CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206307Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # **206307** SUPPL # HFD #

Trade Name: **Xtoro**

Generic Name: **finafloxacin otic suspension**

Applicant Name: **Alcon Research, Ltd.**

Approval Date, If Known: **December 17, 2014**

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)(1)

c) 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.

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:

d) 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

e) 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?

Yes

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).

NDA#

NDA#

NDA#

2. Combination product. **N/A**

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#

NDA#

NDA#

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:

(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:

(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:

(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:

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:

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:

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"):

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 # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(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?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(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:

==========

Name of person completing form: **Michael Puglisi**
Regulatory Project Manager
Division of Transplant and Ophthalmology Products

Name of Office/Division Director signing form: **Wiley A. Chambers, M.D.**
Deputy Director
Division of Transplant and Ophthalmology Products

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

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

/s/

MICHAEL J PUGLISI
12/17/2014

WILEY A CHAMBERS
12/17/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 206307 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Xtoro Established/Proper Name: finafloxacin Dosage Form: otic suspension		Applicant: Alcon Research, Ltd. Agent for Applicant (if applicable): N/A
RPM: Michael Puglisi		Division: DTOP

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)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

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.

Actions	
• Proposed action • User Fee Goal Date is 12/25/14	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ 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	☐ Received
❖ 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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

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

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

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ 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

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)*	☐ Yes ☐ No
❖ 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 – December17, 2014
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)*	☒ Attached to AP Letter
• 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)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ 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 • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Unacceptable – 7/30/14 Acceptable – 11/9/14 Review dates – 7/28/14, 11/5/14
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ None DMEPA: 9/15/14 DMPP/PLT (DRISK): ☒ None OPDP: 10/10/14 SEALD: ☒ None CSS: ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	8/21/14 ☒ Not a (b)(2)
❖ 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 o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 11/5/14 If PeRC review not necessary, explain: _____	11/5/14
❖ 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, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	In Package
❖ 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 *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	9/27/13
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	8/11/14
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	12/17/14
Division Director Summary Review *(indicate date for each review)*	12/4/14
Cross-Discipline Team Leader Review *(indicate date for each review)*	12/10/14
PMR/PMC Development Templates *(indicate total number)*	One – 11/21/14
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	6/4/14, 10/2/14
• 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)*	In 10/2/14, Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ 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)*	REMS Review – 9/19/14
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	In Package
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)*	6/3/14, 9/26/14
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)*	6/24/14, 9/24/14
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)*	6/2/14, 8/19/14
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	10/3/14
• Supervisory Review(s) *(indicate date for each review)*	10/5/14
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	6/4/14, 9/25/14
❖ 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	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	6/13/14, 9/17/14 Biopharmaceutics – 9/25/14
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	5/28/14, 9/17/14
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ 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)*	In 9/17/14, Product Quality Review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: 6/11/14 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	N/A
• Finalize 505(b)(2) assessment	
❖ 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 *Application Product Names* 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 PREA Subcommittee Meeting Minutes
November 5, 2014

PeRC Members Attending:
Robert Nelson (acting as PeRC chair for Lynne Yao)
Rosemary Addy
Jane Inglese
Hari Cheryl Sachs
Wiley Chambers
Tom Smith
Peter Starke
Gregory Reaman
Freda Cooner
Lily Mulugeta
Olivia Ziolkowski
Michelle Roth-Cline (for Robert Nelson)
Julia Pinto

Agenda

NDA	206307	Xtoro (finafloxacin) Partial Waiver/Assessment (Written Request -Exclusivity Granted)	Treatment of acute otitis externa

(b) (4)

[redacted]

Xtoro (finafloxacin) Partial Waiver/Assessment (Written Request -Exclusivity Granted)

- NDA 206307 seeks approval for Xtoro (finafloxacin) for treatment of acute otitis externa.
- The application triggers PREA as a new active ingredient.
- The application has a PDUFA a goal date of December 25, 2014.
- *PeRC Recommendations:*
    - The PeRC agreed with a partial waiver for pediatric patients aged birth to less than 1 year because studies would be impossible or highly impracticable.
    - The PeRC agreed with the assessment for pediatric patients aged 1 to 17 years.

(b) (4)

[redacted]

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/s/

JANE E INGLESE
11/17/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206307

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Alcon Research, LTD
6201 South Freeway
Mail Code TC-45
Fort Worth, TX 76134-2099

ATTENTION: Paul Nitschmann, MD
Head, Regulatory Affairs, Pharma

Dear Dr. Nitschmann:

Please refer to your New Drug Application (NDA), dated and received, April 25, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Finafloxacin Otic Suspension, 0.3 %.

We also refer to

- Your correspondence, dated and received, October 22, 2014, requesting withdrawal of your proposed proprietary name, (b) (4).
- Your correspondence, dated and received, October 24, 2014, requesting re-evaluation of your proposed proprietary name, Xtoro.

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

If any of the proposed product characteristics as stated in your October 24, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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 Mike Puglisi, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
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 on behalf of KELLIE A TAYLOR
11/09/2014

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 3, 2014

TO: NDA 206307 File

FROM: Michael Puglisi, Regulatory Project Manager

SUBJECT: Applicant's Waiving of Late-Cycle Meeting

APPLICATION/DRUG: NDA 206307 – Finafloxacin Otic Suspension

During the August 11, 2014, Mid-Cycle Communication Teleconference, the NDA Applicant, Alcon Research Ltd., was offered 10/24/14 and 10/30/14, as potential dates for the Late-Cycle Meeting. In a correspondence to the NDA file dated 9/24/14, the Applicant stated that they wish to forego the Late-Cycle Meeting, citing their satisfaction with the progress of the review. This decision is acceptable to the Agency. No Late-Cycle Meeting will be held.

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/s/

MICHAEL J PUGLISI
10/03/2014

Puglisi, Michael

From: Puglisi, Michael
Sent: Monday, September 22, 2014 2:19 PM
To: 'Nitschmann, Paul'
Subject: Clinical Information Request for Finafloxacin NDA - NDA 206307

Hi Paul,

Below please find an information request from our clinical reviewer for NDA 206307. Please let me know if you have any questions about this request. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

Reviewer's Comments:
Please specify which, if any, of the pathogens listed in Table 1.11.3-1 and submitted on Sept. 19 were recovered from study ears without S. aureus or P. aeruginosa also being present.

