic susceptibility testing to Ciprofloxacin and other comparators has been performed in both target and non-target pathogens. Antibiotics tested are shown below:

- Fluoroquinolones: Ciprofloxacin, Levofloxacin, Ofloxacin
- Macrolides: Azithromycin
- β -lactams: Amoxicillin, Amoxicillin-Clavulanic acid, Oxacillin and Penicillin
- Cephalosporin: Cefuroxime

1.6.2 Meeting Background Materials

- Aminoglycoside: Gentamicin

Since the isolates are taken from clinical samples of AOMT patients, from a representative cross-section of geographic regions in the US and other countries, SALVAT believes that the results will constitute recent and representative data about the efficacy of Ciprofloxacin against recent clinical isolates of bacteria which are commonly associated with (b)(4) otitis media. The results of the above mentioned studies will be included in the final report of the clinical trials.

Question 2: Does the Agency concur with SALVAT's position?

FDA Response: *We agree with the inclusion of microbiology data from clinical studies. Laboratory reports should include complete descriptions of all methods employed for susceptibility testing, identification of isolates, viral testing, serologic techniques, genotyping (e.g. PVL testing), quality control procedures, and any other pertinent methodology. Quality control testing results should be included in the laboratory report. In addition to the summary microbiology data, please provide the following information in the NDA:*

- (a) *A microbiology analysis dataset for Phase 3 clinical trials CIFLOTIII/10IA02 and CIFLOTIII/10IA04 containing the following information:*
Patient ID, MITT, MPP, visit, clinical outcome, microbiological outcome, isolate ID, pathogen flag (target or non-target pathogen), MIC value against antimicrobials and study drugs tested, serotyping, and PVL status.

(b)  (b)(4)

(c) 

(d)

- (e) *The final report (containing protocol and data) for the study evaluating the activity of ciprofloxacin against Pseudomonas aeruginosa in Cynomolgus monkeys.*

1.2. Chemistry, Manufacturing and Controls (CMC)

The controls for finished product testing include analyses for appearance, clarity, pH, osmolality, viscosity, identification, assay, related substances, dosage uniformity, sterility, bacterial endotoxin and particulate matter. The stability protocol has incorporated a similar analytical plan with the exception of identification and dosage uniformity and the addition of testing for weight loss and leachables.

Question 3: Does the Agency concur that these controls for finished product and stability testing are adequate to demonstrate quality with respect to identity, purity, strength and microbiological attributes to be presented in the marketing application?

FDA response: *Yes, we concur. The proposed finished drug product specification appears to include the quality attributes generally critical for the sterile solution dosage form.*

The release and shelf life specifications provided in Table 11 include testing for sterility per USP <71> and bacterial endotoxins per USP <85>. The appropriateness of each of these acceptance criteria and their respective assay methods is a review issue that will be assessed following submission of the NDA.

Additional information on weight loss and droplet size is expected.

The drug product is a sterile solution packaged in single dose units (b) (4) technology. The release and shelf life specifications provided in Table 11 include testing for sterility per USP <71> and bacterial endotoxins per USP <85>. The appropriateness of each of these acceptance criteria and their respective assay methods is a review issue that will be assessed following submission of the NDA.

SALVAT intends to submit the NDA with stability data from 3 batches stored for 6 months at accelerated conditions, 12 months at intermediate conditions, and 36 months at long term conditions. A shelf-life of 24 months will be proposed for the product based on the results of these studies.

Question 4: Does the Division agree that the stability plan is complete and adequate for an NDA filing?

FDA response: *The proposed stability data of three batches at above conditions are acceptable for NDA submission. The stability data results from the submitted studies will be reviewed to assess the appropriate shelf-life. The stability plan and protocol appear to be in accordance with current ICH guidelines. The stability protocol will be reviewed as part of the NDA for the to be marketed drug product.*

From a product quality microbiology perspective, this appears to be adequate. The appropriateness of the stability program will be assessed following submission of the NDA.

