

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208073Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 208073

SUPPL #

HFD #

Trade Name Xiidra

Generic Name lifitegrast ophthalmic solution

Applicant Name Shire Development LLC

Approval Date, If Known July 11, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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

YES NO

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

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:

c) Did the applicant request exclusivity?

YES NO

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

(b) (4)

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

YES NO

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

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.

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: Eithu Z. Lwin, PharmD
Title: Regulatory Health Project Manager
Date: July 11, 2016

Name of Office/Division Director signing form: Wiley A. Chambers, MD
Title: 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/

EI THU Z LWIN
07/11/2016
NDA 208073, Xiidra

WILEY A CHAMBERS
07/12/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208073 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Xiidra Established/Proper Name: lifitegrast Dosage Form: ophthalmic solution 5%		Applicant: Shire Development LLC Agent for Applicant (if applicable):
RPM: Eithu Z. Lwin		Division: Division of Transplant and Ophthalmology Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>July 22, 2016</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		Complete Response- 10/16/2015
❖ 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 _____		<input type="checkbox"/> 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.

Review priority: Standard Priority
 Chemical classification (new NDAs only): Type 1
(confirm chemical classification at time of approval)

- | | |
|-----------------------------------------------------------|---------------------------------------------------|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

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

NDAs: Subpart H

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

Subpart I

- Approval based on animal studies

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

BLAs: Subpart E

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

Subpart H

- Approval based on animal studies

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

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> 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	<input checked="" type="checkbox"/> No <input type="checkbox"/> 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.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> 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 <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Approval 7/11/2016 Complete Response 10/16/2015
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input type="checkbox"/> Included See labeling attached to action letter
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included 2/25/2015
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input type="checkbox"/> Included See labeling attached to action letter
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included 2/25/2015
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Original applicant-proposed labels • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included 2/25/2015 <input checked="" type="checkbox"/> Included 5/16/2016
❖ Proprietary Name	
<ul style="list-style-type: none"> • Review(s) (<i>indicate date(s)</i>) • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) 	3/8/2016, 4/15/2015 3/10/2016, 4/29/2015
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: 3/24/2015 DMEPA: 5/27/2016 and 6/4/2015 Other: OPDP: 5/9/2016 DMPP/PLT (DRISK): 5/9/2016 DPMH: 9/16/2015 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	4/28/2015
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>6/24/2015</u> If PeRC review not necessary, explain: _____ 	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	5/18/2016, 10/2/2015, 9/29/2015, 8/31/2015, 8/27/2015, 8/14/2015, 6/29/2015, 6/2/2015, 4/7/2015, 3/23/2015, 3/20/2015, 3/12/2015
❖ 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)	PeRC Meeting Minutes 7/8/2015
❖ Minutes of Meetings	
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	Meeting withdrawn, Preliminary Comments issued 12/8/2015
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	5/15/2014
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	12/15/2010
<ul style="list-style-type: none"> Mid-cycle Communication (<i>indicate date of mtg</i>) 	6/4/2015
<ul style="list-style-type: none"> Late-cycle Meeting (<i>indicate date of mtg</i>) 	9/3/2015
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	CMC WRO 12/12/2014
❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> Date(s) of Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	7/11/2016, 10/16/2015
Deputy Division Director Summary Review (<i>indicate date for each review</i>)	6/17/2016, 10/5/2015
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	6/17/2016, 10/5/2015
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical	

❖ Clinical Reviews		
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No separate review
• Clinical review(s) (<i>indicate date for each review</i>)		4/27/2016 and 8/12/2015 Filing: 3/1/2016, 3/19/2015
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)		Page 64-67 of Clinical Review 4/27/2016
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵		COA Review 6/23/2016
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)		<input type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 		6/30/2015
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)		Review Summary: 6/26/2015 OSI letters: 6/24/2015, 6/11/2015, 6/9/2015
Clinical Microbiology		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
Biostatistics		<input type="checkbox"/> None
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)		5/27/2016, 7/22/2015 Filing: 2/11/2016, 3/20/2015
Clinical Pharmacology		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)		4/20/2015 Filing: 3/19/2015
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)		<input checked="" type="checkbox"/> None requested

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

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	4/26/2016, 7/31/2015 Labeling: 3/1/2016 Filing: 3/13/2015
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	5/2/2016, 7/28/2015 Review #1 Addendum: 9/25/2015 Filing: 4/23/2015
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Page 159-160 of Integrated Quality Assessment 7/28/2015
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable, see page 8-11 of IQA Review #1 Addendum 9/25/2015 Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

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

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/

EI THU Z LWIN
07/15/2016
NDA 208073 Action Package Checklist

From: Milstein, Judit
To: [Barry, Alida \(abarry@shire.com\)](mailto:abarry@shire.com)
Cc: [Lwin, Ei Thu \(ElThu.Lwin@fda.hhs.gov\)](mailto:ElThu.Lwin@fda.hhs.gov)
Subject: Following up on your proposed labeling for NDA 208073/Xiidra
Date: Wednesday, May 18, 2016 10:34:00 AM

Alida,

In order to evaluate your proposed revisions to the 8.1 Pregnancy section of the PI, please provide summaries of the testing facility historical data you are using to support your position that the findings in the embryofetal developmental toxicity studies are incidental in both rats and rabbits. The data summarized should include all historical data collected within the last 3-5 years. The historical data summary should calculate litter and fetal incidences, litter and fetal percent, and provide range.

We would appreciate that this information be sent no later than May 25, 2016.

Thank you

Judit Milstein

Chief, Project Management Staff

DTOP/OAP/CDER

Food and Drug Administration

10903 New Hampshire Avenue

Building 22, Room 6180

Silver Spring, MD 20993

Phone: 301-796-0763

Fax: 301-796-9881

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/s/

JUDIT R MILSTEIN

05/18/2016

NDA 208073-Request for Pharm/Tox information



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208073

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Shire Development LLC
300 Shire Way
Lexington, MA 02421

ATTENTION: Alida Barry
Senior Associate, Global Regulatory Affairs

Dear Ms. Barry:

Please refer to your New Drug Application (NDA) resubmission dated and received January 22, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lifitegrast Ophthalmic Solution, 5 %.

We also refer to your correspondence, dated and received, January 22, 2016, requesting review of your proposed proprietary name, Xiidra.

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

If any of the proposed product characteristics as stated in your January 22, 2016, resubmission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact 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 Christina Marshall, Regulatory Project Manager in the Office of New Drugs, at 301-796-3099.

Sincerely,

{See appended electronic signature page}

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

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/s/

TODD D BRIDGES
03/10/2016

Meeting Preliminary Comments
Division of Transplant and Ophthalmology Products

Meeting Date: December 14, 2015

Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Meeting Type: Guidance

Application: NDA 208073

Drug Name: Lifitegrast ophthalmic solution 5%

Indication: Treatment of signs and symptoms of dry eye disease

Sponsor: Shire

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for December 15, 2015, between Shire and the Division of Transplant and Ophthalmology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible.

For the purposes of this response, your questions are in **bold** font and our responses are in *italics* font.

Question 1

Shire seeks the Agency's agreement that the format and content of the planned resubmission application intended to address the deficiencies outlined in the Agency's CRL is sufficient to support its review?

FDA Response:

*We understand that the primary objective of OPUS-3 study was to evaluate the efficacy of lifitegrast ophthalmic solution (5.0%) compared to placebo **in improvement of symptoms of dry eye disease (DED)**, but it is not clear to us from the study protocol as well as from the statistical analysis plan that the results for **the signs of DED** will be included in the clinical study report and in the integrated summary of efficacy.*

The Agency expects that the results for all the signs of DED variables that were provided during the initial NDA submission also be provided for the individual OPUS-3 study and for the integrated summary of efficacy. We otherwise agree with your planned format and content.

