CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208742Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review and Deputy Division Director Summary Review of NDA 208742 Class 2 Resubmission

Date	November 30, 2018
From	William M. Boyd, M.D.; Wiley Chambers, M.D.
Subject	Cross-Discipline Team Leader Review/Deputy Division Director Summary Review
NDA#	NDA 208742
Type	505(b)(2)
Applicant	Ocular Therapeutix
Date of Submission	June 28, 2018
PDUFA Goal Date	December 28, 2018
Name	Dextenza (dexamethasone ophthalmic insert) 0.4 mg
Dosage forms / Strength	0.4 mg intracanalicular insert
Proposed Indication(s)	Treatment of pain associated with (b) (4) surgery
Action:	Approval

1. Introduction

Dextenza (dexamethasone ophthalmic insert) 0.4 mg consists of the active ingredient, dexamethasone; and a known polyethylene glycol hydrogel conjugated with fluorescein, (b) (4) (b) (4) Dexamethasone is a corticosteroid.

Dextenza inserts into the inferior punctum, where it is retained in the vertical canaliculus for release of dexamethasone for up to 30 days. Over this time and through hydrolysis, the hydrogel drug product softens, liquefies, and clears through the nasolacrimal duct.

Throughout this review, Dextenza (dexamethasone ophthalmic insert) 0.4 mg is also referred to as OTX-DP.

This application received a Complete Response letter dated 7/21/2016. Per the letter:

> 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.

This application received a second Complete Response letter dated 7/10/2017, with the same deficiency.

The Applicant's Class 2 resubmission was received June 18, 2018. The NDA was submitted electronically (available internally via \\CDSESUB1\EVSPROD\NDA208742\208742.enx).

2. Background

This is a 505(b)(2) application which references literature to support some of the pharmacology/toxicology labeling statements. The literature identifies, among other products, NDA 13-422 Maxidex (dexamethasone ophthalmic suspension) 0.1% and NDA 11-984 Decadron Sterile Ophthalmic Solution (dexamethasone sodium phosphate ophthalmic solution). In nonclinical studies conducted by the applicant, Dextenza has been demonstrated to have less systemic absorption than Maxidex or Decadron.

Pre-Original Submission regulatory activity included:

5/16/12	PIND 114720 Meeting
9/13/13	EOP2 Meeting
2/11/14	Type C Meeting
8/26/14	pre-NDA CMC Meeting
12/12/14	EOP 2 Meeting (for allergic conjunctivitis indication)
4/14/15	pre-NDA Meeting.

Currently Available Treatments for the proposed or related indications

NDA	Drug	Indication
22-212	Difluprednate ophthalmic emulsion 0.05% (Durezol)	DUREZOL is a topical corticosteroid that is indicated for the treatment of inflammation and pain associated with (b) (4) surgery. DUREZOL is also indicated for the treatment of endogenous anterior uveitis.
202-872	Loteprednol etabonate ophthalmic gel 0.5% (Lotemax)	LOTEMAX is a corticosteroid indicated for the treatment of post-operative inflammation and pain following (b) (4) surgery.
203-168	Bromfenac ophthalmic solution 0.07% (Prolensa)	PROLENSA is a NSAID indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.
21-664	Bromfenac sodium ophthalmic solution 0.09% (Xibrom)	XIBROM is a NSAID indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.
21-664 201-211 202-030 203-395	Bromfenac sodium ophthalmic solution 0.09% (Bromday)	BROMDAY is a NSAID indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.
21-862	Nepafenac ophthalmic suspension 0.1% (Nevanac)	NEVANAC ophthalmic suspension is a NSAID indicated for the treatment of pain and inflammation associated with cataract surgery.
203-491	Nepafenac ophthalmic suspension 0.3% (Ilevro)	ILEVRO (nepafenac ophthalmic suspension), 0.3% is a NSAID indicated for the treatment of pain and inflammation associated with cataract surgery.
22-427	Ketorolac tromethamine ophthalmic solution 0.45% (Acuvail)	ACUVAIL ophthalmic solution is a NSAID indicated for the treatment of pain and inflammation following cataract surgery.
20-037	Diclofenac sodium ophthalmic solution 0.1% (Voltaren Ophthalmic)	VOLTAREN ophthalmic is indicated for the treatment of post-operative inflammation in patients who have