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/s/

MICHAEL J PUGLISI
09/22/2014

Townsend, Karen

From: Nitschmann, Paul <paul.nitschmann@alcon.com>
Sent: Monday, September 08, 2014 4:35 PM
To: Townsend, Karen
Subject: RE: NDA 206307

Hi Karen,

Just checked with my Trade Mark colleagues! We would like to keep XTORO in the books in case we are lucky and get approval before the other Sponsors do, but we have two names in the internal review process as potential back-ups that I will submit as soon as they have been cleared internally.

Best,
Paul

Sincerely,
Paul Nitschmann
Head, Regulatory Affairs Pharmaceuticals

6201 South Freeway, Fort Worth, TX 76134-2099, USA
T +1 817 615 2440 | M (b) (6) | paul.nitschmann@alcon.com

Alcon
a Novartis company

From: Townsend, Karen [mailto:Karen.Townsend@fda.hhs.gov]
Sent: Monday, September 08, 2014 3:01 PM
To: Nitschmann, Paul
Subject: NDA 206307

Hi Paul,

Will you be submitting another proprietary name for NDA 206307 , finafloxacin?

Thank you,
Karen

Karen Townsend

Safety Regulatory Project Manager
Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

KAREN F TOWNSEND
09/21/2014

Puglisi, Michael

From: Puglisi, Michael
Sent: Monday, September 15, 2014 2:24 PM
To: 'Nitschmann, Paul'
Subject: Clinical Information Request for Finafloxacin NDA - NDA 206307

Hi Paul,

Below please find a request from our clinical reviewer for the finafloxacin otic suspension NDA. Please confirm receipt and let me know if you have any questions about anything. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

Reviewer's Comments:

Thank you for your recent submission in response to our September 9, 2014, information request. However, the IR was not clear enough. We would like the same information submitted for the culture positive subset of patients, if possible. We are interested in the proportion of patients who achieved clinical cure for each ***bacterial microorganism*** *that was cultured at baseline, not just the pre-defined pathogens.*

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/s/

MICHAEL J PUGLISI
09/15/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206307 **INFORMATION REQUEST**

Alcon Research, Ltd.
Attention: Paul Nitschmann, MD
Head, Regulatory Affairs Pharma
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Dr. Nitschmann:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Finafloxacin Otic Suspension, 0.3%.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a written response by 17 September, 2014, in order to continue our evaluation of your NDA.

1) We acknowledge your confirmation that the manufacturing process details and specification for (b) (4) will be submitted to the Agency upon completing process validation. Please note that this information should be submitted as a Changes Being Effected-30 Supplement. Please confirm your agreement to this recommended post-approval action and indicate when the Supplement is likely to be submitted.

2) Section 3.2.S.7.3: Table 3.2.S.7.3-4 lists 26 weeks data for accelerated stability and 104 weeks data for the long-term stability for lot# 18966-01. However, in the discussion section, it is mentioned that data for this batch is available for only up to 13 weeks. Please correct this and provide an updated table.

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

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

BALAJEE SHANMUGAM
09/11/2014
Sigining for Dr. Rapti Madurawe

Puglisi, Michael

From: Puglisi, Michael
Sent: Tuesday, September 09, 2014 10:41 AM
To: 'Nitschmann, Paul'
Subject: Information Request for Finafloxacin NDA - NDA 206307

HI Paul,

Below please find a request from our clinical reviewer for finafloxacin. Please confirm receipt and let me know if you have any questions. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

Reviewer's Comments:

Please submit a Table of the proportion of patients who achieved clinical cure for each bacterial pathogen that was cultured at baseline. If this information has already been submitted, please identify where it can be located within prior submissions.

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/s/

MICHAEL J PUGLISI
09/09/2014

Puglisi, Michael

From: Puglisi, Michael
Sent: Tuesday, August 26, 2014 2:40 PM
To: 'paul.nitschmann@alcon.com'
Subject: Pediatric Exclusivity has been Granted for Finafloxacin - NDA 206307

Hi Paul,

Pediatric Exclusivity has been granted for studies conducted on Finafloxacin, effective August 25, 2014, under section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a). This information will be reflected on CDER's pediatric web site and in the monthly update of the Orange Book.

In accordance with section 505A(e)(1) of the Act, as amended by the FDA Amendments Act (Pub. L. No. 110-85), approved drugs for which a pediatric exclusivity determination was made on or after September 27, 2007, shall have a copy of the Written Request and any amendments posted on CDER's pediatric web site.

In addition, we remind you that section 17 of the BPCA, as reauthorized and amended under the FDA Safety & Innovation Act (Pub. L. No. 112-144), requires for 18 months after pediatric labeling is approved, any report received by FDA of an adverse event associated with the drug granted exclusivity will be referred to the Office of Pediatric Therapeutics. This process occurs for all products granted Pediatric Exclusivity regardless of the regulatory action taken. The Director of that Office will provide for a review of the adverse event reports by the Pediatric Advisory Committee (PAC) and will obtain recommendations from that Committee on action FDA should take.

Please confirm you have received this message and let me know if you have any questions about anything. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

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/s/

MICHAEL J PUGLISI
08/26/2014

From: Bhandari, Navdeep
To: "Nitschmann, Paul"
Subject: RE: NDA 206307 Information Request Quick Turnaround Requested
Date: Tuesday, August 26, 2014 9:47:00 AM
Importance: High

Good Morning Paul,

Please see the following comments from my team:

The attached drug product specification is not acceptable. We would like you to submit the revised drug product specification without the product homogeneity test.

Thank you,
Navi

From: Nitschmann, Paul [mailto:paul.nitschmann@alcon.com]
Sent: Monday, August 25, 2014 4:17 PM
To: Bhandari, Navdeep
Subject: RE: NDA 206307 Information Request Quick Turnaround Requested

Dear Navi,

In the response of August 14, 2014 we included in the In-Process Specifications (3.2.P.3.4) and the Drug Product specifications (3.2.P.5.1), a homogeneity test with a specification of 90-110%. The DP specification section is attached as submitted as an example. Is this acceptable or is the Reviewer looking for something else? Thanks!

