CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208742Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 26, 2018
Requesting Office or Division:	Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number:	NDA 208742
Product Name and Strength:	Dextenza (dexamethasone) intracanalicular insert, 0.4 mg
Applicant/Sponsor Name:	Ocular Therapeutix, Inc.
FDA Received Date:	June 28, 2018 and September 14, 2018
OSE RCM #:	2018-1484
DMEPA Safety Evaluator:	Nasim Roosta, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

Division of Transplant and Ophthalmology Products (DTOP) requested that we review the revised container (pouch) label, carton labeling and Prescribing Information (PI) for Dextenza (Appendix A) to determine if they are acceptable from a medication error perspective.

1.1 BACKGROUND

DMEPA previously reviewed the label and labeling for the proposed product, Dextenza, in RCM 2016-1073 dated June 8, 2016.[a] However, NDA 208742 received a Complete Response (CR) on 7/21/2016 due to facilities deficiencies. Thus, the Applicant submitted a complete response to the CR on 1/19/2017 and submitted revised label and labeling on February 28, 2017 and March 22, 2017.

We reviewed proposed container (pouch) label, carton labeling, and PI on May 8, 2017[b] and found the PI and pouch label acceptable from a medication error perspective. However, we

[a] Rutledge M. Label and Labeling Review for Dextenza (dexamethasone) NDA 208742. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 JUN 8. RCM No.: 2016-1073.
[b] Patel M. Label and Labeling Review for Dextenza (dexamethasone) NDA 208742. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 18. RCM No.: 2017-798.

made a recommendation to improve the readability of the carton labeling. On June 28, 2018, the Applicant submitted a class 2 resubmission as a response to the CR; however, the Applicant submitted written descriptions of the proposed carton labeling, so we subsequently requested images of their proposed labeling. On September 14, 2018, the Applicant submitted revised container (pouch) labels and carton labeling for our review during this review cycle.

2 CONCLUSION

We confirmed that our previous recommendation was implemented. However, we have additional recommendations outlined below in Section 3.

3 RECOMMENDATIONS FOR OCULAR THERAPEUTIX, INC.

We recommend the following be implemented prior to approval of this NDA:

A. Pouch label

1. The container label is missing the linear barcode. The linear barcode is an important safety feature necessary to correctly identify the product and to help prevent product selection and administration errors. Per 21 CFR 201.25, the linear barcode must appear on the drug's label (as defined by section 201(k) of the FD&C Act (21 U.S.C. 321(k)), which includes both the carton as well as the container. Thus, there needs to be a linear barcode on both the carton and the container.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON SEPTEMBER 14, 2018

Pouch label:

(b) (4)

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/s/

NASIM N ROOSTA
09/26/2018

OTTO L TOWNSEND
09/26/2018

Division of Transplant and Ophthalmology Products
Associate Director for Labeling Recommendations of the Prescribing Information

Product Title	**DEXTENZA (dexamethasone insert) for intracanalicular use**
Applicant	Ocular Therapeutix
Type of Application/Submission	New Drug Application
Proposed Indication	Treatment of ocular pain following surgery
Date FDA Received Application	January 17, 2017
Review Classification	Class 2 Resubmission
Action Goal Date	July 19, 2017
Review Date	April 6, 2017
Reviewer	Jane Filie, MD
Project Manager	Judit Milstein

This Associate Director for Labeling (ADL) memorandum provides recommendations for consideration by the management of the Division of Transplant and Ophthalmology Products (DTOP), on the content and format of the prescribing information (PI) to help ensure that the PI:

- Is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements[1]
- Is consistent with labeling guidance recommendations[2] and with CDER/OND best labeling practices and policies
- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers
- Is consistent with other PI with the same active moiety, drug class, or similar indication

This is a class 2 resubmission after the applicant received a complete response letter dated July 21, 2016 due to manufacturing issues.