NDA	Drug	Indication
		undergone cataract extraction and for the temporary relief of pain and photophobia in patients undergoing corneal refractive surgery.
206-911	BromSite (bromfenac ophthalmic solution) 0.075%	BROMSITE, a nonsteroidal anti-inflammatory is indicated for the treatment of post-operative inflammation and prevention of ocular pain in patients undergoing cataract surgery
20-474	Vexol (rimexolone ophthalmic suspension) 1%	VEXOL, a corticosteroid, is indicated for the treatment of postoperative inflammation following (b) (4) surgery and in the treatment of anterior uveitis.
208-912	Dexycu (dexamethasone intraocular suspension) 9%	DEXYCU, a corticosteroid is indicated for the treatment of postoperative inflammation
210-656	Inveltys ((loteprednol etabonate ophthalmic suspension) 1%	INVELTYS is a corticosteroid indicated for the treatment of post-operative inflammation and pain following (b) (4) surgery.

3 Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

The data contained in this submission establishes the efficacy of Dextenza (dexamethasone ophthalmic insert) 0.4 mg by demonstrating that it is effective in the treatment of pain associated with (b) (4) surgery**.**
The most common ocular adverse reactions that occurred in patients treated with Dextenza were: anterior chamber inflammation including iritis and iridocyclitis (9%); intraocular pressure increased (5%); visual acuity reduced (2%); eye pain (1%); cystoid macular edema (1%); corneal edema (1%); and conjunctival hyperemia (1%). The most common non-ocular adverse reaction that occurred in patients treated with Dextenza was headache (1%).
The potential benefits of Dextenza (dexamethasone ophthalmic insert) 0.4 mg through the treatment of pain associated with (b) (4) surgery outweigh the identified risks as demonstrated in the clinical studies submitted with this NDA application.

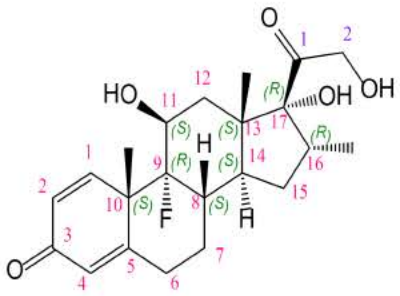
Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Pain, including postoperative pain, is a consequence of a surgical operation that breaks the natural skin, conjunctival or cornea external barrier.	Postoperative pain can be controlled and managed by the operating physician with the use of nonsteroidal or steroid products in the postoperative setting.
Current Treatment Options	Currently available treatments for postoperative pain following (b) (4) surgery include the use of steroidal or nonsteroidal anti-inflammatory drug products.	This product, if approved, would provide an alternative steroid, administered as a single dose, into the inferior punctum, where it is retained in the vertical canaliculus at the end of surgery.
Benefit	Reduction of pain, as expressed by the patient.	Study OTX-13-002, OTX-14-003 demonstrated that Dextenza was superior to placebo for relief of pain caused by the surgical operation.
Risk and Risk Management	Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Use of steroids is also associated with increased risk of posterior subcapsular cataract formation. Prolonged topical use may also suppress the host immune response and increase the hazard of secondary ocular infections.	The clinical trials contained in this application demonstrated that the potential adverse events associated with the use of corticosteroids could be monitored. The observed rates with the use of this product were consistent with rates expected for corticosteroids.

3. CMC

USAN/INN:	Dexamethasone
Compendia name:	Dexamethasone (USP, EP, JP)
Chemical name(s):	Pregna-1,4-diene-3,20-dione, 9- fluoro- 11,17,21-trihydroxy-16- methyl, (11β,16α)-9-Fluoro-11β,17,21-trihydroxy-16α- methylpregna-1,4-diene-3,20-dione
Systematic Chemical Name(s) (IUPAC):	(9R,16R,17S)-9-fluoro-17-glycoloyl- 11,17-dihydroxy-10,13,16-trimethyl-6,7,8,9,10,11,12,13,14,15,16,17- dodecahydro-3Hcyclopenta[a]phenanthren-3-one
Chemical Abstracts Service Number:	50-02-2

Structural formula:



Drug Product

The dexamethasone insert, 0.4 mg appears as [redacted] (b) (4) yellow [redacted] (b) (4), with no visible foreign particulate matter. The proposed drug product consists of the [redacted] (b) (4) API dexamethasone USP and [redacted] (b) (4) [redacted] (b) (4) [redacted] (4-arm polyethylene glycol (PEG) glutarate-trilysine hydrogel conjugated with fluorescein).