Question 2

Does the Agency consider that an Advisory Committee will be convened during the review of the resubmission application?

FDA Response:

There are currently no plans to convene an Advisory Committee during the review of the resubmission application. However, a final decision regarding an Advisory Committee meeting will be made after the application is resubmitted.

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/s/

CHRISTINA D MARSHALL
12/08/2015



NDA 208073

DISCIPLINE REVIEW LETTER

Shire Development, LLC
Attention: Kim McCormick, PharmD
Senior Director, Global Regulatory Affairs
725 Chesterbrook Boulevard
Wayne, PA 19087-5637

Dear Dr. McCormick:

Please refer to your New Drug Application (NDA) dated and received February 25, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lifitegrast ophthalmic solution, 5%.

We also refer to your amendments dated March 25, June 10, June 16, June 18, and July 20, 2015.

Our review of the Chemistry, Manufacturing, and Controls (CMC) section of your submission is complete, and we have identified the following deficiencies:

1. Regarding your response dated June 16, 2015 to the Information Request dated June 2, 2015, you have not provided adequate safety information to support the drug substance specification limit of (b)(4) ppm for (b)(4). Since no detectable levels of (b)(4) were present in the late-stage process batches tested to date (detection limit of (b)(4) ppm), revise the acceptance limit to "less than (b)(4) ppm."
2. The (b)(4) provision proposed for (b)(4) is not acceptable at this time. You will need to demonstrate your understanding of the factors that influence the residual levels of (b)(4) and provide information/data demonstrating that variability of the process produces predictable/acceptable levels of residual (b)(4). Removal of the test for (b)(4) may be requested once adequate information/data are available.
3. In the leachable analysis from your stability study, you have indicated that most of the impurities are drug product degradants and hence are not tracked in the leachables study. Provide evidence that these impurities originate from the drug product. Identify and qualify (i.e. provide safety data) the remaining unknown impurities that you delineated as leachables.

We are providing these comments to you before completing our review of your 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.

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

Sincerely,

**Balajee
Shanmugam -S**

Digitally signed by Balajee Shanmugam -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300217143,
cn=Balajee Shanmugam -S
Date: 2015.10.02 09:54:50 -04'00'

Balajee Shanmugam
Acting Branch Chief
Division of New Drug Products I
Office of New Drug Products
Center for Drug Evaluation and Research

Dear Dr. McCormick,

Please refer to your New Drug Application (NDA) submission received on February 25, 2015. We have the following information request:

We note the submission dated September 9, 2015, which contains the container material make-up for lifitegrast that was used to supply the toxicity studies versus that proposed for the marketed product.

For clarity, please tell us which lifitegrast clinical trials utilized the container proposed for marketing.

Please let me know if you have any questions.

Sincerely,

Christina Marshall, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
Telephone: 301-796-3099

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/s/

CHRISTINA D MARSHALL
09/29/2015
NDA 208073 Information Request



NDA 208073

DISCIPLINE REVIEW LETTER

Shire Development, LLC
Attention: Kim McCormick, PharmD
Senior Director, Global Regulatory Affairs
725 Chesterbrook Boulevard
Wayne, PA 19087-5637

Dear Dr. McCormick:

Please refer to your New Drug Application (NDA) dated and received February 25, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for lifitegrast ophthalmic solution, 5%.

We also refer to your amendments dated March 23, March 25, June 3, June 8, June 10, June 16, June 18, and July 20, 2015.

Our review of the Clinical section of your submission is complete, and we have identified the following deficiencies:

Clinical

Your application does not provide substantial evidence of efficacy for lifitegrast ophthalmic solution, 5%, in the treatment of dry eye disease because none of the submitted studies with efficacy evaluations were successful.

1. The Phase 2 Dry Eye study did not meet its primary efficacy endpoint, inferior corneal staining score at Day 84. None of the lifitegrast groups achieved a statistically significant difference in the inferior corneal staining score at Day 84 compared to vehicle although there were increasing numerical improvements in the inferior corneal staining score with higher lifitegrast doses.
2. The OPUS-1 study, which was designed based on post-hoc analyses of the Phase 2 Dry Eye study, did not meet its co-primary efficacy endpoints; change from baseline to Day 84 in inferior corneal staining score and visual related function Ocular Surface Disease Index subscale score. Statistical significance was only achieved for the objective efficacy endpoint (the change from baseline to Day 84 in inferior corneal staining score).
3. The OPUS-2 study, which was designed based on the results of the OPUS-1 study, did not meet its co-primary efficacy endpoints: change from baseline to Day 84 in inferior corneal staining score and eye dryness score measured on the visual analogue scale.

Statistical significance was only achieved for the subjective efficacy end point (the change from baseline to Day 84 in eye dryness score).

As communicated to you on August 14, 2015, the identified deficiencies preclude discussion of labeling changes and/or postmarketing requirements/commitments at this time.

We are providing these comments to you before completing our review of your 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.

If you have any questions, call Judit Milstein, Chief, Project Management Staff, at 301-796-0763.

Sincerely,

{See appended electronic signature page}

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

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/s/

WILLIAM M BOYD
08/27/2015



NDA 208073

DEFICIENCIES PRECLUDE DISCUSSION

Shire Development, LLC
Attention: Kim McCormick, PharmD
Senior Director, Global Regulatory Affairs
725 Chesterbrook Boulevard
Wayne, PA 19087-5637

Dear Dr. McCormick:

Please refer to your New Drug Application (NDA) dated and received February 25, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for lifitegrast ophthalmic solution, 5%.

We also refer to our April 7, 2015, letter in which we notified you of our target date of July 28, 2015, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals And Procedures – Fiscal Years 2013 Through 2017.

As part of our ongoing review of your application, we have identified deficiencies that preclude discussion of labeling and postmarketing requirements/commitments at this time. This notification does not reflect a final decision on the information under review.

If you have any questions, call Judit Milstein, Chief, Project Management Staff at 301-796-0763.

Sincerely,

{See appended electronic signature page}

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

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/s/

WILLIAM M BOYD
08/14/2015

**PeRC Meeting Minutes
June 24, 2015**

PeRC Members Attending:

Lynne Yao
Linda Lewis
Gettie Audain
Gregory Reaman
Hari Cheryl Sachs
Wiley Chambers
Lily Mulugeta
Gilbert Burckart
Ikram Elayan
Freda Cooner
Daiva Shetty
Kristiana Brugger
Shrikant Pagay

NON-RESPONSIVE

Xiidra (lifitegrast) Full Waiver

- Proposed Indication: Treatment of symptoms of dry eye disease.
- *PeRC Recommendations:*
 - The PeRC agreed with the plan for a full waiver.

NON-RESPONSIVE

NON-RESPONSIVE

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/s/

GETTIE AUDAIN
07/08/2015



NDA 208073

MID-CYCLE COMMUNICATION

Shire Development, LLC.
Attention: Kimberly McCormick, PharmD
Global Regulatory Affairs
725 Chesterbrook Blvd
Wayne, PA 19087-5637

Dear Dr. McCormick:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xiidra (lifitegrast ophthalmic solution), 5.0%.

We also refer to the teleconference between representatives of your firm and the FDA on June 4, 2015. 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 Christina Marshall, Regulatory Project Manager at (301) 796-3099.

