# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 208742Orig1s000

# OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208742

**COMPLETE RESPONSE**

Ocular Therapeutix, Inc.
Attention: Eric P. Ankerud, JD
Executive Vice President
Regulatory, Quality and Compliance
34 Crosby Drive, Suite 105
Bedford, MA 01730

Dear Dr. Ankerud:

Please refer to your New Drug Application (NDA) dated and received September 24, 2015, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for DEXTENZA (dexamethasone ophthalmic insert), 0.4 mg, for intracanalicular use.

We acknowledge receipt of your amendment dated January 19, 2017, which constituted a complete response to our July 21, 2016, action letter.

We also acknowledge receipt of your amendment dated July 10, 2017, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

## PRODUCT QUALITY/FACILITIES INSPECTION

The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product must comply with the current good manufacturing practice regulations in 21 CFR 210 and 211. During a recent inspection of the Ocular Therapeutix, Inc., FEI#3008477155, manufacturing facility for this application, our field investigators conveyed deficiencies to the representatives of this facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

For detailed information on these deficiencies, we refer you to the correspondence issued jointly by the New England District Office and the Office of Process and Facilities on July 10, 2017.

## PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated 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*

## PROPRIETARY NAME

Please refer to the correspondence issued by the Division of Medication Errors and Analysis, Office of Surveillance and Epidemiology, on April 12, 2017, which addresses the proposed proprietary name, DEXTENZA. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application facility inspection-related deficiencies.

## SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the product under consideration regardless of indication, dosage form, or dose level.

## ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues

1. Please update your visual inspection controls to include acceptable quality limits (AQL) and justification for the limits.

2. Please provide a comprehensive list of the manufacturing, equipment and procedural changes and controls that have been put in place since the previous re-submission. Please

provide the updated batch manufacturing instructions and any new production records supporting this NDA.

## OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," March 2015 at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

Sincerely,

*{See appended electronic signature page}*

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

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

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/s/

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RENATA ALBRECHT
07/10/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208742

**COMPLETE RESPONSE**

Ocular Therapeutix, Inc.
Attention: Erik P. Ankerud, JD
Executive Vice President, Clinical, Regulatory and Quality
34 Crosby Drive, Suite 105
Bedford, MA 01730

Dear Dr. Ankerud:

Please refer to your New Drug Application (NDA) dated and received September 24, 2015, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for dexamethasone insert, 0.4 mg, for intracanalicular use.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reason for this action below and, where possible, our recommendation to address these issues.

## FACILITIES INSPECTION

The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product must comply with the current good manufacturing practice regulations in 21 CFR 210 and 211. During a recent inspection of the Ocular Therapeutix, Inc., FEI#3008477155, manufacturing facility for this application, our field investigators conveyed deficiencies to the representatives of this facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

## PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated 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

## PROPRIETARY NAME

Please refer to the correspondence issued by the Division of Medication Errors and Analysis, Office of Surveillance and Epidemiology, on January 27, 2016, which addresses the proposed proprietary name, DEXTENZA. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application facility inspection-related deficiencies.

## SAFETY UPDATE

When you respond to the above deficiency, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the product under consideration regardless of indication, dosage form, or dose level.

## ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

1. The amendment dated June 13, 2016 includes updates to critical material attributes ((b) (4)), critical process parameters ((b) (4)), in-process controls ((b) (4)) and yield limits. The supporting test results for the metrics above were not provided for registration, stability and proposed PQ batches. Your response to information requests has referenced two subsequent lots, Lot No. 03241602 and 04211605 ((b) (4) unit scale, taken through all process steps) generated using the intended commercial process parameters. While you have provided batch size and yield on these lots, the information provided does not include all the relevant details (e.g. batch manufacturing records, in-process test results). Provide these details to support that your updated production and process controls assure that in-process materials and finished product meet the predetermined quality requirements.

2. The application does not provide full information on the intended scale-up strategy beyond the current commercial scale ((b) (4) units). In light of the process complexity, unique dedicated custom-made equipment, extent of manual operations, scale-up for any process operation (e.g. (b) (4)) beyond the stated commercial scale should be submitted as a Prior Approval Supplement (PAS).

**OTHER**

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

Sincerely,

*{See appended electronic signature page}*

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

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

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/s/

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RENATA ALBRECHT
07/21/2016