Table 1: Composition of the Drug Product

Ingredient	Function	Composition (%)	Target Quantity per Insert (µg)
(b) (4) Dexamethasone, USP	API	(b) (4)	(b) (4)
4-arm 20K PEG-SG			
Trilysine Acetate			
NHS-Fluorescein			
Sodium Phosphate Dibasic, USP			
Sodium Phosphate Monobasic (b) (4) USP			
Water for Injection, USP[1]			
(b) (4)			
		Total Insert Weight:	**0.737 mg**

(b) (4)
N/A – not applicable
Source: Module 2.3.P.1

Proposed specifications for dexamethasone insert drug product for release and stability testing:

Table 1: Quality Control Specifications

Test	Method	Specification
Appearance	Visual	(b) (4) yellow (b) (4) essentially free of visible particulates
Visible Particulate	Visual - USP <790>	Solutions of inspected units must be essentially free of visible particulates
Identity	HPLC	Retention time of dexamethasone peak corresponds to reference standard ± (b) (4) minute
	FTIR	Conforms to spectrum of reference standard
Assay	HPLC	90.0 to 110.0% ((b) (4) µg per insert; target: (b) (4) µg)
Impurities	HPLC	Any individual impurity: NMT (b) (4)% Total impurities: NMT (b) (4)%
N-Hydroxy-succinimide (NHS)	UPLC	NMT (b) (4)%

Test	Method	Specification
Water Content	Karl Fischer - USP <921>	< (b) (4)%
Content Uniformity	HPLC - USP <905>	Meets USP <905> requirements (AV ≤ (b) (4))
Visibility	Visual	Insert can be visually seen through a surrogate test model when illuminated with a blue light
Dry Dimensions	Microscopy	Diameter: (b) (4) (b) (4) mm Length: (b) (4) mm
Expansion (10 mins)	Microscopy	Diameter: ≥ (b) (4) mm Length: < dry length
Equilibrium Diameter (24 hrs)	Microscopy	Diameter: (b) (4) mm
In Vitro Release	UPLC - USP <711>	5 hours (0.21 days): (b) (4)% Day 1: (b) (4)% Day 2: % Day 3: % Day 4: NLT (b) (4)%
Subvisible Particulate Matter	Light Obscuration - USP <788>	≥ 10 µm: NMT (b) (4) particles per insert ≥ 25 µm: NMT articles per insert
Endotoxin	Kinetic Turbidimetric LAL - USP <85>	≤ (b) (4) EU/insert
Sterility	(b) (4)	Confirm irradiation with (b) (4) to achieve a sterility assurance level (SAL) of 1x10

Source: Module 2.3.P.5.1

Container/Closure

The dexamethasone insert is placed in a foam carrier, sealed within a (b) (4) foil pouch (b) (4) (Figure 1 below). (b) (6) sensitive to light. (b) (4) protection for the drug product from moisture and light.

Source: Module 2.3.P.7.1

Facilities

Per the ONDQA review in this cycle dated 11/28/2018:

Drug Substance

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Assessment	Final Recommendation
(b) (4)		Manufacturing, processing, packaging, lot release testing and labelling of Dexamethasone (CSN)	• Low	• Acceptable
		(b) (4) (D) (4) (CTL)	• Low	• Acceptable

All sites supporting the drug substance manufacturing and testing remain acceptable.

Drug Product

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Assessment	Final Recommendation
Ocular Therapeutix Inc.	3008477155	Manufacturing Release testing, stability testing, Primary and Secondary Packaging, Labeling (NEC)	• High, Withhold on previous Pre-approval Inspection*	• Acceptable*
(b) (4)		DP: (b) (4) sterilization (b) (4)	• High, due to sterilization operation	• Acceptable
		DP:Stability Testing (Whole Package Integrity),(CTL)	• Medium	• Acceptable
		DP:Release Testing (Endotoxin Limits) (CTL)	• Medium	• Acceptable
		DP:Release Testing (CTL)	• Low	• Acceptable
		DP:Release Testing (LCP)	• High; preapproval inspection*	• Acceptable based on Inspection/ RAI review.*
		DP: Labeling; Secondary Packaging (NEC)	• Low	• Acceptable

DP: Drug Product; * - Updates in SDN-45

Product Quality Summary

Satisfactory information and responses have been submitted to support the quality of Biopharmaceutics, drug substance, drug product and quality micro aspects; refer to IQA#1 dated 6/17/2017 and IQA# 2 dated 7/5/2017. Drug product and quality micro upholds the approval recommendations after evaluating this resubmission. All the deficiencies are found acceptable from manufacturing process perspective.

