

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208259Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 113064

MEETING MINUTES

Aerie Pharmaceuticals, Inc.
Attention: Cindy Martin
Director, Regulatory Affairs
2030 Main Street, Suite 1500
Irvine, CA 92614

Dear Ms. Martin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for netarsudil and latanoprost ophthalmic solution, 0.02%/0.005%.

We also refer to the meeting between representatives of your firm and the FDA on August 18, 2017. The purpose of the meeting was to discuss nonclinical, clinical, and chemistry, manufacturing and control information to support the NDA filing for netarsudil and latanoprost ophthalmic solution, 0.02%/0.005% for the (b) (4) of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure: Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: August 18, 2017, 10:00-11:00 AM
Meeting Location: 10903 New Hampshire Avenue, White Oak Building 22,
Conference Room: 1309, Silver Spring, Maryland 20903

Application Number: IND 113064
Product Name: Netarsudil/latanoprost ophthalmic solution, 0.02%/0.005%
Indication: (b) (4) of elevated intraocular pressure in patients with open-angle glaucoma and ocular hypertension
Sponsor Name: Aerie Pharmaceuticals

Meeting Chair: Wiley A. Chambers, MD
Meeting Recorder: Judit Milstein

FDA ATTENDEES

Renata Albrecht, Director, Division of Transplant and Ophthalmology Products (DTOP)
Wiley A. Chambers, Deputy Director, DTOP
William M. Boyd, Clinical Team Leader, DTOP
Sonal Wadhwa, Clinical Reviewer, DTOP
Lucious Lim, Clinical Reviewer, DTOP
Rhea Lloyd, Clinical Reviewer, DTOP
Maria Rivera, Pharmacology/Toxicology Reviewer, DTOP
Lori Kotch, Pharmacology/Toxicology Team Leader, DTOP
Solomon Chefo, Biostatistics Reviewer, Division of Biometrics IV (DBIV)
Daphne Lin, Deputy Director (DBIV)
Abhay Joshi, Clinical Pharmacology Reviewer, Division of Clinical Pharmacology IV (DCPIV)
George Lunn, CMC Reviewer, Office of Product Quality (OPQ)
Chunchun Zhang, Acting Pharmaceutical Assessment Lead, OPQ
John Metcalfe, Quality Assessment Lead (acting), OPQ
Judit Milstein, Chief, Project Management Staff, DTOP

SPONSOR ATTENDEES

Tom Mitro, President and Chief Operating Officer, Aerie Pharmaceuticals
Theresa Heah, Vice President, Clinical Research and Medical Affairs, Aerie Pharmaceuticals

Casey Kopczynski, Chief Scientific Officer, Aerie Pharmaceuticals
Marvin Garrett, Vice President, Regulatory Affairs and Quality, Aerie Pharmaceuticals
Cindy Martin, Vice President, Regulatory Affairs, Aerie Pharmaceuticals
Kristine Erickson, Vice President, Clinical Research, Aerie Pharmaceuticals
Ken Ruettimann, Vice President, Manufacturing, Aerie Pharmaceuticals
George Baklayan, Director, Regulatory Affairs/Technical Writing, Aerie Pharmaceuticals
Meg Thompson, Director, Analytical Chemistry, Aerie Pharmaceuticals (on the phone)
Alison Floyd, Director, Drug Product Manufacturing, Aerie Pharmaceuticals (on the phone)
Anju Parmar, Manager Regulatory Affairs, Aerie Pharmaceuticals (on the phone)
Avery Funk, Manager, Regulatory Affairs, Aerie Pharmaceuticals (on the phone)
Carrie Ngangngag, Manager, Regulatory Operations (on the phone)
(b) (6) (on the phone)

BACKGROUND

Aerie (the Sponsor) is developing a fixed-dose combination (FDC) therapy of netarsudil 0.02% and latanoprost, 0.005% ophthalmic solution for the treatment of elevated intraocular pressure in patients with open-angle glaucoma and ocular hypertension.

The Sponsor requested a meeting to discuss the nonclinical, clinical, and chemistry, manufacturing and control information to support the NDA filing, as a 505(b)(2) application.