Formatting and content recommendations were made with the aim of improving clarity and readability and are shown throughout the proposed label in track changes and comments. Some recommendations merit further explanation:

1. Product title: During the review of this resubmission discussions occurred regarding the product title which will be "DEXTENZA (dexamethasone (b) (6)." The term "extended-release" previously proposed by the Compendial Operations and Standards Branch, will not be included as the Division of Transplant and Ophthalmology Products (DTOP) justifies that the term is unnecessary because the slow release of the drug is inherent to this particular type of dosage form (insert) for

[1] See *January 2006 Physician Labeling Rule*; 21 CFR 201.56 and 201.57; and *December 2014 Pregnancy and Lactation Labeling Rule* (the PLLR amended the PLR regulations). For applications with labeling in non-PLR "old" format, see 21 CFR 201.56(e) and 201.80.
[2] See *PLR Requirements for PI* website for PLR labeling guidances.

ophthalmic use and this is consistent with another ophthalmic insert, Lacrisert (hydroxypropyl cellulose ophthalmic insert). The route of administration was also discussed and it was recently added to the Structured Product Labeling dictionary. See electronic communication in the Appendix.

2. (b) (6)

3. Omission of section 12.2 Pharmacodynamics: Section 12.2 Pharmacodynamics is omitted from this proposed labeling. The regulation 21CFR 201.57(c)(13)(i) states that the Clinical Pharmacology section of the labeling must contain 12.2 Pharmacodynamics. If there are no relevant PD data, or the PD effects are unknown, this subsection must contain a statement indicating this lack of information 21 CFR (c)(13)(i)(B). However, 21 CFR 201.56(d)(4) allows omission of sections that are not applicable: "Omit clearly inapplicable sections, subsections, or specific information." This section has been deleted and justified by DTOP Deputy Director: this section is not applicable because, even if pharmacodynamic data were known its relevance for this product is unknown and as described in 21 CFR 201.56(d)(4) clearly inapplicable sections, subsections or specific information must be omitted. If the subsection is omitted from the full prescribing information, the heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following statement must appear at the end of Contents: "* Sections or subsections omitted from the full prescribing information are not listed." It is the opinion of this ADL that the omission of 12.2 from the label is justified and is acceptable.

4. Section 8.2 Lactation: The language in section 8.2 Lactation is consistent with other drug labeling in the class, such as Ozurdex and Retisert, with minor differences and in the opinion of this ADL it is acceptable.

In the attached PI, ADL comments (in balloons) begin with the bolded acronym "ADL". The ADL recommendations are presented in track changes (red) throughout the working version of the applicant's draft PI with track changes (green). The document also includes revisions made by the Deputy Director, Dr. Wiley Chambers (blue), clinical reviewer, Dr. Sonal Wadhwa (dark orange), and Dr. Abhay Joshi, clinical pharmacology reviewer (yellow). In order to preserve the comments within each heading in a sequential order, the amended label attached may not reflect the final formatting of the label.

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/s/

JANE FILIE
04/12/2017

RENATA ALBRECHT
05/18/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 8, 2017
Requesting Office or Division:	Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number:	NDA 208742
Product Name and Strength:	Dextenza (dexamethasone) intracanalicular insert, 0.4 mg
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Ocular Therapeutix, Inc.
Submission Date:	February 28, 2017 and March 22, 2017
OSE RCM #:	2017-798
DMEPA Primary Reviewer:	Madhuri R. Patel, PharmD
DMEPA Team Leader (Acting):	Sarah K. Vee, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed container label, carton labeling, and Prescribing Information (PI) for Dextenza (NDA 208742), submitted by Ocular Therapeutix, Inc. on February 28, 2017 and March 22, 2017. The Division of Transplant and Ophthalmology Products (DTOP) requested that DMEPA review the proposed labels and labeling for areas that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA previously reviewed the label and labeling for the proposed product, Dextenza, in RCM 2016-1073 dated June 8, 2016.[a] However, NDA 208742 received a Complete Response (CR) on 7/21/2016 due to facilities deficiencies. Thus the applicant submitted a complete response to the CR on 1/19/2017 and revised label and labeling on February 28, 2017 and March 22, 2017. We reviewed proposed container (pouch) label, carton labeling, and Prescribing Information (PI) to determine whether there are any significant concerns in terms of safety related to preventable medication errors. We find the PI and pouch label acceptable from a medication error perspective. However, we note that the carton labeling can be improved to enhance the prominence of the strength and to help avoid confusion with the net quantity.