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: June 4, 2015, 10:00-11:00AM EST

Application Number: NDA 208073

Product Name: Xiidra (lifitegrast ophthalmic solution), 0.5%

Indication: Treatment of signs and symptoms of dry eye disease

Applicant Name: Shire Development, LLC

Meeting Chair: William M. Boyd, Cross Discipline Team Leader (CDTL)

Meeting Recorder: Christina Marshall, Regulatory Health Project Manager

FDA ATTENDEES

Renata Albrecht, Director, Division of Transplant and Ophthalmology Products, (DTOP)

Wiley A. Chambers, Deputy Director, DTOP

William M. Boyd, Cross Discipline Team Leader (CDTL), DTOP

Rhea Lloyd, Clinical Reviewer, DTOP

Jennifer Harris, Clinical Reviewer, DTOP

Solomon Chefo, Statistics Reviewer, DTOP

Philip Colangelo, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology IV

Lori Kotch, Pharmacology/Toxicology Team Leader, DTOP

Maria Rivera, Pharmacology/Toxicology Reviewer, DTOP

Anamitro Banerjee, Product Quality Team Leader, Office of New Drug Quality Assessment

Pagay Shrikant, Product Quality Reviewer, Office of New Drug Quality Assessment

Carolyn Yancey, REMS Reviewer, Office of Surveillance and Epidemiology

Roy Blay, Reviewer, Office of Scientific Integrity

Roy Wassel, Safety Reviewer, Office of Surveillance and Epidemiology

Christina Marshall, Regulatory Health Project Manager, DTOP

Judit Milstein, Chief Project Management Staff, DTOP

Marc Goldstein, Independent Assessor, Eastern Research Group

SHIRE ATTENDEES

Daryl Dekarske, Vice President, Global Regulatory Affairs

Kim McCormick, Senior Director, Regulatory Affairs

Howard Mayer, Senior Vice President, Head of Clinical Dev.

Reza Haque, Vice-President, Clinical, Therapeutic Area Head

Michael L Nessly, Head, Biostatistics and Statistical Programming

Amir Shojaei, Development Team Lead

Ken Ford, Senior Director, Pharmaceutical Sciences

Philip E. M. Crooker, Director, Global Regulatory Affairs- CMC

Ruth Reeves, Head of Nonclinical Development Pharmacology

Thomas McCauley, Vice President and Head of Global Nonclinical Development

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

There is an expectation that clinical trials supporting a dry eye treatment indication will demonstrate superiority of the test product over its vehicle in a clinical sign of dry eye in two or more clinical trials and will demonstrate superiority of the test product over its vehicle in a clinical symptom of dry eye in two or more clinical trials.

Regarding clinical signs of dry eye:

1. In the Phase 2 trial, the study did not meet its primary endpoint. The 0.1%, 1% and 5% lifitegrast groups were not statistically significantly different from placebo in inferior corneal staining score (ICSS) at Day 84. While a dose response was demonstrated in ICSS mean change from baseline, the analysis was only seen in a post-hoc analysis of the subgroup of artificial tear users.
2. In OPUS-1, the study did not meet both co-primary endpoints. While there was a statistically significant difference between groups in the clinical sign, Inferior Corneal Staining Score (ICSS), ($p < 0.01$) the other co-primary endpoint, Visually Related Ocular Surface Disease Index (VR OSDI) score, was not statistically significant ($p = 0.79$).
3. In OPUS-2, the study did not meet both co-primary endpoints. The clinical sign, ICSS, was not statistically significant ($p = 0.62$).

Regarding clinical symptoms of dry eye:

1. In the Phase 2 trial, the study did not meet its primary endpoint and therefore secondary symptom endpoints would not normally be considered.
2. In OPUS-1, the study did not meet both co-primary endpoints. The Visually Related Ocular Surface Disease Index (VR OSDI) score was not statistically significant ($p = 0.79$).

3. In OPUS-2, the study did not meet both co-primary endpoints. While there was a statistically significant difference between groups in the clinical symptom, Eye Dryness Score (EDS), ($p < 0.01$), the clinical sign, ICSS, was not statistically significant ($p = 0.62$).

Shire asked the Division if the Clinical Group planned to send any additional Clinical Information Requests. The Division stated that the review is ongoing, but at this time it has no plans to send any additional Clinical Information Requests.

3. INFORMATION REQUESTS

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

1. On May 28, 2015, CMC request was issued; Shire agreed to have their responses formally submitted by June 10, 2015.
2. On June 2, 2015, CMC and Pharmacology/Toxicology request was issued with a response due date of June 16, 2015; Shire agreed to have their responses formally submitted by the requested due date.

4. MAJOR SAFETY CONCERNS/RISK MANAGEMENT

We have identified no major safety concerns to date. There are no Risk Evaluation & Mitigation Strategies (REMS) identified to date for this application beyond routine draft professional labeling for the product.

5. ADVISORY COMMITTEE MEETING

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

6. LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The PDUFA goal date for this application is October 25, 2015 (Priority NME- 8 Months). We would expect the Late Cycle Meeting to be held with you no later than two months prior to the October 25th PDUFA goal date. We will work with you to find a mutually-agreeable date.

7. ACTION ITEMS

1. Shire indicated that they would provide a response to the information requests by their prospective due dates.
2. Kimberly McCormick of Shire and Christina Marshall of DTOP will work together to schedule a mutually-agreeable date and time for the late-cycle meeting.
3. Shire plans to request a meeting with the Agency regarding CMC and sterility concerns.
4. Meeting minutes of this teleconference will be issued within 30 days.

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/s/

WILLIAM M BOYD
06/29/2015



**Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and Ophthalmology
Products**

INFORMATION REQUEST SHEET

DATE: June 2, 2015

To: Kim McCormick, PharmD Global Regulatory Affairs Global Regulatory Lead Lifitegrast/BED and US NBU	From: Christina Marshall, M.S. Regulatory Project Manager
Company: Shire Development, LLC	Division of Transplant and Ophthalmology Products
FAX: kmccormick@shire.com	Fax number: (301) 796-9881
Phone number: 484 -595-8829	Phone number: (301) 796-3099

Subject: NDA 208073 information request for NDA submission dated February 25, 2015

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-1600. Thank you.

2. There is no adequate evidence to support the ocular safety of the proposed acceptance criteria of (b) (4) % for impurities (b) (4). Although the justification provided support for systemic safety, no evidence was provided to support these levels are safe for local (eye) administration. Ensure specifications are equal or less than 0.15% as recommended in ICHQ3A. Alternatively, provide data to support local (ocular) safety.
3. Submit the in vitro mutagenicity assay (Ames) and in vitro chromosomal aberration assay conducted with the five impurities listed under # 2.
4. There is no adequate evidence to support the ocular safety of the proposed acceptance criteria of (b) (4) ppm for (b) (4). Since no detectable levels of (b) (4) were present in the late stage process batches tested to date (detection limit of (b) (4) ppm), reduce specifications to as low as reasonably practicable.
5. There is no adequate evidence to support the ocular safety of the proposed acceptance criteria of (b) (4) ppm for (b) (4). Reduce the specification to levels supported by adequate ocular safety data.
6. Please provide a table with a side-by-side comparison of impurity profiles for nonclinical batches used in the chronic ocular toxicity studies in dogs and rabbits (Studies D6336M-SPD606 and L6329M-SPD606) vs. clinical batches. Please include in the table the proposed specifications for each impurity.

Please let me know if you have any questions.

Sincerely,

Christina Marshall, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
Telephone: 301-796-3099

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/s/

CHRISTINA D MARSHALL
06/02/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208073

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Shire Development, LLC
725 Chesterbrook Blvd.
Wayne, PA 19087

ATTENTION: Kimberly McCormick, PharmD
Senior Director, Global Regulatory Affairs

Dear Dr. McCormick:

Please refer to your New Drug Application (NDA), dated and received, February 25, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lifitegrast Ophthalmic Solution, 5%.