Preliminary responses to the questions posted by the Sponsor in their briefing document dated July 12, 2017, were sent on August 8, 2017. In response to these comments, the Sponsor sent a response via e-mail, providing responses and requesting further discussion on questions 2, 3, 6, 10, 13, and Pregnancy and Lactation information.

DISCUSSION

For the purposes of these minutes, the questions posted by the Sponsor in their briefing document are in **bold** format, the Division's preliminary responses are in *italics*, the Sponsor's responses and requests for further clarification are in ***bold italics***, and the meeting discussions are in normal font.

Nonclinical

- 1. As agreed to at the EOP2 meeting, based upon the completed safety pharmacology, reproductive toxicology, genotoxicity and systemic and ocular toxicology studies for netarsudil and the fixed-dose combination (FDC) product, netarsudil 0.02% and latanoprost 0.005% ophthalmic solution, and the historical safety data available for latanoprost, the Sponsor believes they have sufficient nonclinical data to support approval of an NDA for chronic use of netarsudil 0.02% and latanoprost 0.005% ophthalmic solution.**

Does the Agency agree?

FDA Response: We agree that the battery of nonclinical studies appears sufficient to support submission of the NDA. The adequacy of these studies to support approval of the NDA will be a review issue.

Sponsor's response: No further discussion is needed

2. **All nonclinical Sections, Section 2.4 and Section 2.6 (2.6.1 through 2.6.7), will be included in the NDA. Since all nonclinical information generated on the single agent and FDC products is provided in the Sponsor's NDA 208254 for netarsudil ophthalmic solution 0.02%, the Sponsor will refer to NDA 208254 (whether pending or approved) for this information. In addition, for nonclinical information pertaining to latanoprost the Sponsor will rely on the Agency's finding of safety and effectiveness for Xalatan® (latanoprost ophthalmic solution) 0.005%, NDA 020597 (held by Pharmacia and Upjohn) and the current approved Xalatan® prescribing information.**

Does the Agency agree with this approach?

FDA Response: You can refer to NDA 208254 for the studies conducted for netarsudil monotherapy. Please include all studies conducted with the combination product in this NDA. We have the following additional recommendations:

- a. *Impurity specifications that exceed guidance qualification limits should be adequately qualified and the supporting safety data should be provided in the NDA submission. Ensure that ocular and systemic safety are addressed.*
- b. *Please note that, for labeling purposes, the Division prefers exposure multiples based on systemic AUC or C_{max} data (rather than dose multiples) be used in nonclinical label sections 8 and 13. The data and assumptions used to calculate/estimate systemic exposure should be provided.*
- c. *We are unclear by what you mean "the Sponsor intends to reference the Agency's previous findings for the Xalatan® NDA in each nonclinical section (2.4 and 2.6.2 through 2.6.7)". We remind you that without the right of reference, you can only rely on information contained in the labeling for Xalatan® and/or the published literature. Summary data, such as SBAs and published FDA discipline reviews, cannot be relied upon to support the marketing application.*
- d. *If literature is being relied upon to support the NDA, include a summary of all published nonclinical literature being relied upon and a copy of all publications cited. Published literature is viewed at the same level of scrutiny as original data and expected to be of comparable/sufficient quality to support an NDA. In your integrated summary, provide discussion of the potential impact of study shortcomings (e.g. insufficient animal numbers, insufficient endpoint analyses, formulation differences, inadequate test article characterization, etc.), if applicable.*

Sponsor's response: Based on the Agency's response, for the nonclinical sections of the NDA Aerie will:

- ***Rely on the Rhopressa NDA 208254 (whether pending or approved) for applicable nonclinical information on netarsudil***
 - ***Rely on Xalatan™ approved labeling for applicable nonclinical information on latanoprost***
 - ***Summarize and include the four FDC product nonclinical studies in the FDC NDA rather than reference the Rhopressa NDA for this information***
- Is this approach acceptable?***

Meeting Discussion: The Division concurred with the Sponsor's approach.