We also note that the carton labeling contains a (b) (4) is currently limited and we have no concerns from a medication error perspective.

[a] Rutledge M. Label and Labeling Review for Dextenza (dexamethasone) NDA 208742. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 JUN 8. RCM No.: 2016-1073.

4 CONCLUSION & RECOMMENDATIONS

DMEPA finds the Prescribing Information and Pouch label acceptable from a medication error perspective. However, we note that the proposed carton labeling can be improved to increase the readability and prominence of the strength.

4.1 RECOMMENDATIONS FOR OCULAR THERAPEUTIX, INC.

We recommend the following be implemented prior to approval of this NDA:

A. Carton Labeling
    a. Relocate the strength statement from the upper right hand corner to immediately following the established name. This change would help assist with the safe use the product as well as to ensure that the net quantity statement is away from the product strength, as per Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Dextenza that Ocular Therapeutix, Inc. submitted on February 28, 2017 and March 22, 2017.

Table 2. Relevant Product Information for Dextenza	
Initial Approval Date	N/A
Active Ingredient	dexamethasone
Indication	corticosteroid indicated for the treatment of ocular pain occurring after ophthalmic surgery
Route of Administration	Intracanalicular
Dosage Form	Sustained-release intracanalicular insert
Strength	0.4 mg
Dose and Frequency	0.4 mg inserted into the lacrimal canaliculus following ophthalmic surgery. Resorbable and does not require removal
How Supplied	Sterile in a foam carrier within a foil laminate pouch. Carton containing (b) (4) or 10 pouches
Storage	Store refrigerated, between 2°C and 8°C (36˚F and 46˚F). Protect from light, keep in package until use
Container Closure	One resorbable sterile insert in a foam carrier within a foil laminate pouch

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On April 27, 2017, we searched the L:drive and AIMS using the terms, dexamethasone to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous label and labeling review[b] and we confirmed that most of the previous recommendations were implemented.

[b] Rutledge M. Label and Labeling Review for Dextenza (dexamethasone) NDA 208742. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 JUN 8. RCM No.: 2016-1073.

APPENDIX C. HUMAN FACTORS STUDY – N/A

APPENDIX D. ISMP NEWSLETTERS – N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) – N/A

APPENDIX F. OTHER – N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Dextenza labels and labeling submitted by Ocular Therapeutix, Inc. on February 28, 2017 and March 22, 2017.

- Pouch Label
- Carton Labeling

G.2 Label and Labeling Images

(b) (4)

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[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

MADHURI R PATEL
05/08/2017

SARAH K VEE
05/08/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 5, 2016

To: Judit Milstein, Chief, Project Management Staff
Division of Transplant and Ophthalmology Products (DTOP)

From: Meena Ramachandra PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Dextenza™ (dexamethasone insert) for ophthalmic intracanalicular use
NDA 208742

On December 20, 2015, DTOP consulted OPDP to review the draft Package Insert (PI) for Dextenza™ (dexamethasone insert) for ophthalmic intracanalicular use, which provides for a proposed new indication for the treatment of ocular pain occurring after ophthalmic surgery.

OPDP reviewed the proposed substantially complete version of the PI provided by Judit Milstein via e-mail on June 29, 2016 titled "DEXTENZA Package Insert for FDA edits 6_24 (3).docx". OPDP's comments are provided in the attached version of the substantially complete labeling.