The outcome of the most recent inspection of drug product manufacturing facility (Ocular Therapeutix Inc) for this resubmission has resulted in Office of Process and Facilities recommending Approval. An overall acceptable recommendation for all the facilities was issued on 11/28/2018. Therefore, NDA 208742 is recommended for Approval from Product Quality perspective.

4. Nonclinical Pharmacology/Toxicology

See the original Pharmacology/Toxicology review dated 7/11/2016 in DARRTS for this application.

Per the Pharmacology/Toxicology review dated 6/21/17 in DARRTS for this application:

In June 2017, the Quality team alerted Pharmacology/Toxicology to the presence of four specific impurities in the drug substance, (b) (4) with specifications set to not more than (NMT) (b) (4)%. Based on the structures, Quality considered them to be (b) (4), and to be of potential concern.

Table 1: Impurity specifications for the dexamethasone drug substance

Name	Specification (chromatographic purity by HPLC)	Total exposure per 2 inserts[a]	Information from DMF (b) (4) or the published literature
Total impurities	≤ (b) (4)%	≤ (b) (4)µg	
Unspecified impurities	≤ %	≤ µg	
Any individual impurity	≤ %	≤ (b) (4)µg	
(b) (4)	≤ %	(b) (4) µg	Synonyms: (b) (4)

[1] Structures and CAS registry numbers (CASRNs) obtained from Toxnet: US National Institutes of Health (NIH). U.S. National Library of Medicine. Toxnet Toxicology Data Network. Accessed via https://chem.nlm.nih.gov/chemidplus

			(b) (4)
(b) (4)			Synonyms: (b) (4)
			Synonym: (b) (4)

(b) (4)			Synonym: (b) (4)
			(b) (4)

[a]Each Dextenza insert contains a 0.4 mg dose of dexamethasone. Pharmacology/Toxicology assumed placement of inserts in both eyes.

Regarding General Qualification Of The Impurities

- Per ICH Q3A[2], the identification threshold is (b) (4)%, and the qualification threshold is (b) (4)%.
- For the 35-day toxicity study of the dexamethasone punctum plug in dogs (report # TR0161) tested drug product lots 02151201 and 02151203, manufactured by the Applicant using drug substance with the same specification (i.e. referenced to (b) (4) DMF (b) (4) Therefore, this reviewer considers the impurities qualified.
    - Note that this determination is made without prejudice to other toxicology studies that may have been conducted using (b) (4) dexamethasone drug substance.

Regarding Potential Mutagenic Potency

- Neither the Applicant nor the referenced DMF identified toxicity information for these impurities. Likewise, a literature search by this reviewer identified no experimental information relevant to genotoxicity or carcinogenicity.
- As the Quality team noted, the presence of (b) (4) raise concern for (b) (4) activity, and therefore genotoxicity. In the absence of additional information, this reviewer presumes each of these four impurities are mutagenic.
- Dextenza is an ophthalmic intracanalicular insert that is inserted in the lower lacrimal punctum and into the canaliculus following ophthalmic surgery. A single Dextenza releases a 0.4 mg dose of dexamethasone for up to 30 days following insertion.
    - Pharmacology/Toxicology assumed Dextenza treatment of both eyes.
- Per ICH M7[3], intake of an individual mutagenic impurity at 120 µg/day for ≤ 1 month is acceptable. Intake of an individual impurity at 1.5 µg/day for a lifetime is acceptable. Therefore, DTOP has no regulatory concerns for the safety of the exposures listed in Table 1 of this review.

[2] CDER/CBER 2008 Guidance for Industry. ICH Q3A Impurities in New Drug Substances. Accessed via: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073385.pdf
[3] CDER/CBER 2015 Guidance for Industry. ICH M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk. Accessed via https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347725.pdf

5. Clinical Pharmacology/Biopharmaceutics

From the original the Clinical Pharmacology review dated 6/14/2016 in DARRTS for this application:

The Clinical Pharmacology information provided by the Applicant in this submission is acceptable, and the Clinical Pharmacology review team recommends that this NDA for Dextenza be approved for the treatment of ocular pain associated with the ophthalmic surgery.