Best,
Paul

Sincerely,
Paul Nitschmann
Head, Regulatory Affairs Pharmaceuticals

6201 South Freeway, Fort Worth, TX 76134-2099, USA
T +1 817 615 2440 | M + (b) (6) | paul.nitschmann@alcon.com

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a Novartis company

by return e-mail and delete all copies of this message and any attachments.

Thank you.

From: Bhandari, Navdeep [mailto:Navdeep.Bhandari@fda.hhs.gov]
Sent: Monday, August 25, 2014 11:43 AM
To: Nitschmann, Paul
Subject: NDA 206307 Information Request Quick Turnaround Requested
Importance: High

Hello Paul,

My review team has provided the following comments. A response date of 8/29/2014 is requested.

We acknowledge your response dated 8/21/2014 adding product homogeneity as an in-process test. We remind you to submit the revised drug product specification to reflect this change.

Thank you,
Navi

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/s/

NAVDEEP BHANDARI
08/26/2014

From: Bhandari, Navdeep
To: "Nitschmann, Paul"
Subject: NDA 206307 Information Request Quick Turnaround Requested
Date: Monday, August 25, 2014 12:42:00 PM
Importance: High

Hello Paul,

My review team has provided the following comments. A response date of 8/29/2014 is requested.

We acknowledge your response dated 8/21/2014 adding product homogeneity as an in-process test. We remind you to submit the revised drug product specification to reflect this change.

Thank you,
Navi

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/s/

NAVDEEP BHANDARI
08/25/2014

From: Bhandari, Navdeep
To: "Nitschmann, Paul"
Bcc: Shanmugam, Balajee
Subject: RE: NDA 206307 Information Request
Date: Monday, August 18, 2014 2:38:00 PM

Hello Paul,

My team has provided the following response:

We agree to Alcon's previous response dated 31-Jul-2014 regarding specification for (b) (4)

We acknowledge that the solvent levels are controlled at the (b) (4) stage. However since (b) (4) the drug substance specification. While we note that the levels of the metals tested are low, the data available is from limited number of batches. Therefore, include tests for heavy metals in the drug substance specification. The specification for heavy metals can be revisited when data from more number of batches becomes available.

We remind you of providing specification for (b) (4).

Regards,
Navi

From: Nitschmann, Paul [mailto:paul.nitschmann@alcon.com]
Sent: Thursday, August 14, 2014 6:55 PM
To: Bhandari, Navdeep
Subject: RE: NDA 206307 Information Request

Dear Navi,

The team is assessing the questions. We noted the statement "We would like to remind you that the following issues from our previous information request were not addressed in your 31-July-2014 dated response." Attached please find the Word version of our response of July 31. Can you please confirm that the Reviewer has seen this and considers that it does not respond to the request for information? Thanks a lot!

Best,
Paul

Sincerely,
Paul Nitschmann
Head, Regulatory Affairs Pharmaceuticals

6201 South Freeway, Fort Worth, TX 76134-2099, USA
T +1 817 615 2440 | M + (b) (6) | paul.nitschmann@alcon.com

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/s/

NAVDEEP BHANDARI
08/18/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206307 **INFORMATION REQUEST**

Alcon Research, Ltd.
Attention: Paul Nitschmann, MD
Head, Regulatory Affairs Pharma
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Dr. Nitschmann:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Finafloxacin Otic Suspension, 0.3%.

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 August 22, 2014, in order to continue our evaluation of your NDA.

Drug Substance

Section 3.2.S.2.2

We acknowledge that [redacted (b) (4)]. Please provide specification for [redacted (b) (4)] under section 3.2.S.2.3 and update relevant sections of NDA to reflect this change. Also, update the flow diagram/synthetic scheme of the manufacturing process given under figure 3.2.S.2.2-2.

We would like to remind you that the following issues from our previous information request were not addressed in your 31-July-2014 dated response.

1) **Section 3.2.S.2.3 Page-2,** [redacted (b) (4)]

The [redacted (b) (4)]

2) Section 3.2.S.2.6 Page-4, Step 5

[redacted] Therefore, please discuss the control and risk mitigation strategy you have in place to mitigate the potential of any undesirable polymorphs in the drug product. You can include this discussion under the drug product.

3) Section 3.2.S.4.1

The proposed drug substance specification does not include test for residual solvents, residual [redacted] and heavy metals. Since [redacted] is not a solvent, justification for its limit is not covered by the ICH Q3C guidance and therefore the proposed acceptance criterion should be justified with data. Given the limited manufacturing experience and data available at this time, we recommend including the above quality tests in the drug substance specification. Please provide an updated specification for the drug substance and update the relevant sections of NDA to reflect this change.

Drug Product

1. We acknowledge your response dated 7/31/2014 to the drug product question #4 regarding adding an in-process test for content uniformity in the [redacted]. Instead, we note that a test for product homogeneity is included in the drug product specification. Since the test is performed doing the [redacted], we recommend that it be considered as an in-process control. Please submit the revised drug product specification to reflect this change and update appropriate section(s) of the NDA to indicate product homogeneity testing as an IPC.

2. Confirm that the [redacted] fill volume will not be marketed in the U.S.

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

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

BALAJEE SHANMUGAM
08/14/2014
Signing on behalf Dr. Rapti Madurawe

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206307

MID-CYCLE COMMUNICATION

Alcon, Inc.
Attention: Paul Nitschmann
Head, Regulatory Affairs Pharmaceuticals
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Dr. Nitschmann:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for finafloxacin otic suspension.

We also refer to the teleconference between representatives of your firm and the FDA on August 11, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Michael Puglisi, Regulatory Project Manager at 301-796-0791.