Thank you for the opportunity to review and provide comments on this proposed labeling. If you have any questions please contact Meena Ramachandra (240) 402-1348 or Meena.Ramachandra@fda.hhs.gov.

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/s/

MEENA RAMACHANDRA
07/05/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	June 8, 2016
Requesting Office or Division:	Division of Transplant and Ophthalmology Product (DTOP)
Application Type and Number:	NDA 208742
Product Name and Strength:	Dextenza (Dexamethasone) Punctum Plug, 0.4 mg
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Ocular Therapeutix
Submission Date:	September 24, 2015
OSE RCM #:	2015-2299
DMEPA Primary Reviewer:	Michelle Rutledge, PharmD
DMEPA Team Leader:	Yelena Maslov, PharmD

1 REASON FOR REVIEW

The Division of Transplant and Ophthalmology Products (DTOP) requested that we review the proposed Dextenza (Dexamethasone) Punctum Plug 0.4 mg pouch labels, box labeling, carton labeling, and prescribing Information for areas that may lead to medication error. The applicant is proposing an indication for the treatment of ocular pain occurring after ophthalmic surgery.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Ocular Therapeutix Health is seeking approval for Dextenza (Dexamethasone) Punctum Plug 0.4 mg, a corticosteroid for the treatment of ocular pain occurring after ophthalmic surgery. The proposed therapy will provide an alternate dosage form option for this indication.

We reviewed the proposed label and labeling and identified the following areas of vulnerability to errors:

- Prominence of important product information on the
  - pouch label
  - box labeling
  - carton labeling

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels can be improved to increase prominence of important product information and promote the safe use of the product.

4.1 RECOMMENDATIONS FOR OCULAR THERAPEUTIX

We recommend the following be implemented prior to approval of this NDA:

A. Carton labeling

1. Add strength immediately following established name, to help assist with the safe use the product.
2. Add the route of administration, such as "For intracanalicular use", per 21 CFR 201.100(b)(3)[1] to assist with the correct use of this product.
3. Add the "Rx only" statement to the carton labeling per 21 CFR 201.100(b)(1)[2]to help assist with the correct use of this product.
4. Add the storage information such as, "Storage: Store refrigerated, between 2°C and 8°C (36˚F and 46˚F)" to assist with the appropriate use of this product.
5. Add the appropriate net quantity of pouches that the respective packaging contains to assist with the correct use of this product.
6. Add "Usual Dose" statement information on the label per 21 CFR 201.100(b)(2)[3] to assist with the correct use of this product.
7. Add the "each (b) (4) contains" statement to assist with the correct use of this product.
8. Consider adding the NDC number to appear prominently in the top third of principal display panel to help assist with the safe use of the product.
9. Add a drug barcode to each individual package as required per 21 CFR 201.25(b)(1)(ii)[4] to assist with the correct use of this product.
10. Ensure that the font size of established name is to at least ½ the size of the proprietary name per 21 CFR 201.10(g)(2) to increase readability of this important information on the principal display panel (PDP)[5] .
11. Add the statement, such as "Single-dose only. Discard any opened, unused product." to assist with the correct use of this product.

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[1] Labeling, per 21 CFR 201.100(b)(3)

[2] Labeling per 21 CFR201.100(b)(1)

[3] Labeling per 21 CFR 201.100(b)(2)

[4] Labeling, 21 CFR 201.25(b)(1)(ii)

[5] Labeling, 21 CFR 201.10(g)(2), 2015

B. Pouch label

1. See A1 above and implement accordingly.

2. Ensure that the font size of established name is to at least ½ the size of the proprietary name per 21 CFR 201.10(g)(2) to increase readability of this important information on the principal display panel (PDP)[1].

3. Add the statement, such as "Single-dose only. Discard any opened, unused product." to assist with the correct use of this product.