We also refer to your correspondence, dated and received, February 25, 2015, requesting review of your proposed proprietary name, Xiidra.

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

If any of the proposed product characteristics as stated in your February 25, 2015, submission are altered prior to approval of the marketing application, the proprietary name must be resubmitted for review.

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact 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 Christina Marshall, Regulatory Project Manager in the Office of New Drugs, at 301-796-3099.

Sincerely,

{See appended electronic signature page}

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

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/s/

KELLIE A TAYLOR on behalf of TODD D BRIDGES
04/29/2015



NDA 208073

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

Shire Development, LLC.
Attention: Kimberly McCormick, PharmD
Global Regulatory Affairs
725 Chesterbrook Blvd
Wayne, PA 19087-5637

Dear Dr. McCormick:

Please refer to your New Drug Application (NDA) dated and received on February 25, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Xiidra (lifitegrast ophthalmic solution), 5.0%.

We also refer to your amendment dated March 23, 2015.

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**. Therefore, the user fee goal date is October 25, 2015. 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>.

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 July 28, 2015. This date conforms to the 21st Century Review timeline for your application. In addition, , the planned date for our internal mid-cycle review meeting is May 21, 2015. We are not currently planning to hold an advisory committee meeting to discuss this application, however a final decision will be made upon completion of the review of your application.

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

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](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

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

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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We reference the full waiver granted on July 22, 2014, for the pediatric study requirement for this application.

If you have any questions, call Christina Marshall, Regulatory Project Manager, at (301) 796-3099.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, MD
Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

CHRISTINA D MARSHALL
04/07/2015

RENATA ALBRECHT
04/07/2015

Dear Dr. McCormick,

Please refer to your New Drug Application (NDA) submission received on February 25, 2015. We have the following information request regarding the pharmacology/toxicology:

Please submit to the IND a request for a waiver, along with a justification for not conducting the carcinogenicity studies.

Please let me know if you have any questions.

Sincerely,

Christina Marshall, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
Telephone: 301-796-3099

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/s/

CHRISTINA D MARSHALL
03/23/2015

Dear Dr. McCormick,

Please refer to your New Drug Application (NDA) submission received on February 25, 2015. We have the following information request regarding the Statistical Analysis:

In the primary efficacy analysis for Study 1118-DRY-300 (OPUS-2), you stated that '*ANCOVA model of change with treatment, stratum, and treatment by stratum interaction; weights set to stratum size*' was used to assess the treatment effect. However, in the SAS program you referred to in the clinical study report (i.e., **t-eff.sas**), a two sample t-test was used for treatment comparison. Please clarify and submit the right SAS code that was used to produce the primary efficacy results for this study.

Please let me know if you have any questions.

Sincerely,

Christina Marshall, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
Telephone: 301-796-3099

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/s/

CHRISTINA D MARSHALL
03/20/2015



NDA 208073

NDA ACKNOWLEDGMENT

Shire Development, LLC.
Attention: Kimberly McCormick, PharmD
Global Regulatory Affairs
725 Chesterbrook Blvd
Wayne, PA 19087-5637

Dear Dr. McCormick:

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: Xiidra (lifitegrast ophthalmic solution) 5.0%

Date of Application: February 25, 2015

Date of Receipt: February 25, 2015

Our Reference Number: NDA 208073

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 April 26, 2015, 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

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, call, at (301) 796-3099.

Sincerely,

{See appended electronic signature page}

Christina Marshall, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTINA D MARSHALL
03/12/2015
NDA 208073-ACK letter



IND 77885

**MEETING REQUEST-
WRITTEN RESPONSES**

Shire Development LLC
Attention: Philip E. M. Crooker
Director, Global Regulatory Affairs - CMC
725 Chesterbrook Blvd
Wayne, PA 19087

Dear Mr. Crooker:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SPD606 (Lifitegrast) 5.0% Sterile Ophthalmic Solution.

We also refer to your submission dated October 15, 2014, containing a Type B meeting request. The purpose of the requested meeting was to discuss the CMC aspects of the development program for lifitegrast.

Further reference is made to our phone conversation on October 27, 2014, where it was agreed that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your October 29, 2014, background package.

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

Enclosure:
Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: B
Meeting Category: Pre-NDA CMC Meeting

Application Number: IND 77885
Product Name: SPD606 (Lifitegrast) 5.0% Sterile Ophthalmic Solution
Indication: Lifitegrast (5.0%) sterile ophthalmic solution is intended for the treatment of the signs and symptoms of dry eye disease.

Sponsor/Applicant Name: Shire Development LLC
Regulatory Pathway: 505(b)(1)

1.0 BACKGROUND

The proposed indication for the investigational drug product, lifitegrastis for the treatment of the signs and symptoms of dry eye disease.

The objective of the meeting is to discuss specific issues raised in the meeting information package to facilitate NDA submission and filing.

2.0 QUESTIONS AND RESPONSES

1. In the April, 22, 2014 meeting preliminary written comments which served as the official meetings minutes form the follow-up EOP2 CMC meeting, the Agency agreed with Shire that the original drug substance and drug product primary stability batches that contained atypical matter were valid as supportive stability data and could be used to determine the re-test and shelf-life dating. The Agency noted that that Shire should proceed with the proposal to manufacture additional batches and to submit three (3) months real-time and accelerated stability data on the new batches at time of NDA submission. The Agency further noted that Shire should submit a stability update with six (6) months data from these supplemental batches prior to the mid-cycle review.

Shire will provide the six (6) month stability data for both the drug substance and drug product supplemental batches no later than the mid-cycle review milestone. Shire will provide three (3) month stability data for the drug product supplemental batches at time of NDA submission. For the drug substance supplemental batches, Shire will provide three (3) months data on one (1) engineering batch and one (1) month stability data on three (3) process validation batches at time of NDA submission. Shire believes that this plan is consistent with the April 22, 2014 meeting preliminary written comments and will support NDA submission, filing and review.

Agency Response: We agree that the plan is consistent with the April 22, 2014 meeting.

2. The vendor (b) (4) for the proposed (b) (4) has recently received adverse observations resulting from an Agency inspection, including issues related to data integrity. Shire will propose plans to resolve three (3) issues: (1) certifying data associated with the manufacture and testing (b) (4) for NDA review; (2) future batch certification and quality remediation plan for the vendor; and (3) qualifying an alternate vendor in parallel with the quality remediation program. Shire plans to qualify an alternate supplier (b) (4)
- (b) (4)
- Depending on the final vendor selection and technology transfer timeline, those equivalency data may be available by the mid-cycle review. If they are, then Shire would propose to provide those data to the Agency no later than the mid-cycle review. To facilitate the qualification process, Shire would then propose to provide confirmatory equivalency data using (b) (4) supplied by the current and alternate vendor as a post-approval commitment. Does the Agency agree that: (1) equivalency to support qualification of an alternate supplier may be demonstrated (b) (4) and (2) if they are available, will the Agency accept (b) (4) equivalency data to qualify the alternate vendor no later than the mid-cycle review milestone?

Agency Response: We do not agree with the proposal to submit any new information (b) (4) during the NDA review cycle. We refer you to the EOP2 meeting minutes dated August 3, 2011 where only a tentative agreement on the designation of regulatory (b) (4) was made. The specifications (b) (4) were found inadequate due to the lack of acceptance criteria for individual impurities. In addition, it was recommended that further information regarding the designation of the regulatory (b) (4) include: levels of individual impurities levels found in the batches, fate of these impurities in the drug substance, their levels and/or how these impurities are removed or purged during the manufacturing process. We recommend that at the time of the NDA submission complete CMC information including all the information (b) (4) is provided.