According to an Agency suggestion during the pre-IND meeting, SALVAT included particulate matter and bacterial endotoxins acceptance criteria and tests for the drug product specifications

1.6.2 Meeting Background Materials

and evaluated samples at the 36 month time point only for the G10098, G10099 and G10100 batches, coinciding with the end of the stability study.

Question 5: Does the Agency agree with this approach?

FDA response: *We do not agree with this approach. Since you have proposed a 24-month shelf life, evaluation should be performed at expiry.*

Although water loss stability results from the G10098, G10099 and G10100 batches during the proposed shelf life of 24 months are considered acceptable for small containers by the ICH Q1A (R2) (all the physical and chemical parameters are within specifications), some inconsistencies were observed. After an investigation, it was concluded that the inconsistencies were due to the water loss method used. As a result, SALVAT decided to start a new stability and water loss study with batch 2M07. In this new stability study, the water loss was determined by two methods. The water loss results obtained with this batch were consistent and within specifications at all climatic conditions, independently of the method, thus confirming the acceptability of water loss for the drug product.

Question 6: Is this approach acceptable to the Agency?

FDA response: *The comparative approach taken to provide consistent and accurate results for the primary stability batches and the additional supporting batch for the NDA submission is acceptable. The study should incorporate a comparative weight loss study using the two methods. The additional batch 2M07 may then be evaluated as supporting primary batches.*

1.3. Clinical Pharmacology

Not applicable.

1.4. Clinical

1.4.1. Clinical Efficacy

SALVAT believes that the data from the Phase III studies, CIFLOTIII/10IA02 and CIFLOTIII/10IA04, demonstrate that Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% Otic Solution is efficacious and well tolerated for the treatment of AOMT and supports the NDA filing and potential approval of Ciprofloxacin plus Fluocinolone Acetonide Otic Solution in the treatment of AOMT.

Question 7: Does the Agency concur?

FDA response: *The summary of efficacy results of the Phase 3 trials, CIFLOTIII/10IA02 and CIFLOTIII/10IA04, as presented in the briefing package, appear adequate to support an NDA submission. Upon review of the NDA, we will determine whether Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% Otic Solution is safe and efficacious in the treatment of AOMT.*

(b)(4)

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safety data from the two twin AOMT phase III studies and the post-marketing experience of the multiple dose products marketed outside the U.S.

(b)(4)



Some sites participated in both AOMT studies, however, sites were never simultaneously active in both trials and no patient participated in both studies. Since SALVAT followed FDA recommendations and avoided the transfer of sites that enrolled a large proportion of subjects in the CIFLOTIII/10IA04, the Sponsor considers that it is not necessary to investigate the potential influence of site sharing on the individual study results either in the ISS or ISE (July 23, 2013 FDA Letter).

Question 9: Is this acceptable by the Agency?

FDA response: *We acknowledge the extensive measures taken to reduce site sharing to ensure independent evidence of treatment effect from each of these studies. However, as there were 15 sites enrolling patients across both trials, we recommend that the potential influence of site sharing be investigated.*

Provide a graphical depiction of the distributions of subjects enrolled across sites by trial. Also show the overlap in the two distributions by superimposing one distribution on the other.

1.6.2 Meeting Background Materials

SALVAT used 5 different drug product batches in the CIFLOTIII/10IA02 study and 3 different batches in the CIFLOTIII/10IA04 study. The FDA was informed following the manufacture of each new batch and has not expressed any concern pertaining to this issue. In response to serial amendment numbers 0010, 0020, 0027 and 0040, the Agency's recommended that a sub-analysis of the principal endpoints by batch be performed. SALVAT has complied with this recommendation and believes that this analysis is sufficient to demonstrate the absence of influence of the different batches on the results.

Question 10: Does the Agency concur that the sub-analysis of the primary endpoints is sufficient to demonstrate the lack of influence thereby bridging the different batches used?