Clinical

3. **Efficacy data are available for two FDC netarsudil 0.02% and latanoprost 0.005% ophthalmic solution Phase 3 trials, PG324-CS301 and PG324-CS302 (QD PM dosing). For these studies, the Sponsor compared the FDC product to its individual components: netarsudil and latanoprost. This three-armed study design was powered to demonstrate statistical superiority of the FDC product over each of its components at all time points, assuming at least a 1.5 mmHg point estimate benefit of the FDC product over latanoprost 0.005% and a 2 mmHg difference over netarsudil 0.02% at all time points. The primary endpoint for both studies was at 3 months. The study duration of PG324-CS301 was 12 months and for PG324-CS302 was 3 months. In both studies, statistical superiority to both components was demonstrated in the primary analysis. The Sponsor intends to file an NDA for FDC netarsudil 0.02% and latanoprost 0.005% ophthalmic solution (QD PM dosing) with a request for priority review based on the safety and efficacy results from the CS301 and CS302 Phase 3 trials.**

Does the Agency agree with the Sponsor's NDA filing plans?

FDA Response: The Agency's decision on whether the application would be designated a priority review would be made once a complete application is submitted. Statistical superiority of the combination product alone is not sufficient. The combination product efficacy results would also have to be clinically significant/clinically meaningful.

The Agency will inform you in writing of a priority review designation by day 60 of the review; alternately, the Agency will inform you in writing of a standard review designation by day 74 of the review. Applications that are not filed do not receive a review designation. Refer to the guidance document on Expedited Programs for Serious and Conditions-Drugs and Biologics.

Sponsor's response:

Studies CS301 and CS302 demonstrated superiority of the combination product over each of the individual components by a statistically significant amount at all 9 of the planned time points measured.

In addition, categorical analyses of the primary analysis population were pre-specified secondary endpoints. Analyses of IOP also included summarizing the number and percentage of study eyes achieving mean diurnal IOP reduction from baseline of ≥ 4 to ≥ 12 mmHg in 2 mmHg increments and percent reduction from baseline of $\geq 5\%$ to $\geq 40\%$ in 5% increments at Week 2, Week 6, and Month 3. Additionally, the number and percentage of study eyes attaining a mean diurnal IOP of ≤ 22 to ≤ 14 mmHg in 1 mmHg increments was summarized at Week 2, Week 6, and Month 3. Fisher's exact test (2-sided p-values) was used to test the pair wise differences between treatment groups for each category at each visit.

Higher percentages of subjects in the combination product treatment group achieved clinically significantly lower diurnal mean IOPs than in either the netarsudil or latanoprost treatment groups: approximately 32.1 to 32.5% combination product subjects achieved IOPs ≤ 14 mmHg at Month 3 compared to approximately 8.3 to 13.6% netarsudil and approximately 8.9 to 14.8% latanoprost subjects (PG324-CS302 and PG324-CS301, respectively for each treatment group). In terms of IOP percent reduction from baseline, approximately 85.5 to 87.5% combination product subjects achieved IOP percent reduction from baseline of $\geq 20\%$ at Month 3 compared to approximately 50% to 56.1% netarsudil and approximately 72.3% to 78% latanoprost subjects (PG324-CS302 and PG324-CS301, respectively for each treatment group).

In the Agency's response to priority review designation, can the Agency provide further clarification on the comment that the combination product efficacy results would have to be "clinically significant/clinically meaningful"? Would the categorical IOP analyses of the primary analysis population qualify as clinically significant/clinically meaningful?

Meeting Discussion: The Division indicated that an IOP reduction of 5-6mmHg or more relative to the individual components would be considered clinically meaningful; it was noted that in these trials no individual patient target pressure was pre-specified as an endpoint.

The Division clarified that the decision on priority designation is made at the time of filing of the NDA, and that based on the information provided, it is not likely that such priority would be granted. The Division referred the Sponsor to MaPP 6020.3-Review Designation Policy: Priority (P) and Standard (S). At the Sponsor's inquiry, the Division mentioned that although it did not identify it as a fatal flaw, it noted that there is no data comparing the individual concomitant administration of both netarsudil and latanoprost vs the combination product.