Sincerely,

{See appended electronic signature page}

William M. Boyd, MD
Cross Discipline Team Leader
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: August 11, 2014, 12:30-1:00 PM, EST

Application Number: NDA 206307
Product Name: finafloxacin otic suspension
Indication: Treatment of acute otitis externa
Applicant Name: Alcon, Inc.

Meeting Chair: William M. Boyd, Cross Discipline Team Leader (CDTL)
Meeting Recorder: Judit Milstein, Chief, Project Management Staff

FDA ATTENDEES

John Farley, Deputy Director, Office of Antimicrobial Products
Renata Albrecht, Director, Division of Transplant and Ophthalmology Products
Wiley A. Chambers, Deputy Director, DTOP
William M. Boyd, Cross Discipline Team Leader (CDTL), DTOP
Rhea Lloyd, Medical Officer, DTOP
Martin Nevitt, Medical Officer, DTOP
Jennifer Harris, Medical Officer, DTOP
Lori Kotch, Pharmacology/Toxicology Team Leader, DTOP
Diana Willard, Chief, Project Management Staff, DTOP
Yunfan Deng, Statistics Reviewer, Division of Biometrics IV
Yan Wang, Statistics Team Leader, Division of Biometrics IV
Philip Colangelo, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology IV
Mariappan Chelliah, CMC reviewer, Office of New Drug Quality Assessment
Balajee Shanmugam, CMC Lead, Office of New Drug Quality Assessment
Banu Zolnik, Biopharmaceutics Reviewer, Office of New Drug Quality Assessment
Angelica Dorantes, Biopharmaceutics Team Leader, Office of New Drug Quality Assessment
Christopher Sese, Independent Assessor, Eastern Research Group
Judit Milstein, Chief, Project Management Staff, DTOP

APPLICANT ATTENDEES

Eric Carlson, Therapeutic Unit Head External Diseases
Firoz Vohra, Project Head Anti-Infectives
Paul Nitschmann, Head, Regulatory Affairs Pharmaceuticals

1. INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2. SIGNIFICANT ISSUES

To date, no significant review issues have been identified.

The Division agreed with Alcon's proposal to develop an appropriate *in-vitro* dissolution method for the proposed drug product as a post-marketing commitment. Alcon indicated that they are having difficulties finding the best method for the dissolution test. The Division invited Alcon to further discuss the method development details of this test.

3. INFORMATION REQUESTS

To date, there are two pending responses to Information Requests:

1. Clinical request issued on July 28, 2014, regarding tables for Clinical Cure and Microbiology Success. Alcon indicated that they are in the final stages of quality control and that this information would be officially submitted no later than August 12, 2014.

2. Non-Clinical request issued on June 6, 2014, with multiple requests for revisions to the labeling. Alcon indicated that the requested information was expected to be officially submitted on August 12, 2014.

4. MAJOR SAFETY CONCERNS/RISK MANAGEMENT

To date, no major safety concerns or need for REMS have been identified

5. ADVISORY COMMITTEE MEETING

To date, the Division has no plans to request an Advisory Committee Meeting

6. LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

Two potential dates were offered to Alcon for the late-cycle meeting:

October 24, 2014, 12:00-1:00 PM, EST or
October 30, 2014, 10:00-11:00 AM, EST.

7. ACTION ITEMS

1. Alcon indicated that they would provide a response to the potential dates in the next few days.

2. The Division also stated that labeling proposal will be sent to Alcon no later than September 25, 2014.

3. Minutes of this teleconference will be issued within 30 days.

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/s/

WILLIAM M BOYD
08/12/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206307

PROPRIETARY NAME REQUEST
UNACCEPTABLE

Alcon Research, LTD.
6201 South Freeway
Mail Code: TC-45
Fort Worth, TX 76134-2099

ATTENTION: Richard Reese
Global Regulatory Project Manager
External Disease and Exploratory Projects

Dear Mr. Reese:

Please refer to your New Drug Application (NDA), dated and received, April 25, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Finafloxacin Otic Suspension, 0.3 %.

We also refer to your correspondence, dated and received May 7, 2014, requesting review of your proposed proprietary name, Xtoro.

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

> This name could result in medication errors due to confusion with two other products that are also under review. Therefore, the ultimate acceptability of your proposed proprietary name, Xtoro, is dependent upon which underlying application is approved first. If another product is approved prior to your product, with a name that would be confused with your proposed name of Xtoro, you will be requested to submit another name.

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. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names,* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

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 Mike Puglisi, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KELLIE A TAYLOR
07/30/2014

Puglisi, Michael

From: Puglisi, Michael
Sent: Monday, July 28, 2014 6:27 PM
To: Tezel, Amy (amy.tezel@alcon.com)
Subject: Clinical Information Request for Finafloxacin - NDA 206307

Hi Amy,

Below please find a request from our clinical reviewer for NDA 206307 for finafloxacin otic suspension, which was submitted on April 25, 2014. Please confirm you have received this request and let me know if you have any questions about it. Also, if possible, please provide an estimate of the expected timing of your response to this request. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

Reviewer's Comments:

Please provide a table for Clinical Cure and for Microbiological Success (or one table for Overall Cure) by age that specifically includes the 12 mo. to 13 years age bracket. A table similar to Table 14.2-46 would be acceptable although the efficacy information is of primary interest. This table is requested for completeness since the Pediatric Written Request mentions this age bracket in particular.

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/s/

MICHAEL J PUGLISI
07/28/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206307

INFORMATION REQUEST

Alcon Research, Ltd.
Attention: Amy Tezel, PhD
Director, Global Regulatory Affairs
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Mrs. Tezel:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Finafloxacin Otic Suspension, 0.3%.

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 1st August in order to continue our evaluation of your NDA.

Drug Substance:

1. **Section 3.2.S.2.2 Description of Manufacturing Process and Process Controls**

Your response to our information request indicates that (b) (4) We accept the proposal. Please update the appropriate sections in the NDA, including 3.2.S.2.2 with this new information. Additionally, we recommend that you update the process description with the following details for each step:

- Specify the order of addition of reagents and solvents where it is not obvious
- Provide the typical concentrations of the reaction mixture
- Indicate actual temperatures instead of room temperature
- If before a particular operation a reaction mixture was cooled, indicate the temperature that the reaction mixture was cooled to that the reaction mixture was cooled to
- Specify whether solids were isolated via filtration or centrifuge
- Specify drying conditions used for isolated solids (time, temperature and pressure).