***FDA response:** Your approach to conduct a sub-analysis of the principal endpoints by batch is reasonable. Whether this analysis will be sufficient to demonstrate the influence of the different batches on the results will be a review issue.*

As the FDA was previously informed some patients were thought to have received Fluocinolone Acetonide drug product that did not meet the stability specification for related substances content SALVAT's investigations revealed that the out of specification finding was observed only in the stability samples, and that this was the result of improper shipping conditions. However, the study drug administered to the patients was in compliance. SALVAT has performed a sub-analysis of the primary endpoint and the principal secondary endpoint excluding patients who were administered drug product that presumably was out of specification. This sub-analysis was performed in order to eliminate any potential influence on the study results and demonstrated that these patients had no influence on these studies.

Question 11: Does the Agency concur with this strategy?

***FDA response:** Your approach to conduct a sub-analysis of the principal endpoints excluding patients who were administered drug product that presumably was out of specification is reasonable.*

1.4.2. Clinical Safety

Question 12: Does the FDA agree that the integrated safety data from the 2 completed studies (CIFLOTIII/10IA02 and CIFLOTIII/10IA04) provide adequate information to evaluate (b)(4) safety profile for the treatment of AOMT?

***FDA response:** A summary of the safety results of the two trials ((CIFLOTIII/10IA02 and CIFLOTIII/10IA04) as presented in the briefing package, appear to be appropriate to support an NDA submission. However an assessment of the safety profile will be conducted during the NDA review. Provide safety evaluation in the Integrated Summary of Safety (ISS) for adverse events related to fungal infections, comparator class effects and antibacterial related effects.*

The NDA should contain integrated summaries of safety and effectiveness (ISS/ISE) as required by 21 CFR 314.50. Assessment of safety as per the Guidance for Industry: Pre-marketing Risk

1.6.2 Meeting Background Materials

Assessment available at:

<http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126958.pdf>

Provide complete CRFs for all patients with serious adverse reactions, in addition to deaths and discontinuations due to adverse reactions. You should be prepared to supply additional CRFs upon request. Provide narratives for patients with serious adverse reactions related to the study drug. Provide universal subject ID USUBID for all patients in the phase 3 trials prior to your NDA submission so that we can generate a list of random sample of CRFs to be included in the NDA.

SALVAT has generated extensive post-marketing safety data with Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% Otic Solution (b) (4)

Question 13: Does the FDA agree that the

(b) (4)

(b) (4)

FDA response: *This appears reasonable and further comments will be provided during the NDA review.*

According to 21 FFD&CA 355-1 a Risk Evaluation and Mitigation Strategy (REMS) may be necessary under certain circumstances. Considering the drug substances contained in the proposed NDA, Ciprofloxacin and Fluocinolone Acetonide are well-known drug substances; they do not meet the criteria to submit a REMS. Therefore, SALVAT does not intend to include a REMS in the initial NDA.

Question 14: Does the Agency agree?

FDA response: *We agree. The need for REMS will be decided upon review of the NDA.*

Additional clinical comments that can be addressed in the NDA submission:

(b)(4)

1.6.2 Meeting Background Materials

5. *For patients listed as discontinued due to “investigator decision”, “sponsor request”, “withdrew consent”, or “other”, the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated. In addition, the verbatim description from the CRF should be included as a variable in the adverse event data set.*
6. *Use a single version of MedDRA for the submission. We recommend that the WHO drug dictionary be used for concomitant medications. Refer to the CDISC terminology for lab test names. Issues regarding ranges for laboratory measurements should be addressed.*
7. *To facilitate the review, provide analyses and discussion, where applicable, including:*
 - *Less common adverse reactions (between 0.1% and 1%).*
 - *Marked outliers and dropouts for laboratory abnormalities.*
 - *Analysis of vital signs focused on measures of central tendencies and marked outliers*
 - *Analysis and summary of the reasons and patterns of discontinuation of the study Drug; identify for each patient, the toxicities that result in study discontinuation*
 - *Possible factors associated with a higher likelihood of early study termination; include demographic variables, study site, region, and treatment assignment.*
 - *Time dependency for adverse finding*
 - *Data summarizing the length of time subjects experience adverse reactions*

1.5. Statistics

SALVAT intends to submit the raw data from studies CIFLOTIII/10IA02 and CIFLOTIII/10IA04 in CDISC compliant format (b)(4) in SAS transport (Xport) file format (as SAS datasets).