The original submission package contains the clinical study report of a human pharmacokinetic (PK) study, OTX-14-009, which assessed systemic exposures to dexamethasone resulting from a single administration of the proposed drug product in healthy volunteers.

In Study OTX-14-009, the observed systemic exposures to dexamethasone were negligible following the administration of Dextenza. Dexamethasone plasma levels were undetectable (< LLOQ 50 pg/mL) in 5 of the 16 enrolled healthy volunteers (31.3%) at all time-points. In the remaining 11 subjects, dexamethasone plasma concentrations were below the lower limit of quantification (LLOQ) of 50 pg/mL at 1 and 2 hours post-insertion and at the Visits on Day 15, 22 and 29. Overall, plasma concentrations of dexamethasone were detectable in 11% of samples (21 of 187), and ranged from 0.05 ng/mL to 0.81 ng/mL. These observed low systemic exposures to dexamethasone are similar to the reported minimal dexamethasone exposures following intravitreal injection of 0.7 mg dexamethasone, as per the prescribing information for Ozurdex.

6. Clinical Microbiology

Not applicable for this application.

7. Clinical/Statistical- Efficacy

From the original Medical Officer review dated 7/7/2016:

Table of Clinical Studies

Study	Design	Study Control and Drugs	Number of Subjects by Arm Completed Study	Diagnosis/Inclusion Criteria	Primary Endpoint
OTX-12-002 (Phase 2)	Prospective, randomized, double-masked, vehicle-controlled, parallel group	OTX-DP (sustained release dexamethasone 0.4 mg) PVPP (no drug punctum plug)	OTX-DP: 28 PVPP: 29	≥ 21 years who underwent cataract surgery with implantation of an IOL	Absence of anterior chamber cells on Day 8 Absence of ocular pain on Day 8

OTX-13-002 (First Phase 3 Study)	Prospective, randomized, double-masked, vehicle-controlled, parallel group	OTX-DP (sustained release dexamethasone 0.4 mg) PVPP (no drug punctum plug)	OTX-DP: 163 PVPP: 81	≥ 18 years who underwent cataract surgery with implantation of an IOL	Absence of anterior chamber cells on Day 14 Absence of ocular pain on Day 8
OTX-14-003 (Second Phase 3 Study	Prospective, randomized, double-masked, vehicle-controlled, parallel group	OTX-DP (sustained release dexamethasone 0.4 mg) PVPP (no drug punctum plug)	OTX-DP: 159 PVPP: 76	≥ 18 years who underwent cataract surgery with implantation of an IOL	Absence of anterior chamber cells on Day 14 Absence of ocular pain on Day 8

The primary support for efficacy includes adequate and well-controlled clinical studies (Studies OTX-12-002, OTX-13-002 and C-14-003). The trials were designed to be similar well-controlled studies. The major difference pertained to the Study Schedule; OTX-13-002 had the Day 120 visit as the next visit post-Day 60 and OTX- 14-003 had the Day 90 visit as the next visit post-Day 60. There are no other major differences in study design, inclusion/exclusion criteria, etc. between the two Phase 3 trials.

OTX-12-002 was a prospective, multicenter, randomized, parallel-arm, double-masked, vehicle controlled phase 2 study evaluating the safety and efficacy of OTX-DP for the treatment of ocular inflammation and pain after cataract surgery. The primary endpoints in OTX-12-002 were the proportion of subjects with an absence of cells (i.e. score of "0") in the anterior chamber of the study eye at Day 8, and the proportion of subjects with an absence of pain (i.e. score of "0") in the study eye at Day 8.

The primary efficacy variables in the OTX-13-002 and C-14-003 studies were anterior chamber cells and ocular pain. The primary endpoints were the proportion of subjects with an absence of cells (i.e. score of "0") in the anterior chamber of the study eye at Day 14, and the proportion of subjects with an absence of pain (i.e. score of "0") in the study eye at Day 8. Assessment of anterior chamber cells serves as a hallmark sign of ocular inflammation associated with ophthalmic surgery. Vehicle control was a placebo drug (b) (4) punctum plug.