3. Shire plans to implement a limited number of minor changes to the drug product manufacturing process prior to NDA submission as a normal consequence of process (b) (4). These changes will all be included as part of the (b) (4) validation campaign. Shire will demonstrate that the changes result in drug product that is considered comparable to the Phase 3 clinical trial material and the entire body of primary and supplemental drug product stability data. A confirmatory stability study will be initiated from samples taken during the completion of process (b) (4) as added assurance of product quality, process control and performance for the proposed commercial process. Does the Agency agree that Shire's approach to executing the proposed (b) (4) commercial process validation campaign is acceptable?

Agency Response: The approach to evaluating the minor changes to the manufacturing process appears reasonable. All supportive data including batch release data should be submitted in the NDA for evaluation. It is unclear how you distinguish (b) (4) stages of the

process. We remind you that for a sterile ophthalmic product such as your proposed drug product, sterility validation data for the commercial process should be provided in the NDA. In addition, the proposed manufacturing facility with the commercial process equipment in place should be ready for inspection at the time of NDA submission.

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/s/

DOROTA M MATECKA
12/12/2014



IND 77885

MEETING MINUTES

Shire Development, LLC
Attention: Mary Newman, MS
Sr. V.P., Regulatory Affairs and CMC
1000 Marina Blvd; Suite 250
Brisbane, CA 94005

Dear Ms. Newman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SPD606 (lifitegrast ophthalmic solution), 5.0%.

The purpose of the May 15, 2014, meeting is to discuss the results of the lifitegrast clinical development program and to discuss the proposed clinical data package that will support registration of lifitegrast for the treatment of the symptoms of dry eye disease.

If you have any questions, call Jacquelyn Smith, M.A., Senior Regulatory Project Manager at 301 796-1600.

Sincerely,

{See appended electronic signature page}

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

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Date: May 15, 2014
Meeting Location: CDER WO22/RM 1315
Meeting Type: B (Pre-NDA)
Application: IND 77885
Drug: SPD606 (lifitegrast ophthalmic solution), 5.0%
Indication: Treatment of the symptoms of dry eye disease
Sponsor: Shire Development, LLC

Division of Transplant and Ophthalmology Products (DTOP)

Renata Albrecht, MD	Director
Wiley Chambers, MD	Deputy Director
Rhea Lloyd, MD	Clinical Reviewer
Martin Nevitt, MD	Clinical Reviewer
Jennifer Harris, MD	Clinical Reviewer
Philip Colangelo, PharmD, PhD	Clinical Pharmacology Team Leader
Yan Wang, PhD	Statistics Team Leader
Dongliang Zhuang, PhD	Statistics Reviewer
Jacquelyn Smith, MA	Senior Regulatory Project Manager

Shire Development, LLC

Randall Brenner, MS	Senior Vice President, Global Regulatory Affairs
Daryl Dekarske, PhD	Vice President, Global Regulatory Affairs
Kim McCormick, PharmD	Director, Regulatory Affairs
Mary Newman, MS	Director, Regulatory Affairs
Howard Mayer, MD	Senior Vice President, Head of Clinical Dev.
Charles Semba, MD	Vice-President, Clinical Medicine
Reza Haque, MD	Vice-President, Clinical, Therapeutic Area Head
Amy Manley, BS	Director, Clinical Operations
Jay Getsy, MD	Senior Director, Clinical Pharmacology
Michael L Nessly, MS	Head, Biostatistics and Statistical Programming
Aparna Raychaudhuri, PhD	Associate Director, Biostatistics
Amir Shojaei, Pharm.D., PhD	Development Team Lead

Purpose of the meeting:

The purpose of the May 15, 2014, meeting is to discuss the results of the lifitegrast clinical development program and to discuss the proposed clinical data package that will support registration of lifitegrast for the treatment of the symptoms of dry eye disease.

Background:

FDA provided preliminary responses (via email on May 7, 2014) to Shire's questions posed in the briefing package dated April 14, 2014. Shire requested (via email on May 8, 2014) that the meeting focus on questions 1-3 and stated that no further discussion is needed for questions 4-11. The questions are presented in **bold** font, preliminary responses are presented in *italic* font and the meeting discussion is presented in normal font.

Preliminary comments**Clinical****Question 1:**

Shire believes that the data from Studies 1, 2, and 3 provides substantial evidence to support an NDA for lifitegrast for the proposed indication as a treatment for symptoms of DED.

Does the Agency agree?**FDA Response:**

The Agency cannot answer the question without a review of the full study reports for all of the completed studies. The review of completed studies is performed after submission of an NDA. As reported in the briefing package, an objective sign, inferior corneal staining score (ICSS) in Study 2, and a subjective symptom, eye dryness score, in Study 3, each demonstrated a statistically significant treatment group difference in the respective studies. The Division expects that each of these positive results would be replicated in at least another trial to demonstrate robustness of results and support a claim of substantial evidence.

Meeting Discussion:

In response to the FDA's preliminary comments, Shire notified FDA that the responses to the preliminary comments for items 4-11 were acceptable and required no further discussion. Shire provided on May 8, 2014, a brief slide deck intended for discussion at the meeting which focused on preliminary comments to Question 1 and Question 3.

Shire stated that the heart of the clinical argument supporting substantial evidence of efficacy to be submitted in the planned NDA would be replicative evidence of a lifitegrast treatment effect for the objective measure (inferior corneal staining; ICSS) in Studies 1 and 2 (Phase 2 and OPUS-1) and replicative evidence for the subjective measure (eye dryness score: EDS) in Studies 2 and 3 (OPUS-1 and OPUS-2), particularly the robust statistical outcome in OPUS-2 for symptoms (EDS).

FDA stated that, as indicated in the preliminary comments, there appeared to be demonstration of efficacy in a sign in at least one trial and a symptom in at least one trial, but FDA was not prepared to state that each had been replicated in more than one study. Whether a lifitegrast NDA would be

approvable with the current data package could not be determined from the briefing package. FDA stated that this would be a review issue when the NDA is submitted and reviewed. The use of subpopulations to demonstrate efficacy and the inability to pre-specify study endpoints that achieve significance were potential issues that would come up during an NDA review.

Shire asked if their understanding was correct that FDA considered that these issues would be review issues and not filing issues. FDA stated that these were review issues, and the clinical portion of an NDA with the current clinical data package was likely fileable. Approvability of a submitted NDA would be a review issue.

Shire asked for FDA's input on whether any additional study that they might conduct should focus on sign or symptom endpoints. FDA indicated that Shire should consider an additional study which focused on replicating findings which were statistically significant in a subset of a previous study but had not been statistically significant in the pre-specified full population of that study. FDA was open to a study that would be similar in design to OPUS-2. FDA acknowledged that sign and symptom may not be achievable in the same study and was amenable to four single endpoint trials in which the same symptom is replicated in two trials and the same sign is replicated in two trials.

Shire asked a question regarding likelihood of a lifitegrast NDA undergoing Advisory Committee (AC) review. FDA would not commit to an AC at this time, although as a new molecular entity, if the Agency did not hold an Advisory Committee meeting, the FDA would need to include the rationale for not having the meeting in any action letter on the application.

Question 2:

Shire believes that lifitegrast has demonstrated objective evidence of biologic plausibility as measured by ICSS, which provides additional support for the proposed indication as a treatment for symptoms of DED.

Does the Agency agree?

FDA Response:

The Division would need to review the full study report to answer the question. Biologic plausibility is not a criterion for demonstrating substantial evidence of efficacy or safety.