Question 15: Is this acceptable to the Agency?

FDA Response: *We recommend that raw data from study (b)(4) also be submitted in CDISC compliant format.*

1.6. Regulatory

In accordance with FDA’s Draft Guidance for Industry, *Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document*, SALVAT proposes to place the text portions of the ISE and ISS (i.e., for the two phase 3 studies combined) in support of the AOMT indication, (b)(4), within Module 2, as the Summary of Clinical Efficacy and Summary of Clinical Safety, (b)(4).

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As suggested per CTD guidance, (*Registration of Pharmaceuticals for Human Use: Efficacy, M4E(R1), Clinical Overview and Clinical Summary of Module 2, Module 5: CSRs, 12SEPT2002*),

(b) (4)

(b) (4)

Question 16: Does the FDA agree with this approach?

FDA Response: *We agree. In addition, provide an integrated summary of safety for the all phase 3 trials. Provide safety data distribution by age groups.*

Within the last year, the United States *Code of Federal Regulations* and legislation put into effect, under the *Pediatric Research Equity Act (Public Law 108-155) (PREA)* amendments to the *Federal Food, Drug, and Cosmetic Act section 505B (21U.S.C. 355B) Pediatric Research Equity Act (PREA)* stipulate that new drug applications (NDAs) filed on or after January 5, 2014, should have an initial pediatric study plan (iPSP) submitted no later than 210 days prior to NDA submission or not later than 60 days after the date of the end-of-phase 2 meeting.

SALVAT's AOMT clinical development program, which included pediatric patients, had been planned, initiated and was in the advanced patient recruitment stage well before the most recent PREA legislation was activated and implemented. SALVAT is committed to complying with the PREA regulations. Because the SALVAT program is now complete, SALVAT proposes discussion with the Division to address administrative arrangements to reconcile its submission path forward for filing its NDA on the planned timeline while satisfying PREA statutes.

The following questions are related to SALVAT's plan to comply with PREA, in light of its pre-NDA status and nearing NDA filing goals.

- a. Currently, SALVAT's NDA is scheduled for submission at the end of 1Q2015 which places its marketing authorization timeline outside of the 210 day pre-NDA or 60 day post EOP2 windows recommended for iPSP submissions. SALVAT requests a pre-NDA meeting agreement for its NDA that would entail a specified commitment for iPSP submission so as to avoid an automated, administrative-based Refusal To File (RTF) at the time of NDA filing. SALVAT suggests an agreement that stipulates the iPSP accompany the NDA at the time of filing. The iPSP would be filed to the IND. The iPSP and associated agreement for the iPSP submission plan would be referenced in the NDA according to eCTD structure and submission build guidelines.

Question 17: Does the Agency agree to this approach as a route to comply with PREA?

FDA response: *You can submit the PSP with any waiver/exemption requests at the time of your NDA submission.*

1.6.2 Meeting Background Materials

- b. SALVAT enrolled and treated pediatric patients in its clinical studies and development of the 505(b)(2) AOMT program. Pediatric patients were screened, enrolled and completed treatment, although the sample sizes varied in representative age ranges related to prevalence of the condition(s) in children examined from ages 6 months to 10 years. The indication sought for SALVAT's AOMT product includes treatment in children based on the Phase 3 efficacy and safety data collected. SALVAT proposes to file an iPSP requesting a waiver/exemption from performing additional PREA pediatric studies beyond the pediatric work already performed and presented in its NDA. SALVAT's request will be based on demonstrating, in the iPSP content, that adequate AOMT pediatric data was collected in the pivotal studies and children were a targeted treatment population for the AOMT product resulting in clinical trial work that both support and fulfill the goals of PREA.

Question 18: Does the Agency concur with this plan?

FDA Response: *Submit your waiver requests at the time of your NDA submission, specifying the age groups for whom you are seeking a waiver. Your request will be reviewed and discussed at the Pediatric Review Committee and a decision will be made if the studies can be waived or if additional pediatric studies will be required.*

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/s/

CARMEN L DEBELLAS
12/10/2014

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/s/

SUMATHI NAMBIAR
01/15/2015