4. For the NDA, the Sponsor proposes reporting treatment emergent adverse events for each study individually. In addition, as a resource for an anticipated discussion of labeling with the Agency, the Sponsor also proposes to present treatment emergent ocular or non-ocular adverse events that occur at a frequency $\geq 3\%$, using treatment group data integrated across both studies. If this proposal is acceptable, the Sponsor intends to group ocular adverse events occurring at frequencies of 3-5%, those occurring at frequencies of 6-10%, and then separately mentioning those adverse events that occur at a frequency greater than 10%.

Does the Agency agree with this proposal?

FDA Response: We would expect the treatment emergent events reported several ways. We would first want to see all TEAEs for each study separately; we would then want to see TEAEs >1% for each study separately. Based on the review of the NDA we may ask for additional analysis of TEAEs. Labeling is a review issue, and we cannot commit that your proposal at this time is acceptable.

Sponsor's response: No further discussion is needed

5. The Summary of Clinical Safety Section of the NDA (2.7.4) will include a by-study analysis of the three completed netarsudil and latanoprost ophthalmic solution studies, one Phase 2 study, PG324-CS201, and two Phase 3 studies, PG324-CS301 and PG324-CS302, while the Integrated Summary of Safety (ISS) will include analyses based upon pooled data from the two completed Phase 3 studies.

Does the Agency accept this approach?

FDA Response: Acceptable.

Sponsor's response: No further discussion is needed

6. The Summary of Clinical Safety Section of the NDA (2.7.4) will also include a statement that the Sponsor is relying on the Agency's finding of safety and effectiveness for Xalatan[®] (latanoprost ophthalmic) 0.005%, NDA 020597 (held by Pharmacia and Upjohn) in accordance with the FDA Guidance for Industry Applications Covered by Section 505(b)(2). In addition, this section will reference the most current approved Xalatan package insert, including the postmarketing experience adverse reactions. The Sponsor will rely on the safety information from the 3 completed FDC product studies (PG324-CS201, PG324-CS301 and PG324-CS302) for additional safety information on latanoprost.

Does the Agency accept this approach?

FDA Response: We have no objection to the submission of your proposed application as a 505(b)(2) application if you are referencing material that you do not have the right to reference and you can make an appropriate link between the material you reference and your product.

Sponsor's response:

Regarding the Agency's response on making an appropriate link between the material we reference and our combination product, Aerie plans on including a table summarizing the information that supports the application, similar to the table format the Agency included on pages 13 & 14 of the response under "505(b)(2) REGULATORY PATHWAY". In addition, Aerie plans on including an RLD (reference listed drug) file, which will provide information on the single agent ophthalmic solutions, Xalatan and Rhopressa, demonstrating the similarities of the single agent solutions to the combination product solution. The table summary and RLD information will be provided as an attachment to the NDA cover letter. Is this acceptable?

Meeting Discussion: The Division indicated that an explanation on the relevance to their product was needed for each section of the labeling "borrowed" from the Xalatan labeling.

- 7. The statistical analysis plans for the Phase 3 PG324-CS301 and CS302 studies individually require that the primary efficacy analyses be conducted with the intent to treat (ITT) population as the primary population for efficacy analyses (as discussed in the EOP2 Meeting on 15 April 2015; [FDA Meeting Minutes dated 6 May 2015, Question 3](#)) and will be used to summarize all efficacy variables and will summarize subjects as randomized. The per protocol population (PP) will be the secondary population for efficacy analyses and will be used to summarize a subset of efficacy variables. The integrated summary of efficacy (ISE) will follow this similar strategy.**

Does the Agency agree to this plan?

FDA Response: Using ITT as the primary population for the efficacy analysis and the MCMC(Markov chain Monte Carlo) approach for imputation for missing data is acceptable.

We expect that the ITT analysis results will be supported by the PP analysis results. You should provide clear explanation in the event the results based on the two populations are not consistent.

Please also include analysis results for the change in IOP from baseline data at each time points of each visit using both analysis populations.

Sponsor's response: ***No further discussion is needed***

- 8. Both the ISE and the ISS will summarize key measures by the following strata: Age (< 65 years and ≥ 65 years); Gender (Female and Male); Race (Caucasian and Non-Caucasian); Iris Color (Blue/Grey/Green, Brown/Black, and Hazel); Prior Therapy (Prior Prostaglandin Use, No Prior Prostaglandin Use, and No Prior Hypotensive**

Therapy); and Study Eye Diagnosis (Open Angle Glaucoma and Ocular Hypertension).