2. **Section 3.2.S.2.3 Control of Materials/3.2.S.2.3 , Page-2,** (b) (4)

(b) (4)

5. Page-6; table 3.2.S.2.4-5; Specification of (b) (4)

Please include a list of known impurities, in the specification for (b) (4). The GC chromatogram 3.2.S.2.4-3 on page 9 indicates multiple impurities.

6. Section 3.2.S.2.4 , Page-11; table 3.2.S.2.4-5; Specification of (b) (4)

In the table, instead of specifying "Any other impurity", include the specification for known and unknown impurities separately. Please follow ICH recommendations in reporting impurities.

7. Section 3.2.S.2.6 Manufacturing Process Development/3.2.S.2.6 , Page-4, Step 5

8. Section 3.2.S.4.1 Specification

Drug substance specification does not include residual solvents, residual (b) (4) and heavy metals. Please provide justification for not including them in the specification. Since the drug substance batch analysis data indicates (b) (4)% enantiomeric excess, we recommend revising the specification of enantiomeric excess to NLT (b) (4)%.

9. Section 3.2.S.5 Reference Standard

Provide the COA data for the reference sample (R, R)-finafloxacin used for the determination of enantiomeric excess of finafloxacin.

Drug Product:

1. Please submit technical reports TDOC-0015262 and TDOC-0016590 or indicate where in the NDA the reports are located.

2. In the drug product specification, we recommend you use a more robust analytical method other than TLC for the identification test.

3. Please comment on the impact, if any, of the (b) (4) process on the quality of finafloxacin. Indicate possible changes in the level and/or profile of the impurities.

4. We note that (b) (4) are identified as critical process parameters. For a robust (b) (4), we recommend that you include a content uniformity test as an in-process control in Section 3.2.P.3.4. A description of the stratified sampling plan should be included.

5. The Post Approval Stability Protocol and Stability Commitment does not include accelerated testing for the first three commercial batches, but only proposes testing at 25ºC/40%RH long-term condition. The stability protocol should follow ICH Q1A(R2)

recommendations Therefore, amend the Post Approval Stability Protocol Stability Commitment to include accelerated testing at 40ºC/75%RH out to 6 months on the first three commercial batches.

6. We note that you have a cautionary statement "Do Not Freeze" on the label, please provide a one-time freeze-thaw cycling study.

7. On the basis of drug product release and stability data, we recommend revising the acceptance criterion for redispersibility to NMT (b) (4).

8. Two lots of drug products from the primary stability batches have been tested for leachables for 47 and 49 weeks. We recommend this study be conducted through the proposed expiration date (b) (4)

9. Include in the drug product specification a test with acceptance limits for weight change.

Biopharmaceutics:
Although we acknowledge that your proposed drug product is locally acting, we do not agree with your conclusion provided in Amendment Serial 004 dated 6/27/2014, stating that a dissolution test is not needed for your drug product. We recommend that you develop an in vitro dissolution method, which testing conditions (i.e., equipment, volume, speed, medium etc.) are relevant for your proposed otic suspension product. We also recommend that you include the dissolution test in the specifications evaluating the quality of your drug product.

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

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

BALAJEE SHANMUGAM
07/18/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206307

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Alcon Research, Ltd.
Attention: Amy Tezel, Ph.D.
Director, Global Regulatory Affairs
6201 South Freeway, Mail Code: TC-45
Fort Worth, TX 76134-2099

Dear Dr. Tezel:

Please refer to your New Drug Application (NDA) dated and received on April 25, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Finafloxacin Otic Suspension, 0.3%.

We also refer to your amendments dated May 7 and June 13 and 18, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm. Therefore, the user fee goal date is December 25, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process.
If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by the week of September 25, 2014, approximately. In addition, the planned date for our internal mid-cycle review meeting is July 25, 2014. We are not currently planning to hold an advisory committee meeting to discuss this application.

PRESCRIBING INFORMATION

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. 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.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable. We note that you have submitted pediatric studies with this application, and you have not requested a partial waiver or deferral for any additional studies. Once the review of this application is complete, we will notify you whether you have fulfilled the pediatric study requirement for this application.

If you have any questions, call Michael Puglisi, Regulatory Project Manager, at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

WILEY A CHAMBERS
06/23/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206307

METHODS VALIDATION
MATERIALS RECEIVED

Alcon Research Ltd.
Attention: Paul Nitschmann
6201 South Freeway
Mail code TC-45
Fort Worth, TX 76134-2099

Dear Paul Nitschmann:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Finafloxacin Otic Suspension, 0.3% and to our June 5, 2014, letter requesting sample materials for methods validation testing.

We acknowledge receipt on June 10, 2014, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
06/18/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206307 **INFORMATION REQUEST**

Alcon Research, Ltd.
Attention: Richard Reese
Global Regulatory Project Manager, External Disease and Exploratory Projects
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Mr. Reese:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Finafloxacin Otic Suspension, 0.3%.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a written response by June 30th in order to continue our evaluation of your NDA.

1. Since your proposed drug product is a suspension, the dissolution test should be added to the specifications of the drug product. Therefore, develop an in vitro dissolution test that is optimal for your proposed otic suspension product.

2. Provide the dissolution method development report with the following information/data:

    a) Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product. It is noted that in general, lower rotation speeds are used for the dissolution of suspensions (25 rpm). If a surfactant is used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified.

    b) Provide the complete dissolution profile data (individual, mean, SD, profiles) generated during the method development. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim);

    c) A list of all relevant manufacturing variables and material attributes affecting the dissolution of your proposed product;

d) Data supporting the discriminating capability of the proposed dissolution method for meaningful manufacturing changes implemented to your proposed product. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e., ± 10-20% change to the specification-ranges of these variables) for the most relevant manufacturing variables (e.g. drug substance particle size etc.).