4. Add established name and strength to each detachable label on the pouch label for completeness.

C. Box labeling

1. Add proprietary name, established name and strength on the top of the box labeling to read such as:

Dextenxa

Dexamethasone (b) (4), 0.4 mg

2. See B2 above and implement accordingly.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Dextenza that Ocular Therapeutix submitted on September 24, 2015.

Table 2. Relevant Product Information for Dextenza	
Initial Approval Date	N/A
Active Ingredient	sustained release dexamethasone
Indication	treatment of ocular pain associated with ophthalmic surgery
Route of Administration	intracanalicularly
Dosage Form	intracanalicular depot
Strength	0.4 mg
Dose and Frequency	insert into the canaliculus following ophthalmic surgery for up to 30 days
How Supplied	foam carrier within a foil laminate pouch: • Carton containing 10 pouches (b) (4) [redacted]
Storage	store refrigerated, between 2°C and 8°C (36˚F and 46˚F)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On June 3, 2016, we searched the L:drive using the terms, Dextenza, to identify reviews previously performed by DMEPA.

B.2 Results

No previous label and labeling reviews were identified.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On June 3, 2016, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newletter(s)	Dextenza
Search Strategy and Terms	Match Exact Word or Phrase: Dextenza

D.2 Results

No articles were found.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[6] along with postmarket medication error data, we reviewed the following Dextenza labels and labeling submitted by Ocular Therapeutix on September 24, 2016.

- Pouch label
- Box labeling
- Carton labeling
- Prescribing Information (not listed)

G.2 Label and Labeling Images

(b) (4)

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[6] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

MICHELLE K RUTLEDGE
06/08/2016

MICHELLE K RUTLEDGE on behalf of YELENA L MASLOV
06/08/2016

Clinical Inspection Summary

Date	3/07/2016
From	Sharon Gershon, Pharm.D.
To	William Boyd, Medical Team Leader Sonal Wadhwa, Medical Officer Judit Milstein, Regulatory Health Project Manager Division of Non Prescription Drug Products
NDA #	208742
Applicant	Ocular Therapeutics
Drug	Dextenza™ 0.4 mg Intracanilicular (b) (4)
NME	No
Therapeutic Classification	Priority
Proposed Indication	Treatment of ocular inflammation and pain associated with ophthalmic surgery
Consultation Request Date	October 21, 2015
Summary Goal Date	April 1, 2016
Action Goal Date	May 1, 2016
PDUFA Date	July 24, 2016

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATION

Three domestic clinical investigator inspections were conducted in support of NDA 208742. Pivotal study OTX-13-002 was audited at Dr. Walters and Dr. Levenson's sites and study OTX-14-003 was audited at Dr. Silverstein's site. No regulatory violations were found during the inspections and all inspections were classified as NAI. OSI recommends the data be considered acceptable in support of the NDA.

II. BACKGROUND

Ocular Therapeutics, Inc. has developed Dextenza (sustained release dexamethasone) 0.4 mg Intracanalicular (b) (4) (OTX-DP) with a proposed clinical use for ocular pain and inflammation in subjects (b) (4)

The following two studies were used to demonstrate efficacy for this application:

OTX-13-002: A Prospective, Multicenter, Randomized, parallel-Arm, Double-Masked, Vehicle Controlled Phase 3 Study Evaluating the Safety and Efficacy of OTX-DP for the Treatment of Ocular Inflammation and Pain after Cataract Surgery

OTX-14-003: A Prospective, Multicenter, Randomized, Parallel-Arm, Double-Masked, Vehicle Controlled Phase 3 Study Evaluating the Safety and Efficacy of OTX-DP for the Treatment of Ocular Inflammation and Pain after Cataract Surgery

Each study enrolled approximately 240 subjects at 16 sites in the United States. Each study was a prospective, multicenter, randomized, parallel-arm, double-masked, vehicle controlled study to evaluate the safety and efficacy of OTX-DP compared to placebo drug (b) (4) (PVPP) for the treatment of post-surgical inflammation and pain in subjects undergoing ocular surgery. There were no substantive design differences between the two protocols. Subjects underwent follow-up visits at post-operative Days 2, 4, 8, 14, 30, and 60.