Does the Agency agree to this plan?

FDA Response: Acceptable.

Sponsor's response: No further discussion is needed

9. There are 3 completed FDC product clinical studies, one Phase 2 (PG324-CS201) and two Phase 3 (PG324-CS301 and PG324-CS302). All three clinical studies commenced prior to 17 December 2016. CDISC [SDTM (SDTMIG V3.2), ADaM (V1.0), and Define (V2.0)] documentation and datasets in accordance with the FDA Study Data Technical Conformance Guide will be provided for the two Phase 3 trials, PG324-CS301 and PG324-CS302, and the ISE and ISS only.

Does FDA agree?

FDA Response: We would prefer that the Phase 2 study also be submitted in CDISC study data standard format.

Sponsor's response: Aerie will provide datasets in CDISC study data standard format for the Phase 2 study, PG324-CS201, as requested by the Agency. No further discussion is needed.

10. All clinical sections will be included in the NDA. For clinical sections where there is no new information on the FDC product, such as Section 2.7.1 (Summary of Biopharmaceutic Studies and Associated Analytical Methods) and Section 2.7.2 (Summary of Clinical Pharmacology), the Sponsor will reference the netarsudil ophthalmic solution 0.02% NDA 208254 (whether pending or approved) and the Xalatan® (latanoprost ophthalmic solution) 0.005% NDA 020597. For example: Section 2.7.2 of the NDA will state:

For a summary of clinical pharmacology studies on netarsudil, refer to the Sponsor's NDA 208254 for netarsudil ophthalmic solution 0.02%. For a summary of clinical pharmacology studies on latanoprost, the Sponsor is relying on the Agency's finding of safety and effectiveness for Xalatan® (latanoprost ophthalmic solution) 0.005%, NDA 020597 (held by Pharmacia and Upjohn) and the current approved Xalatan® prescribing information.

Does the Agency agree with this approach?

FDA Response: Yes, we agree with the approach of relying on current approved Xalatan prescribing information for a summary of clinical pharmacology studies on latanoprost.

With respect to the summary of clinical pharmacology studies on netarsudil, we agree with the proposed approach of relying on information submitted under NDA 208254 for netarsudil ophthalmic solution 0.02%. We remind you that the information submitted under Sections 2.7.1 and 2.7.2 of NDA 208254 for netarsudil 0.02% ophthalmic solution

is to be submitted under the same sections of your future NDA submission for the FDC of netarsudil 0.02% and latanoprost 0.005% ophthalmic solution.

Sponsor's response:

Please clarify what is meant by the last sentence of your response. "We remind.....solution." Does the Agency mean that we cannot cross-reference to the Rhopressa NDA 208254 for NDA Sections 2.7.1 and 2.7.2 and that the same information provided in the Rhopressa NDA should be provided in the combination product NDA?

Meeting Discussion: The Division indicated that the information on netarsudil can be cross-referenced to the Rhopressa NDA, although it would be preferable to resubmit the information in the new NDA to provide for efficiency in the review.

It is our understanding that every NDA section must be included in the 505(b)(2) application whether we are providing new information or cross-referencing to information provided in the Rhopressa NDA or Xalatan labeling. Is this correct?

Meeting Discussion: The Division indicated that every section needs to be included. For those sections that do not apply, a statement to that effect should be included.

- 11. In the EOP2 meeting it was agreed that it is acceptable to submit a plan for a waiver for subjects 0-17 years of age as part of the Sponsor's Pediatric Study Plan in the NDA. The proposed pediatric waiver request has been drafted.**

Is the proposed pediatric waiver request acceptable?

FDA Response: The proposed pediatric waiver request appears acceptable; however a final decision on acceptability is made after consultation with the Pediatric Review Committee (PeRC) when the application has been submitted.

Sponsor's response: No further discussion is needed.