The primary efficacy analyses in the three studies were conducted based on all randomized subjects (ITT) using a Pearson's chi-square test.

For additional detail, see the Clinical Team Leader Memo dated 7/18/2016 from the original NDA review cycle.

Efficacy Summary Statement

There is evidence from adequate and well-controlled clinical trials that Dextenza is effective in the treatment of pain associated with (b) (4) surgery**.**

At the time of the original submission, there was not sufficient evidence from adequate and well-controlled clinical trials to establish that Dextenza is effective in the treatment of post-surgical inflammation**.** The original safety update includes study (OTX-15-003), which upon review may provide the additional

confirmatory evidence needed to support an indication for treating post-surgical inflammation. To date, the applicant has not requested an indication for the treatment of inflammation associated with (b) (4) surgery.

8. Safety

From the original Medical Officer review dated 7/7/2016:

Adequate and well-controlled clinical studies OTX-13-002 and OTX-14-003 were used to evaluate safety. Between the 2 studies there were 324 patients in the safety database who received OTX-DP.

Safety Update

Subsequent to the original submission of NDA 208742 seeking approval of Dextenza (dexamethasone ophthalmic insert), 0.4 mg for intracanalicular use for the treatment of ocular pain occurring after ophthalmic surgery, four additional clinical trials have been completed with the drug product. The trials include one Phase 3 evaluation of the safety and efficacy of Dextenza in the treatment of ocular pain and inflammation following cataract surgery (OTX-15-003), two Phase 3 trials to assess the safety and efficacy of Dextenza for the treatment of allergic conjunctivitis (OTX-14-007 and OTX-15-002), and one feasibility trial to assess the safety and efficacy of Dextenza for the treatment of dry eye (OTX-14-006). An overview of these trials is presented in Module 2 of the 1/19/2017 submission.

No new information contrary to the findings in the original submission was identified in the safety update provided in the 6/18/2018 submission.

Safety Summary Statement

There is evidence from adequate and well-controlled clinical trials that Dextenza is safe in the treatment of pain associated with (b) (4) surgery**.**

The most common ocular adverse events in any treatment group or study were anterior chamber inflammation (described as anterior chamber inflammation, iritis, iridocyclitis, anterior chamber cell, eye inflammation), corneal edema, ocular discomfort, visual acuity reduced, IOP increased, and corneal abrasion.

The most common non-ocular adverse events were headache, nausea, pneumonia and sinusitis.

For additional detail, see the Clinical Team Leader Memo dated 7/18/2016 from the original NDA review cycle.

9. Advisory Committee Meeting

There were no issues raised during the review of this supplemental application that were believed to benefit from discussion at an Advisory Committee meeting.

10. Pediatrics

Safety and effectiveness of Dextenza in pediatric patients below the age of 18 years has not been established.

This application was presented at PeRC on May 11, 2016. Per the agreed Pediatric Study Plan, deferrals (for each or all age groups) were deemed acceptable since the adult studies are completed.

The deferred pediatric study required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act/FDCA is a required postmarketing study. This required study is listed below.

3548-1	Efficacy of Dextenza (dexamethasone ophthalmic insert), 0.4 mg for intracanalicular use for the treatment of ocular pain following surgery for childhood cataracts

Final Protocol Submission:	September 2018
Study/Trial Completion:	June 2022
Final Report Submission:	April 2023

11. Other Relevant Regulatory Issues

This submission was of sufficient quality to allow for a substantive review without requiring additional clinical information from the applicant. The clinical studies contained in this application were conducted in accordance with International Conference on Harmonization (ICH) guidelines and Good Clinical Practice (GCP).

OSI
As part of the original review cycle, the Office of Scientific Investigations completed a Clinical Inspection Summary dated 3/10/2016. 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. The sites chosen for inspection had high enrollment for their respective study.

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.

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.

Financial Disclosures
Ocular Therapeutix has adequately disclosed financial arrangements with the clinical investigators who participated in the development program for adalimumab. There were two (2) investigators who disclosed financial ties to the applicant. A review of these arrangements does not raise questions about the integrity of the results.

(b) (6) (significant equity interest) (b) (6) patients in the OTX-14-003 trial (b) (6) (significant equity interest) only enrolled (b) (6) patients in the OTX-13-002 trial which would be insufficient to alter the trial results.