Meeting Discussion:

There was no further discussion of this item at the meeting.

Question 3:

Shire believes that the clinical efficacy data presented demonstrate a paradoxical relationship between the sign and symptom covariables, therefore the clinical study data should be assessed on the merit of the individual endpoint results.

Does the Agency agree?

FDA Response:

Clinical study data may be assessed on the merit of the individual endpoint results. However, all positive results are recommended to be replicated to demonstrate robustness of the results for each sign and symptom studied for the indication. Safety and efficacy is recommended to be demonstrated in at least two adequate and well-controlled, multi-center, independent trials. You may wish to consider demonstrating efficacy based on subjective findings in a different patient group or in a different clinical study than the patient group or clinical study which demonstrates efficacy based on objective findings.

Meeting Discussion:

Refer to Question 1. FDA acknowledged that achieving a sign and symptom endpoint within the same study may not always occur and was willing to accept a symptom-only primary endpoint or a sign-only primary endpoint in a clinical study, as long as ultimately both the sign and symptom findings were replicated (i.e., potentially 4 studies).

Question 4:

Shire believes that the extent and duration of patient exposure from the lifitegrast DED clinical program is sufficient to support the NDA.

Does the Agency agree?

FDA Response:

The duration and exposure of lifitegrast 5% dosed BID, as summarized in the studies submitted in the briefing package, appear adequate to support NDA review. A determination of the adequacy of the data to support the approval of an application requires submission and review of all completed studies.

Meeting Discussion:

There was no further discussion of this item at the meeting.

Statistical

Question 5:

The statistical analysis plan for the integrated summary of efficacy (ISE), which includes a table of contents for the ISE, is included in Appendix 2.

Does the Agency agree with the analysis plans for the ISE?

FDA Response:

Agree.

Meeting Discussion:

There was no further discussion of this item at the meeting.

Question 6:

The statistical analysis plan for the integrated summary of safety (ISS), which includes a table of contents for the ISS is included in Appendix 4.

Does the Agency agree with the analysis plans for the ISS?

FDA Response:

Agree.

Meeting Discussion:

There was no further discussion of this item at the meeting.

Question 7:

Shire intends to submit the summary-level clinical site data for 4 studies (Study 1 [Phase2], Study 2 [OPUS-1], Study 3 [OPUS-2], and SONATA). A single summary-level dataset and DEFINE.pdf will be provided in the format described in the draft guidance “Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER’s Inspection Planning” dated December 2012. The dataset will contain the principal investigator name and information only. The MAXIMUM FINANCIAL DISCLOSURE AMOUNT and FINANCIAL DISCLOSURE INFORMATION will be presented by principal investigator, but will reflect the financial disclosure information for all subinvestigators listed on the 1572.

Does the Agency agree with the plans for the submission of the summary-level clinical site data in the NDA?

FDA Response:

Agree.

Meeting Discussion:

There was no further discussion of this item at the meeting.

Question 8:

Shire plans to submit the 6 study’s (Phase 1, Phase 2 DED, Phase 2 Allergic Conjunctivitis, OPUS-1, OPUS-2, SONATA) datasets in Clinical Data Interchange Standards Consortium Study Data Tabulation Model (Implementation Guide Version 3.1.2 or later) and Analysis Data Model (ADaM) Implementation Guide (Version 1.0 or later) format (including subject-level analysis dataset) with associated metadata including the DEFINE.xml. As such, Shire does not intend to submit patient profiles for these studies. The Statistical Analysis System programs for the studies (OPUS-1, OPUS-2, SONATA) deriving the ADaM datasets based on raw data will be included in the NDA. Additionally, the programs for the primary efficacy and secondary efficacy analysis from ADaM data will be included in the NDA. The analysis programs will include the statistical models with the necessary data steps using the ADaM datasets as source.

Does the Agency agree with the plans for the datasets, Statistical Analysis System programs, and the documentation to be included in the NDA?

FDA Response:

Agree.

Meeting Discussion:

There was no further discussion of this item at the meeting.

Regulatory

Question 9:

Based on the unmet medical need for improvement in symptoms of DED, Shire intends to request priority review.

Does the Agency agree with this proposal?

FDA Response:

A decision regarding priority review would be made at the time of NDA submission.

Meeting Discussion:

There was no further discussion of this item at the meeting.

Question 10:

Shire plans to submit the NDA in eCTD (electronic common technical document) format according to Shire's eCTD Table of Contents. A copy of the proposed eCTD Table of Contents (Appendix 5) has been included in the briefing package.

Does the Agency agree that the eCTD Table of Contents is acceptable?

FDA Response:

Acceptable.

In the NDA submission, include publications related to the systemic and ocular (e.g., tear fluid) PK exposure of lifitegrast ophthalmic solution 5% in human subjects.

You are referred to the following guidance pertaining to sterilization validation information to be submitted in the NDA:

Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, Final 11/1994 and MAPP 5040-1, for CTD format. Sterilization validation information to be submitted in the NDA application must include (and is not limited to) the following:

- *Product-specific (b) (4) bacterial retention studies (b) (4) used in the (b) (4) manufacturing process.*
- *Most recent validation of sterilizers used in sterilization and or depyrogenation of the filling equipment and components that come in product contact.*
- *Most recent validation of (b) (4) (b) (4).*
- *Media fill simulations that include simulation of holding times.*
- *Environmental monitoring program (action levels and methods).*
- *Container-closure integrity studies for the container-closure system.*
- *Method suitability studies for the sterility and bacterial endotoxins tests for the finished product.*

Meeting Discussion:

There was no further discussion of this item at the meeting.

Question 11:

As per the FDA’s Guidance for Industry Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document, Shire intends to split the ISE and ISS across Module 2 and Module 5, with the narrative portion located in Section 2.7.3 or 2.7.4 and the appendices of tables, figures, and datasets located in Section 5.3.5.3. A clear explanation of where the parts are located will be placed both in Module 2 (Section 2.7.3 or 2.7.4) and in Module 5 (Section 5.3.5.3).

Does the Agency agree with Shire’s plan for the provision of integrated summaries of efficacy and safety?

FDA Response:

Acceptable.

Meeting Discussion:

There was no further discussion of this item at the meeting.

Minutes Preparer: Jacquelyn Smith, M.A., Senior Regulatory Project Manager, DTOP

Chair Concurrence: Wiley Chambers, M.D., Deputy Director, DTOP

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/s/

WILEY A CHAMBERS
06/13/2014



IND 077885

MEETING MINUTES

SARcode Corporation
Attention: Mary S. Newman, MS
Vice President, Regulatory Affairs
1000 Marina Boulevard, Suite 250
Brisbane, CA 94005

Dear Ms. Newman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SAR 1118.

We also refer to the meeting between representatives of your firm and the FDA on December 15, 2010. This was an End-of-Phase 2 meeting to discuss Phase 3 clinical and nonclinical development plans.