3. Note that the discriminating ability is not only determined by the dissolution method settings but also by the selected specification-sampling time point and specification value. For the selection of the dissolution acceptance criterion of your product, the following points should be considered:

   - The complete dissolution profile data (e.g., 15, 20, 30, 45, 60, etc. minutes) from the pivotal clinical and PK batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criteria of your product.

   - Specifications should be based on average in vitro dissolution data (n=12).

   - The specification-time point should be selected when Q = (b) (4)% dissolution occurs.

4. ICH Q11 notes that impurities introduced or created early in the manufacturing process typically have more opportunities to be removed in purification operations than impurities generated late in the manufacturing process. In this context we note that (b) (4) [redacted] is carried out under cGMP.

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

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

BALAJEE SHANMUGAM
06/10/2014

Puglisi, Michael

From: Puglisi, Michael
Sent: Friday, June 06, 2014 8:15 AM
To: Tezel, Amy (amy.tezel@alcon.com)
Subject: Nonclinical Information Request - NDA 206307

Hi Amy,

Below please find an information request from our nonclinical reviewer for the finafloxacin NDA. Please confirm receipt and let me know if you have any questions. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

Reviewer's Comments:

1. *Provide human equivalent dose (HED) estimates for both pediatric and adult patients calculated by AUC and C_{max}, for each dose in each GLP toxicology study to the NDA, or indicate where in the NDA this information is located. Please provide the calculations and assumptions used.*

2. *Regarding the draft label Section 13.1 Carcinogenesis, mutagenesis, impairment of fertility, the support for the statement* (b) (4) *was not identified in the NDA. Either indicate where in the NDA the list was provided, or provide to the NDA a list of each fluoroquinolone in the class which you consider relevant to the evaluation of the carcinogenic potential of finafloxacin.*

3. *Regarding the draft label Section 13.1 Carcinogenesis, mutagenesis, impairment of fertility, the support for the statement "* (b) (4) *" was not identified in the NDA. Either indicate where in the NDA the list was provided, or provide to the NDA a list of each class to which you refer, including each class member which you consider relevant to the evaluation of the genotoxic potential of finafloxacin.*

4. *From a nonclinical perspective, the differences between AL-60371 and AL-60371A are unclear. In the Pharmacology Written Summary (module 2.6.2.1), you reported that "Finafloxacin hydrochloride (AL-60371A), the hydrochloride salt of finafloxacin, free base (AL-60371), was used in early in vitro studies. Due to stability issues, the free base was used in later in vivo studies." The ongoing review notes that AL-60371A was used for oral dosing in the healthy volunteer trial # C-10-007, as well as one safety pharmacology study, several pharmacokinetic studies, and the 14-day GLP rabbit study (TDOC-0012256).*

a. *Either indicate where an explanation of the two test articles is provided in the NDA, or provide to the NDA an explanation and comparison of the physical and ADME properties of AL-60371 and 60371A.*

b. *Please verify that BYK60621 (CAS # 209342-41-6) is finafloxacin free base.*

5. *Initial review found that several of the nonclinical toxicology study reports (e.g. # 197/2000, 202/2009, 45/2001, 63/2001) have GLP comments regarding the computer systems that raise questions about the validity of the reports. It is not entirely clear why these comments were added to the reports. For each report with non-GLP computer systems: define and explain each abbreviation used to describe the computer problems; explain what was outside GLP; and explain if/how the issues affected the collection and analysis of data.*

   a. *E.g. The 14-day rat study (report # 202/209) states (page 6), "Comment: Computer system usage and maintenance of the department FIT/OI (standard commercial components) did not fulfill GLP requirements. However, general system features and application-specific software design, documentation and validation assure data integrity."*

   b. *E.g. the rat 4-week oral toxicity study (report # 197/2000) states (page 5), "Comment: Computer system usage and maintenance of the department AOI (standard commercial components) do not fulfill GLP requirements. However, general systems features and application-specific software design, documentation and validation assure data integrity."*

   c. *E.g. The rat embryofetal study (report # 63/2001) and the 2-week dog study (report # 45/2001) each state on page 5 that "Computer system usage and maintenance of the department ADI, FIT/OI or HIS, respectively (standard commercial components) did not fulfill GLP requirements before 1th January 2006. However, general systems features and application-specific software design, documentation and validation assure data integrity."*

6. *Two of the* (b) (4) *study reports (#202/2009 and #45/2001) have lines of illegible text (presumably due to pdf rendering); the meaning is not always clear from the context. Submit fully legible study reports to the NDA.*

7. *Initial review of the GLP toxicology studies did not identify complete information regarding the test article characterization for all reports [e.g. certificates of analysis (COA), strength, purity, individual impurities, homogeneity, and stability]. For report # 49/2006 (non-GLP) and each GLP toxicology report lacking this information, either indicate where in the NDA the information is located, or provide the information to the NDA.*

   a. *For the non-GLP rat fertility and early embryonic development study (report # 49/2006), review noted the summary information (page 8) but has not found the supporting information.*

   b. *E.g. the rat embryofetal study (report # 63/2001). Review noted the summary information (page 13), with the statement "analysis of the test solutions was not performed."*

   c. *E.g. the rabbit embryofetal study (372001). Review noted the summary statements (page 11) but has not find supporting information.*

   d. *E.g. the Ames study (report # 198/2000).*

   e. *E.g. the two guinea pig studies (report # 0013396 and # 1108012).*

   f. *E.g. a rat 2-week study (report # 202/2009).*

g. *E.g. the 4-week rat study (report #197/2000) mentioned in the draft label (section 8.1).*

h. *E.g. the iv dog study (report # 45/2001).*

8. *For the 4-week rat study (report #197/2000) and the iv dog study (report # 45/2001), the composition of the test article vehicle and the control test article was not clear upon initial review. Please indicate where in the study reports these data are located, or provide them to the NDA.*

9. *For the toxicology study reports, ensure that all sections written in German already have English translations in the study report, or provide English translations to the NDA. For example, for report # 372001, it is not clear whether page 186 is completely translated.*

10. *Regarding the proposed draft label section 12.1 Mechanism of action, the initial review noted the submission of the three publications (Emrich et al. 2010; Higgins et al. 2010; Dalhoff et al. 2011). If you have other information supporting the proposed language "finafloxacin … targets bacterial DNA gyrase and topoisomerase IV enzymes. … Evidence that finafloxacin targets DNA gyrase and/or topoisomerase IV was shown", please either indicate where in the NDA the data are located, or provide these data to the NDA.*

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/s/

MICHAEL J PUGLISI
06/06/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206307

REQUEST FOR METHODS VALIDATION MATERIALS

Alcon Research Ltd.
Attention: Richard Reese
6201 South Freeway, Mail code TC-45, Fort Worth, Texas 76134-2099
FAX: (817) 551-4630

Dear Richard Reese:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Finafloxacin Otic Suspension, 0.3%.