The primary efficacy endpoints were:

- Absence of cells (i.e., score of '0') in the anterior chamber of the study eye at Day 14 (inflammation)
- Absence of pain (i.e., score of '0') in the study eye at Day 8

The secondary efficacy endpoints evaluated were:

- Cells in the anterior chamber in the study eye at Days 2, 4, 8, and 30
- Flare in the anterior chamber in the study eye at Days 2, 4, 8, (14 for Study OTX-14-003) and 30
- Pain in the study eye at Days 2, 4, 14, and 30

DEXTENZA was superior to Placebo Drug (b) (4) (PVPP) in treating ocular pain following cataract surgery. A significantly greater proportion of subjects in the DEXTENZA vs. PVPP treatment group (79.0% vs. 47.7%) reported an absence of ocular pain in the study eye at the Day 8 Visit.

Reasons for Site Selection: The sites chosen for inspection had high enrollment for their respective study.

III. RESULTS (by site):

Name of CI, Address	Protocol # , Site #, and # of Subjects	Inspection Date	Final Classification
Site 01 Thomas Walters Austin, TX 78731	OTX-13-002 38 subjects	1/11-15/2016	NAI
Site 02 Jeffrey Levenson Jacksonville, FL 32204	OTX-13-002 33 subjects	12/14-16/2015	NAI
Site 04 Bruce Silverstein Redding, CA 96002	OTX-14-003 48 subjects	2/22 – 25/16	NAI

Key to Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. **Thomas Walters**
   5715 Balcones Drive
   Austin, TX 78731

   a. ***What was inspected:*** This inspection was conducted as a data audit of Protocol OTX-13-002 under NDA 208742. Dr. Thomas Walters has 26 IND studies in the CDER COMIS database. A previous FDA inspection of Dr. Walters' site was conducted in November 2015 and was classified as NAI.

   Dr. Walter's site was chosen for inspection because he had high enrollment for Study OTX-13-002. At this site, 40 subjects were screened, 38 subjects were enrolled and completed the study. The field investigator reviewed 19 subject files.

   b. ***General observations/commentary:*** There was no evidence of under-reporting of adverse events, and the primary efficacy endpoint data was verified and consistent with the data listings. No Serious Adverse Events (SAEs) were reported during the study.

   Monitoring was done by the sponsor and the frequency of visits appeared adequate.

   Test article accountability and disposition records were reviewed and no discrepancies were found. The temperature monitoring records for refrigeration were reviewed and no deficiencies observed.

   c. ***Assessment of data integrity:*** No deficiencies were found and no Form FDA-483, Inspectional Observations, was issued. In general, the data appear acceptable in support of the respective indication

2. **Jeffrey Levenson**
   Levenson Eye Associates, Inc.
   751 Oak St., Suite 200
   Jacksonville, FL 32204

   a. ***What was inspected:*** This inspection was conducted as a data audit of Protocol OTX-13-002 under NDA 208742. Dr. Jeffrey Levenson has eleven IND studies

in the CDER COMIS database. He was last inspected in June 2013. That inspection covered a large study under an assignment issued by CDRH. The inspection was classified as VAI for the site's failure to conduct the study in accordance to the investigational plan. Specifically, subjects were enrolled into that study without meeting the eligibility criteria, a required test was not conducted, and medication was not used in accordance to the protocol.

Dr. Levenson's site was chosen for inspection for this study because he had high enrollment for Study OTX-13-002.