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

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager at (301) 796-1202.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Acting Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: December 15, 2010, Wednesday, 12:30 pm – 1:30 pm
Meeting Location: Conference Room 1315, Building 22
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Application Number: IND 077885
Product Name: SAR 1118
Indication: Treatment of the signs and symptoms of [REDACTED] (b) (4)
(dry eye)

Sponsor/Applicant Name: SARcode Corporation

Meeting Chair: Wiley A. Chambers, MD
Meeting Recorder: Jane A. Dean, RN, MSN

FDA ATTENDEES

Division of Anti-Infective and Ophthalmology Products:

Charles Bonapace, PharmD	Clinical Pharmacology Team Leader
William M. Boyd, MD	Clinical Team Leader
Wiley A. Chambers, MD	Acting Director
Jennifer Harris, MD	Clinical Reviewer
Aryun Kim, PharmD	Clinical Pharmacology Reviewer
Rhea Lloyd, MD	Clinical Reviewer
Martin Nevitt, MD	Clinical Reviewer
Mushfiqur Rashid, PhD	Statistics Reviewer
Wendelyn Schmidt, PhD	Pharmacology/Toxicology Team Leader
Yan Wang, PhD	Statistics Team Leader

SPONSOR ATTENDEES

SARcode Corporation:

Mary Newman, MS	Vice President, Regulatory Affairs
Charles Semba, MD	Chief Medical Officer

Consultants:

[REDACTED] (b) (4)

[REDACTED] (b) (4)

1.0 BACKGROUND

SARcode Corporation (hereafter referred to as SARcode) submitted an End-of-Phase 2 meeting request on October 1, 2010. The meeting was granted and on November 12, 2010, SARcode submitted a meeting package which contained questions for the Agency. The questions are repeated below as **Question X**. The Agency sent preliminary responses via email on December 6, 2010. The responses are identified as **FDA Response to Question X**. If there was further discussion of the responses during the meeting, they can be found under **Meeting Comments**.

2. DISCUSSION

1.3.1 NONCLINICAL

Question 1

1a. Does the Agency agree that the nonclinical safety program completed to date, along with the proposed fertility and early embryonic development study in the rat and embryofetal developmental toxicology studies in the rat and rabbit, together with a 9month repeated daily (TID dosing) topical ocular toxicology study in dogs are adequate to support the Phase 3 program and an NDA?

FDA Response to Question 1a: The completed and proposed studies appear to be adequate, although the final assessment will be made upon full review. New toxicities arising during clinical trials may also necessitate further studies.

1b. Does the Agency agree that a carcinogenicity program is not indicated for SAR 1118 Ophthalmic Solution given its lack of in vitro and in vivo mutagenic effects and the low systemic exposure following topical ocular administration?

FDA Response to Question 1b: Yes.

1.3.2 CLINICAL

Question 2

2a. Does the Agency agree that the design of the proposed Phase 3 clinical studies, including selected endpoints, dose(s), and study duration, is adequate to demonstrate the efficacy of SAR 1118 Ophthalmic Solution for the treatment of dry eye?

FDA Response to Question 2a: No. The same Inclusion and Exclusion Criteria should be used for all of the proposed Phase 3 clinical studies.

If secondary endpoints are intended to support labeling claims, they should be predefined (i.e., identified prior to any interim analyses and prior to any unblinding of the data) and appropriate corrections for multiplicity should be made.

Meeting Comments: SARcode understood that the Inclusion and Exclusion criteria should be the same for the Phase 3 efficacy studies. The use of a Controlled Adverse Environment (CAE) chamber will not be required for the safety study; however, the patients with dry eye in the safety study should be similar to the patients with dry eye in the efficacy study.

2b. Does the Agency agree with the statistical approach for determination of efficacy in the Phase 3 pivotal studies?

FDA Response to Question 2b: Yes. However, the full protocol should specify the analysis methods for handling missing data. The full protocol should also discuss measures to minimize the occurrence of missing data. The Agency may provide additional comments when the full protocol is submitted for review.

Meeting Comments: SARcode agreed to include the Agency's recommendations in the study protocols and data analysis plans.

2c. Are there any other study design issues to be considered for the proposed efficacy studies in order to meet the basis for approval of a New Drug Application?

FDA Response to Question 2c: We recommend that inclusion criteria identify patients with dry eye. We also recommend that subjects have a diagnosis of dry eye or documented history of the signs and symptoms of dry eye rather than a patient-reported history of dry eye.

Dry eye secondary to scarring (such as that seen with irradiation, alkali burns, Stevens-Johnson syndrome, cicatricial pemphigoid) or the destruction of conjunctival goblet cells (as with vitamin A deficiency) represent a specific, severely affected patient population. Patients with these conditions should usually be studied separately from more routine dry eye conditions.

We recommend that endothelial cell count and dilated fundus examinations be performed at baseline and at the end of trial in at least one study.

We recommend that a patient comfort examination be performed at every visit.

The Agency has found that drug diaries which rely on patient recall of longer than several hours to be unreliable. Therefore, we recommend that drug diary recording of symptoms and compliance be performed as instantaneously as possible.

Meeting Comments: SARcode will ensure that the subjects enrolled in the studies have confirmation of the diagnosis of dry eye.

They also agreed that the more severely affected patients (such as those with dry eye disease that is secondary to scarring or to destruction of conjunctival goblet cells) will be excluded from study protocols.

SARcode will follow the Agency's recommendation to conduct dilated fundus examinations at baseline and at the end of the trials and to collect endothelial cell counts in at least 100 drug-exposed subjects.

In reference to the patient comfort examination, SARcode clarified that "comfort" referred to "drop comfort." Also, in reference to the diaries, they would be used to record drug administration only. The Agency agreed with this approach.

Question 3

3a. Does the Agency agree with the design and scope of the proposed safety study including the number of subjects exposed and the duration of ocular and systemic exposure to SAR 1118 Ophthalmic Solution?

FDA Response to Question 3a: The proposed design and scope of the proposed safety study appears to be adequate.

We recommend that the topical clinical program include enough patients to identify adverse events that occur at a rate of 1% or greater. To accomplish this, we recommend that approximately 500 or more subjects using the test drug product complete treatment with a concentration of the test drug product at least as high as proposed for marketing with a frequency at least as frequent as proposed for marketing. Prior to an NDA submission, we also recommend that at least 300 patients would have completed at least 6 weeks of follow-up after the initiation of treatment and at least 100 patients would have completed 12 months of follow-up after the initiation of treatment. The proposal meets the above recommendations.

3b. Are there any other study design issues to be considered for the safety study in order to meet the basis for approval of a New Drug Application?

FDA Response to Question 3b: No. Refer to the response to Question 2 and 3a.

Question 4

4. Is the planned safety database adequate to support product registration?

FDA Response to Question 4: Refer to the response to Question 2 and 3a. The adequacy of the safety database is a review issue.

Meeting Comments: The Agency clarified that the use of the CAE would not have any anticipated restrictions on potential label claims or the indication. The indication of “treatment of the signs and symptoms of dry eye” will be evaluated once the Phase 3 trials results are reviewed.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues that required further discussion.

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Provide meeting minutes within 30 days	FDA	January 14, 2011
SARcode will incorporate the Agency’s recommendations	SARcode	TBD

5.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts.

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/s/

WILEY A CHAMBERS
01/10/2011

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 208073

LATE-CYCLE MEETING MINUTES

Shire Development, LLC.
Attention: Kimberly McCormick, PharmD
Global Regulatory Affairs
725 Chesterbrook Blvd
Wayne, PA 19087-5637

Dear Dr. McCormick:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xiidra (lifitegrast ophthalmic solution) 5%. We also refer to the Late-Cycle Meeting (LCM) teleconference between representatives of your firm and the FDA on September 3, 2015.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes. If you have any questions, call Judit Milstein, Chief, Project Management Staff at 301-796-0763.