We will be performing methods validation studies on Finafloxacin Otic Suspension, 0.3%, as described in NDA 206307.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

HPLC Assay and Identification of Finafloxacin Drug Substance and Impurities

Samples and Reference Standards

(b) (4)

Equipment

1 (b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
06/05/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206307

NDA ACKNOWLEDGMENT

Alcon Research, Ltd.
Attention: Richard Reese
Global Regulatory Project Manager
6201 South Freeway, Mail Code: TC-45
Fort Worth, TX 76134-2099

Dear Mr. Reese:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Finafloxacin Otic Suspension, 0.3%

Date of Application: April 25, 2014

Date of Receipt: April 25, 2014

Our Reference Number: NDA 206307

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 24, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions

to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please call me at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Michael Puglisi
Regulatory Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

MICHAEL J PUGLISI
05/06/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 110576

MEETING MINUTES

Alcon Research, Ltd.
Attention: Richard O. Reese
Global Project Regulatory Manager
6201 South Freeway, Mail Code R3-50
Fort Worth, TX 76134-2099

Dear Mr. Reese:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AL-60371 (finafloxacin otic suspension) 0.03%.

We also refer to the Type-B, Pre-NDA teleconference held between representatives of your firm and the FDA on September 27, 2013.

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 Michael Puglisi, Regulatory Project Manager, at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Date/Time:	September 27, 2013, 10:00 am
Meeting Location:	Teleconference
Meeting Type:	Type B – Pre-NDA
Application:	IND 110576
Drug:	AL-60371 (finafloxacin otic suspension)
Sponsor:	Alcon Research, Ltd.
Indications:	For the ototopical treatment of acute bacterial otitis externa
Meeting Chair:	Wiley Chambers
Meeting Recorder:	Michael Puglisi

FDA PARTICIPANTS:
Edward Cox/ Director, Office of Antimicrobial Products
David Roeder/ Associate Director for Regulatory Affairs
Richard Moscicki/ Deputy Director, Center for Drug Evaluation and Research
Renata Albrecht/ Division Director
Wiley Chambers/ Deputy Division Director
William Boyd/ Clinical Team Leader
Sonal Wadhwa/ Medical Officer
Rhea Lloyd/ Medical Officer
Martin Nevitt/ Medical Officer
Simone Shurland/ Clinical Microbiology Reviewer
Solomon Chefo/ Statistics Reviewer
Dongliang Zhuang/ Statistics Reviewer
Yoriko Harigaya/ Clinical Pharmacology Reviewer
Philip Colangelo/ Clinical Pharmacology Team Leader
Michael Puglisi/ Regulatory Project Manager

INDEPENDENT ASSESSOR FOR PDUFA V:
So Hyun Kim/ Eastern Research Group, Inc.

SPONSOR PARTICIPANTS:
Mike Brubaker/ Therapeutic Unit Head, External Disease
Firoz Vohra/ Project Head
Paul Nitschmann/ Regulatory Affairs
Richard Reese/ Regulatory Affairs
Krista Crenshaw/ Biostatistics
Sally Scheib/ Clinical Sciences
Celeste Mclean/ Clinical Sciences
Joe Dajcs/ Research
Napoleon Alejandro/ Toxicology

Kyong Bae/ Medical Safety
Brent Boudreaux/ CMC

MEETING OBJECTIVE:
To discuss the planned submission of an NDA for AL-60371 (finafloxacin otic suspension) for the ototopical treatment of acute bacterial otitis externa.

SUMMARY OF DISCUSSION:
Agency responses to the questions outlined in the August 26, 2013, background package (see bolded text below) were provided to the Sponsor in an email dated September 23, 2013 (see text in italics below). This meeting served to clarify those responses. Discussion during the meeting is reflected in normal font.

QUESTIONS FOR DISCUSSION:

Clinical:

1. **An integrated analysis of exposure data and adverse event data across the 4 clinical studies (C-10-007, C-10-022, C-10-018 and C-10-019) will be included in this submission. In addition, exposure data and adverse event data will be integrated separately for the 2 Phase 3 clinical studies, C-10-018 and C-10-019.**

   Does the Agency agree with this proposal for integration of safety data?

   Agency Response:

   Yes, the proposal is acceptable. Additionally, patient narratives and case report forms for those who discontinue for any reason should be included.

   Meeting Discussion: The Agency stated it is acceptable to provide narratives only for discontinuations related to adverse events provided that case report forms for all discontinuations are submitted.

2. **Does the Agency agree with the content, format, and location of the proposed efficacy results for the NDA?**

   Agency Response:
   The proposed presentation of the pooled efficacy results is acceptable. However, the individual study reports and datasets for each study should also be included in Module 5 of the NDA submission.

   We recommend that in any of the pooled results you also present the individual study results together as in Table formats 1 and 2 below and by study visit (Day 3, Day 8, and Day 11).