CMC

- 12. Does the Agency agree with the proposed commercial specifications for netarsudil 0.02% and latanoprost 0.005% ophthalmic solution? The Antimicrobial Effectiveness Test (AET) will be conducted for registration stability studies, but not for release and stability of the commercial product. Does the Agency agree?**

FDA Response:

The tests proposed are reasonable for the proposed dosage form. The adequacy of the limits proposed will be determined during the NDA review and additional tests and/or tightening of the limits may be required.

Please provide a commitment to conduct antimicrobial effectiveness testing according to USP <51> or equivalent methodology on at least one primary stability batch at the end

of the proposed shelf life (see ICH Q1A Stability Testing of New Drug Substances and Products for new drug products or Guidance for Industry).

Sponsor's response: *Aerie will conduct antimicrobial effectiveness testing according to USP <51> on at least one primary stability batch at the end of the proposed shelf life as requested by the Agency. No further discussion is needed.*

13. Does the Agency agree that the registration stability lots which were manufactured utilizing slightly different container closures from those planned for commercial drug product lots will be adequate to support the proposed commercial product expiration date?

FDA Response: *No, in agreement with ICH Q1A (R2), we expect stability testing to be conducted on the dosage form packaged in the proposed commercial container closure system to demonstrate its ability to protect the quality of the product over its shelf-life.*

Additionally, please provide droplet volume evaluation from multiple container batches for all the container closure systems.

Sponsor's response: *Aerie would like to discuss further the registration stability lots that will be filed in the NDA. At the time of NDA filing, Aerie will have 12 months long term and 6 months accelerated data on 6 registration lots, all manufactured using the identical container closure (b) (4) for the bottles, tips and caps. The only difference between the 6 lots is with the tip as summarized below.*

- *Three (3) 2.5 mL fill lots with the (b) (4) tip (b) (4) as described in the meeting package)*
- *Three (3) 2.5 mL fill lots with the (b) (4) white tip (b) (4)*

In addition, container closure integrity has been established for the bottle/tip/cap (b) (4). The 6 stability lots above justify the commercial tip configuration (b) (4) and can be used to support the stability of the commercial drug product. The first 3 commercial lots and 1 lot annually thereafter will be placed on stability and reported in the NDA annual reports.

Aerie will provide droplet volume data as requested.

Does the Agency agree that 12 months long term and 6 months accelerated data for the 6 registration stability lots are acceptable for NDA filing to support the commercial drug product expiration dating?

Meeting Discussion: The Division indicated that the registration lots need to be in the commercial configuration. Aerie then indicated that they would market the product with (b) (4) white tip. The three registration batches will have (b) (4) white tip and 12 months of long-term stability data will be available for each batch at the time of NDA submission. The three batches with (b) (4) tip will provide supportive stability data. Post-NDA approval Aerie will submit a Prior Approval Supplement to change the container-closure system (b) (4). The Division agreed with this proposal.

14. The Sponsor plans on filing the NDA with 9 months of stability data for the drug product registration stability lots and submit the 12 months data within 30 days after NDA filing.

Does the Agency agree with this approach?

FDA Response: No, we expect the NDA at the time of submission to include 12-months long-term and 6-months accelerated stability data for three registration batches in the intended commercial configuration. Any data submitted during review may or may not be reviewed depending on resources available.

In addition, the following one-time tests are recommended in the NDA submission:

- a. *Leachables/extractables on container/closure by using screening analytical methods (such as HPLC, GC etc) and studies on at least one stability batch through expiry.*
- b. *Freeze-thaw cycling studies (3 cycles).*

Sponsor's response:

As requested by the Agency, Aerie will file the original NDA with 12 months long-term and 6 months accelerated stability data on the registration lots and include the following one-time tests: a) leachables/extractables on the container/closure by using screening analytical methods and studies on at least one registration stability batch, which will continue through the proposed expiration date, and b) results from a freeze-thaw cycling study. No further discussion is needed.