The current inspection included review of subject source documentation, informed consent forms, efficacy endpoint data, medical and ocular histories, source worksheets, ocular pain assessments, anterior chamber cell and flare measurements, visual acuity measurements, punctum exams, test article insertions and assessments, dilated fundus examinations, and a few other areas. Protocol adherence, adverse events, concomitant medications, institutional review board approvals, site reporting, sponsor correspondence, monitoring activities, and investigational product accountability was also covered during this inspection. Source documentation was compared against the electronic case report forms and the data listings provided in the assignment background materials

b. ***General observations/commentary:*** The site's records were legible, complete, and very well organized. Subject records included source documentation and the individual subject case history files. Patient medical charts were also available for review for each subject enrolled into the study. In addition, the site maintained electronic case report forms for each subject. The data required by the study was captured in the study source documentation and transcribed into the electronic case report form (eCRF).

Dr. Levenson was blinded during the study and oversaw the conduct of study activities. He also conducted the informed consent process, determined subject eligibility, conducted cataract surgeries, inserted the investigational product, conducted subject examinations, evaluated adverse events, and conducted other study-related activities.

The inspection revealed some areas in which the protocol was not followed. These areas included use of a prohibited eye drop in the study eye two days prior to surgery and surgery on the non-study eye just prior to the Day 14 study visit. Each of these protocol deviations occurred one time, and the site immediately performed corrective action. The site also made an error in which a subject did not receive the investigational product to which the subject was randomized. The subject required a second attempt and the surgical technician made an error when providing the investigational product to the clinical investigator for this second try. Corrective action included the implementation of new procedures and cross-checking the investigational product.

Subject (b) (6) experienced a serious adverse event (SAE). The subject had the cataract surgery and investigative product insertion on (b) (6) At day 4, this subject had

profound intraocular inflammation and a hypopion (presence of pus on the anterior chamber). The site informed the monitor of the subject's decreased vision and excessive inflammation at the onset on (b) (6) Dr. Levenson stated that he felt the subject's sight was threatened and began rescue therapy. He also broke the blind and found out this subject was randomized to placebo.

c. ***Assessment of data integrity:*** No significant deficiencies were observed and no FDA 483 was issued. The study appears to have been conducted adequately, and the data submitted by this site may be used in support of the respective indication.

3. Bruce Silverstein
Shasta Eye Medical Group
3190 Churn Creek Road
Redding, CA 96002

a. ***What was inspected:*** This inspection was conducted as a data audit of Protocol OTX-14-003 under NDA 208742. Dr. Bruce Silverstein has 12 IND studies in the CDER COMIS database and had one prior FDA inspection in 11/2009 that was classified NAI. Dr. Silverstein's site was chosen for inspection because he had high enrollment for Study OTX-14-003. At the time of inspection, no issues had been identified to suggest a problem with data integrity.

The field investigator conducted a comprehensive review of subject case histories with emphasis on source data verification of the primary and secondary efficacy endpoints that included Ocular Pain Assessments on Post-Operative Days 2, 8, 14, and 30, as well as Post-Operative Day 14 Anterior Chamber Cells and Flare for all 48 subjects; the primary safety endpoint (e.g. adverse events), subject disposition, protocol adherence including eligibility, completion of study visits and events, adverse events including serious adverse event reporting, concomitant medication exposure and reporting, study drug exposure, drug accountability, and randomization.

For 16 of 54 subjects, the field investigator reviewed:
- General adherence to the protocol;
- Randomization sequence;
- Protocol deviations;
- Subject eligibility;
- Concomitant and prior medication use;

b. ***General observations/commentary:*** Records were well organized, legible, reliable, and appropriate. Adequate documentation existed to show subjects were alive and available for the duration of their participation in the study. Data was transcribed from source document worksheets into an electronic data capture system by the study coordinators. Case report forms were made available during the current inspection. Financial disclosure records were on file

for each clinical investigator listed on the FDA Form 1572. No financial interests were reported to the sponsor by any investigator. The site visit log showed the frequency of monitoring to be adequate.

c. ***Assessment of data integrity:*** No FDA-483, Inspectional Observations, was issued at the close of this inspection. The data from the site appear acceptable in support of the respective indication

{See appended electronic signature page}

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