Table Format 1: Clinical Cure Rate at Day 11 (TOC) for Pathogen Positive Subsets of ITT Population

STUDY C-10-018					
	Fina (N = 147) n (%)	**Veh (N = 130) n (%)**	**Difference**	**95% CI**	**p-Value**
	101 (68.7)	52 (40.0)	28.7	(17.4, 40.0)	<0.001
STUDY C-10-018					
	Fina (N = xxx) n (%)	**Veh (N = xxx) n (%)**	**Difference**	**95% CI**	**p-Value**
	xxx (xx.x)	xx (xx.x)	xx.x	(xx.x, yy.y)	x.xxx
POOLED					
	Fina (N = xxx) n (%)	**Veh (N = xx) n (%)**	**Difference**	**95% CI**	**p-Value**
	xxx (xx.x)	xx (xx.x)	xx.x	(xx.x, yy.y)	x.xxx

We also recommend that your Table Format 2 be presented in the format below including in the table: the number and percent of subjects with the event, the median time and confidence interval, point and 95% confidence interval (CI) estimates for the difference in the two medians, and the point and 95% confidence interval estimates for the hazard ratio.

Table Format 2: Time to Cessation of Pain for Pathogen Positive Subset of ITT Population

	STUDY C-10-018		**STUDY C-10-018**		**POOLED**	
	Fina (N = 147)	**Veh (N = 130)**	**Fina (N = xxx)**	**Veh (N = xxx)**	**Fina (N = yyy)**	**Veh (N = yyy)**
Event	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Median (95% CI)	xx.x (xx.x,xx.x)	xx.x (xx.x,xx.x)	xx.x (xx.x,xx.x)	xx.x (xx.x,xx.x)	xx.x (xx.x,xx.x)	xx.x (xx.x,xx.x)
Difference in Medians (95% CI) [a]	xx.x (xx.x, xx.x)		xx.x (xx.x, xx.x)		xx.x (xx.x, xx.x)	
Hazard Ratio (95% CI)	xx.x (xx.x, xx.x)		xx.x (xx.x, xx.x)		xx.x (xx.x, xx.x)	

p-value	x.xxx	x.xxx	x.xxx

Meeting Comment: There was no discussion of this matter.

3. **Does the Agency agree with the content, format, and location of the proposed microbiological results for the NDA?**

Agency Response:
The proposed presentation of the pooled microbiological results (Table 4 of meeting package) is acceptable. However, the microbiological results including the datasets for each study should also be included in Module 5 of the NDA submission.

With respect to the content, format and location of the proposed microbiological results for the NDA package; the microbiology information and data should also include the following:

- *Provide time kill and bactericidal concentrations of the activity of finafloxacin against potential pathogens*
- *Provide data from studies that investigated the development of resistance to finafloxacin.*
- *The methodology for in vitro susceptibility testing should be performed using standardized method, such as the methods recommended by the Clinical and Laboratory Standards Institute (CLSI). Quality Control (QC) procedures and data should be provided which involve performance testing against standard reference strains recognized by the Agency such as those obtained from the American Type Culture Collection (ATCC).*
- *The details of the microbiological methods used in the clinical trial or a copy of the Laboratory manual should be provided which describe the methods used for collection, shipping, transport, identification and speciation of bacterial isolates.*
- *Submit clinical microbiology datasets for the clinical trials in standardized format which provides:*
    - *All isolates cultured from patients during the conduct of the clinical trials (at baseline, end of treatment and/or test of cure) including the in vitro susceptibility results. The methods used for susceptibility testing should be similar to the methods used in non-clinical studies and performed using standardized methods such as those recommended by CLSI. Routine QC procedures and data should accompany all susceptibility results.*
    - *A correlation of the baseline pathogen with clinical outcome (cure, failure) as well as microbiological outcome (eradication, presumed eradication and persistence).*
    - *Determine resistance development by correlating changes in the phenotype (such as in vitro susceptibility) and/or genotype (such as mutations) of the baseline and pathogens collected at other time points with clinical and microbiological outcome.*

*For further information, please refer to the **FDA Guidance for Industry: Microbiological Data for Antibacterial Drug Products – Development, Analysis, and Presentation.** While this document is meant primarily for the development of clinical microbiology data for systemic antibacterials, it can be used to provide information on the type of data we like to have submitted for an NDA application. A link to document can be found at the following website:*
(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM182288.pdf)

Meeting Discussion: In regard to susceptibility testing, citing a lack of systemic breakpoint data at this time, the Sponsor asked if NDA could be submitted without this information. The Agency stated that the sponsor should provide the information they have and provide an explanation for what is not available at the time of the NDA submission.

4. **Does the Agency agree with the content and format of the proposed efficacy results for the package insert?**

Agency Response:
While labeling is a review issue, it is unlikely that the proposed microbiological efficacy results will be included in any labeling.

Meeting Comment: There was no discussion of this matter.

5. **Alcon will provide the Agency with specifications of the submission data package including the individual studies and the integrated analyses.**
Does the Agency agree with this proposal for the submission data package?

Agency Response: We agree with the proposed submission package. However, you stated that:

"SAS programs will be provided for the key efficacy endpoints of studies C-10-018 and C-10- 019 as well as for the integrated efficacy analyses. SAS programs will not be provided for studies where the analyses are mainly descriptive (ie, C-10-007 and C-10-022)".

We recommend that you submit all datasets and SAS programs used to generate the efficacy and safety results reported in your clinical study report. We may request additional data information during the review process if deem necessary.

You also stated that:

"Although the datasets to be submitted will not be fully CDISC compliant, they include certain elements of the CDISC standards such as use of maximum of 8 characters for the variable name lengths and have labels no more than 40 characters in length. At the beginning of each define.pdf will be a listing of the relevant datasets, with descriptive

labels and a link to the actual data file. The define.pdf will also provide information on derivations and sources, as appropriate, for each dataset."

We strongly encourage you to consider the implementation and use of data standards for your NDA submission especially for the phase 3 studies and for the ISS and ISE analyses. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

Meeting Discussion: The Sponsor stated they do not yet have CDISC standards in place and they will use existing standards for data reporting. The Agency stated this is acceptable as this is not a requirement but a strong recommendation. The Sponsor stated that they are working towards meeting the CDISC standard.

The Sponsor stated that they are targeting October 31, 2013, for submission of the NDA. They confirmed the NDA will be complete at the time of submission.

ACTION ITEMS:
The Agency agreed to issue minutes of this teleconference within 30 days.

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

/s/

WILEY A CHAMBERS
10/25/2013