15. As requested by the Agency for the single agent product, netarsudil ophthalmic solution 0.02% (NDA 208254), the Sponsor plans to conduct a one time in-use stability study for one registration stability lot of netarsudil 0.02% and latanoprost 0.005% after 24 months of storage (or end of expiration) at the long term storage condition of 2-8°C. Samples from this lot will be placed at 25°C for an additional 4 or 6 weeks and tested at the end of that period to ensure it continues to meet specifications. (b) (4)

Until this study is conducted, the drug product will be labeled to allow storage only at the long term storage condition of 2-8°C during use. The stability protocol for this study will be

provided in the NDA. Results from the study [REDACTED] (b) (4) will be provided in the NDA annual report if results continue to meet specifications.

Does the Agency agree with this approach?

FDA Response: While we agree that this approach for in-use stability testing to be performed following complete validation studies which demonstrate that there is no negative impact on the drug product, [REDACTED] (b) (4)

Antimicrobial effectiveness testing should be included in the stability study to ensure preservative effectiveness after the maximum storage and in-use period.

Sponsor's response: As requested by the Agency, Aerie agrees to file a prior approval supplement with in-use stability data on one registration lot [REDACTED] (b) (4)

The in-use stability protocol will be filed in the original NDA. No further discussion is needed.

16. All chemistry, manufacturing and controls sections will be included in the NDA. For drug substance sections that will not be different from the information provided in the netarsudil ophthalmic solution 0.02% NDA 208254, the Sponsor will reference the NDA (whether pending or approved).

Does the Agency agree with this approach?

FDA Response: Yes, we agree.

Sponsor's response: No further discussion is needed

Regulatory

17. As applicable, statements from the approved Xalatan prescribing information will be included in the netarsudil 0.02% and latanoprost 0.005% prescribing information.

Does the Agency agree with this approach?

FDA Response: Please, refer to the 505(b)(2)Regulatory Pathway information included below.

Sponsor's response: No further discussion is needed

18. It is the Sponsor's understanding that for this 505(b)(2) NDA that patent certification information for Xalatan is required. All four patents for Xalatan are no longer listed in the Orange Book because they expired from 2009 through 2011. For the NDA the Sponsor plans on submitting a "Paragraph II Certification" for each patent.

Does the Agency agree with this approach?

FDA Response: The adequacy of the paragraph certification will be made at the time of the NDA submission.

Sponsor's response: No further discussion is needed

Sponsor's request for additional clarification:

Aerie would like clarification on the drug use in pregnant and lactating information statements made above.

- *Aerie is currently unaware of any available published literature regarding use of latanoprost ophthalmic solution 0.005% in pregnant and lactating women. Aerie will search and review the published literature closer to the expected NDA filing date. If any new published literature is available, Aerie will provide a summary of this literature in the NDA.*
- *Aerie will include a review and summary of any post-marketing reports of latanoprost ophthalmic solution 0.005% in pregnant and lactating women obtained from the Pharmapendium database.*
- *Aerie will also review and provide a summary of reports from Aerie's pharmacovigilance database on netarsudil ophthalmic solution 0.02% use in pregnant and lactating women from clinical studies and any post-marketing events (provided netarsudil 0.02% is approved and commercialized prior to filing the combination product NDA).*
- *Aerie will also review and provide a summary of any reports on pregnant and lactating women from the combination product clinical studies.*

Is this acceptable?

Meeting discussion: The Division agreed with this proposal. The Division also stated that the Sponsor will need to provide any available animal or human information to support the proposed labeling information regarding pregnant and lactating women.

ISSUES REQUIRING FURTHER DISCUSSION

None

ACTION ITEM

The Division will issue the minutes of the meeting within 30days

ATTACHMENTS AND HANDOUTS

None

PREA REQUIREMENTS

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

We acknowledge the Division's agreement with your initial Pediatric Study Plan submitted on August 28, 2015.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

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

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. As of **May 5, 2017**, the following submission types: **NDA**, **ANDA**, and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

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

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

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

Corresponding names and titles of onsite contact:

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

505(b)(2) REGULATORY PATHWAY

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

If you intend to submit a 505(b)(2) application that relies for approval on FDA’s finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a “bridge” (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

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

If you intend to rely on the Agency’s finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA’s

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

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

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

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

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)

<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication A</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section B</i>
<i>4.</i>	

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

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

/s/

WILEY A CHAMBERS
09/10/2017