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: Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: September 3, 2015, 10:00-11:00 AM
Meeting Format: Teleconference
Application Number: NDA 208073
Product Name: lifitegrast ophthalmic solution, 5%
Applicant Name: Shire Development, LLC

Meeting Chair: William M. Boyd, MD
Meeting Recorder: Judit Milstein

FDA ATTENDEES

John Farley, Deputy Director, Office of Antimicrobial Products
Wiley Chambers, Deputy Director, Division of Transplant and Ophthalmology Products (DTOP)
William Boyd, Clinical Team Leader, DTOP
Rhea Lloyd, Clinical Reviewer, DTOP
Maria Rivera, Pharmacology/Toxicology Reviewer, DTOP
John Sinclair, Pharmacology/Toxicology Reviewer, DTOP
Mary Lewis, Pharmacology/Toxicology Reviewer, DTOP
Lori Kotch, Pharmacology/Toxicology Team Leader, DTOP
Solomon Chefo, Biostatistics Reviewer, Division of Biometrics IV
Yan Wang, Biostatistics Team Leader, Division of Biometrics IV
Philip Colangelo, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology IV
Shrikant Pagay, CMC reviewer, Office of Product Quality, OPQ
Monica Cooper, CMC reviewer, OPQ
Anamitro Banerjee, CMC Lead, OPQ
Suchitra Balakrishnan, Clinical Reviewer, Pediatric and Maternal Health Staff
Veronica Sansing, Epidemiologist, Division of Epidemiology II
Judit Milstein, Chief Project Management Staff, DTOP

EASTERN RESEARCH GROUP ATTENDEES

Marc Golstein-Consultant

APPLICANT ATTENDEES

David Altarac, Senior Vice President, Global Regulatory Affairs
Daryl Dekarske, Vice President, Global Regulatory Affairs
Kim McCormick, Senior Director, Global Regulatory Affairs
Phil Vickers, Senior Vice President, Head of Research and Development
Howard Mayer, Senior Vice President, Head of Clinical Dev.
Reza Haque, Vice-President, Clinical, Therapeutic Area Head
Aparna Raychaudhuri, Team Lead, Biostatistics and Statistical Programming
Amir Shojaei, Vice President, Clinical, Development Team Lead

BACKGROUND

NDA 208073 was submitted and received on February 25, 2015 for lifitegrast ophthalmic solution, 5%.

Proposed indication: Treatment of signs and symptoms of dry eye disease

PDUFA goal date: October 25, 2015

FDA issued a Background Package in preparation for this meeting on August 31, 2015.

DISCUSSION

1. Introductory Comments

Discussion: After introductions, the Cross Discipline Team Leader (CDTL) stated the ground rules for this teleconference and the objectives of the meeting. The CDTL also stated that a Clinical Discipline Review letter was issued on August 27, 2015.

2. Discussion of Substantive Review Issues

The application does not support the efficacy of Xiidra (lifitegrast ophthalmic solution) 5% in the treatment of dry eye disease.

Discussion: The applicant stated that they are conducting an additional study, OPUS 3 and inquired if this study would provide the additional data necessary to support the approval of the product. The Division stated that in principle, OPUS 3 might provide additional data to support a finding that Xiidra improves symptoms of patients with dry eyes, but no decision can be made without the review of the complete package. The Division noted that the lack of the ability to replicate a clinical finding raises questions about the validity of that finding. The applicant stated that they understood.

The Division also stated that the Quality Assessment and Facilities review is not complete, and therefore, no final assessment could be made on any potential deficiencies in the Product Quality. However, the following issues were identified:

- a. The specification for (b) (4) is recommended to be revised such that the acceptance criterion is at the limit of detection.
- b. A (b) (4) provision for a specification is not recommended until there is greater experience in manufacturing the drug product. The Office of Product Quality stated that the applicant could submit a supplement at the later date, once additional experience has been obtained and reviewed.

- c. *The comparability protocol is not acceptable, and recommendations will be made once the review is complete.*

The applicant inquired as to whether a Discipline Review Letter would be issued for the above mentioned Product Quality issues. The Division replied that a letter will be issued if the review is completed substantially ahead of an action letter on the application, but could not commit to a timeline because the Quality Assessment and Facilities review is not complete.

3. Discussion of Minor Review Issues

Discussion: *The Division stated that they noticed leachable impurities in (b) (4) in the to be marketed formulation, and asked the applicant if these vials were the same ones used in the Pharmacology/Toxicology studies. If so, such impurities might be qualified. The applicant stated they did not have this information at hand, but that they will investigate and provide it to the application.*

4. Information Requests

Discussion: *The applicant will provide information as to whether the vials used in the “to be marketed” formulation are the same as the ones used in the Pharmacology /Toxicology studies.*

5. Discussion of Upcoming Advisory Committee Meeting

The Division stated that an Advisory Committee Meeting is not planned at this time.

Discussion: *None*

6. Major Labeling Issues

A “Deficiencies Preclude Labeling Discussions” Letter was issued on August 14, 2015.

Discussion: *None*

7. Review Plans

Discussion: *None*

8. Wrap-up and Action Items

A Discipline Review letter will be issued by the Office of Product Quality regarding the (b) (4) specification, (b) (4) provision and comparability protocol, if the review is completed substantially ahead of the action letter.

The applicant will send information regarding the (b) (4) used in the Pharmacology/Toxicology studies and the to be marketed formulation

This application has not yet been fully reviewed by the signatory authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

WILLIAM M BOYD
09/29/2015



NDA 208073

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Shire Development, LLC.
Attention: Kimberly McCormick, PharmD
Global Regulatory Affairs
725 Chesterbrook Blvd
Wayne, PA 19087-5637

Dear Dr. McCormick:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xiidra (lifitegrast ophthalmic solution) 5%.

We also refer to the Late-Cycle Meeting (LCM) scheduled for September 3, 2015. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Judit Milstein, Chief, Project Management Staff at 301-796-0763.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Transplant and Ophthalmology
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:

Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: September 3, 2015, 10:00-11:00AM EST
Meeting Location: Teleconference

Application Number: NDA 208073
Product Name: Xiidra (lifitegrast ophthalmic solution) 5%.
Indication: Treatment of the signs and symptoms of dry eye disease
Sponsor/Applicant Name: Shire Development, LLC.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

In addition to the contents of this background document, please refer to the following Discipline Review letters already provided to you:

CLINICAL – August 27, 2015.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

CLINICAL

1. The application does not provide substantial evidence of efficacy for lifitegrast ophthalmic solution, 5%, in the treatment of dry eye disease because none of the submitted studies with efficacy evaluations were successful.
 - a) The Phase 2 Dry Eye study did not meet its primary efficacy endpoint, inferior corneal staining score at Day 84. None of the lifitegrast groups achieved a statistically significant difference in the inferior corneal staining score at Day 84 compared to vehicle although there were increasing numerical improvements in the inferior corneal staining score with higher lifitegrast doses.
 - b) The OPUS-1 study, which was designed based on post-hoc analyses of the Phase 2 Dry Eye study, did not meet its co-primary efficacy endpoints; change from baseline to Day 84 in inferior corneal staining score and visual related function Ocular Surface Disease Index subscale score. Statistical significance was only achieved for the objective efficacy endpoint (the change from baseline to Day 84 in inferior corneal staining score).
 - c) The OPUS-2 study, which was designed based on the results of the OPUS-1 study, did not meet its co-primary efficacy endpoints: change from baseline to Day 84 in inferior corneal staining score and eye dryness score measured on the visual analogue scale. Statistical significance was only achieved for the subjective efficacy end point (the change from baseline to Day 84 in eye dryness score).

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned during this review cycle.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes William M. Boyd, M.D. (CDTL)
Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Substantive Review Issues – 15 minutes
Each issue will be introduced by FDA and followed by a discussion.
 - The application does not support the efficacy of Xiidra (lifitegrast ophthalmic solution) 5% in the treatment of dry eye disease.

3. Review Plans – 5 minutes

- Quality Assessment and Facilities review is outstanding. Awaiting completion.

4. Wrap-up and Action Items – 10 minutes

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/s/

RENATA ALBRECHT
08/31/2015