Biostatistics
Per the original Biostatistics review dated 6/14/2016 in DARRTS for this application:

The primary evidence for the safety and efficacy of Dextenza comes from two prospective, multicenter, randomized, parallel-arm, double-masked, vehicle-controlled Phase 3 studies (OTX-13-002 & OTX-14-003). The two primary efficacy endpoints were the proportion of subjects with absence of cells (i.e., score of '0') in the anterior chamber of the study eye at Day 14 and the proportion of subjects with absence of pain (i.e., score of '0') in the study eye at Day 8.

The primary efficacy analyses were conducted based on all randomized subjects (ITT) using a Pearson's chi-square test. A fixed sequence hierarchical testing procedure was used to control the type-I error rate due to the test of two primary efficacy endpoints. The difference in the proportion of subjects with absence of pain at Day 8 was tested only after the difference in the proportion of subjects with absence of anterior chamber cells at Day

14 was statistically significant in favor of Dextenza. The last observation carried forward (LOCF) method was used to impute missing data. Subjects who received a rescue medication prior to the evaluation of the primary efficacy endpoints were set as treatment failures.

StudyOTX-13-002 provided statistically significant evidence in favor of Dextenza for both primary efficacy endpoints. The proportion of subjects with absence of pain at Day 8 (Dextenza vs Vehicle) was [80% vs 43%; diff (95% CI): 37% (24%, 49%)]. Study oxt-14-003 however did not demonstrate the superiority of Dextenza over Vehicle for the proportion of subjects with absence of cells at Day 14. Consequently, because of the pre-specified fixed sequence hierarchical testing procedure, no formal statistical conclusion could be made for the pain outcome in this study. However, in this study, the proportion of subjects with absence of pain at Day 8 in the Dextenza arm was fairly consistent with the result seen in study oxt-13- 002, and the treatment difference was numerically favorable to the Dextenza arm (Table 1).

Table 1: Summary of primary efficacy analysis (ITT: LOCF)

		Proportion of subjects with absence of pain		
Study	**Visit**	**Dextenza**	**Vehicle**	**Difference (%) (Asymptotic 95% CI)**
Oxt-13-002	Day 8	131/ 164 (80%)	36/83 (43%)	37% (24%, 49%)
Oxt-14-003	Day 8	124/ 161 (77%)	47/80 (59%)	18% (6%, 31%)
Proportion of subjects with absence of anterior chamber cells				
Oxt-13-002	Day 14	54/ 164 (33%)	12/83 (14%)	18% (8%, 29%)
Oxt-14-003	Day 14	63/ 161 (39%)	25/80 (31%)	8% (-5%, 21%)

Source: Adapted from Table 11-2 of the study reports. Subjects who received a rescue therapy were set as treatment failures.

In summary, compared to Vehicle, the Dextenza arm had higher proportion of subjects with absence of pain at Day 8 in all studies and had a relatively favorable risk-benefit profile. However, conclusive inferential claim for the pain outcome could only be made in one study. Therefore, the overall-risk benefits evaluation and the subsequent determination for approval of this product is deferred to the clinical review team.

OPDP
The Office of Prescription Drug Promotion (OPDP) completed a review of the substantially complete label dated in the 7/5/2016 in the original review cycle.

DMEPA
The Division of Medication Error Prevention and Analysis (DMEPA) completed a review this cycle of the substantially complete label on 9/26/2018.

DMEPA found the proprietary name, Dextenza, to be conditionally acceptable on 9/28/2018.

12. Labeling

NDA 208742 Dextenza (dexamethasone ophthalmic insert) 0.4 mg is recommended for approval for the treatment of pain associated with (b) (4) surgery with the labeling found in the appendix of this review.

13. Regulatory Action

- Regulatory Action

NDA 208742 Dextenza (dexamethasone ophthalmic insert) 0.4 mg is recommended for approval for the treatment of pain associated with (b) (4) surgery now that all manufacturing facilities are found to be incompliance with current Good Manufacturing Practices (cGMPs).

The Approval letter should contain Required Pediatric Assessments language consistent with the following:

REQUIRED PEDIATRIC ASSESSMENTS

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

We are deferring submission of your pediatric study until April 30, 2023, because this product is ready for approval for use in adults and the pediatric study has not been completed. Your deferred pediatric study required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act/FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the Federal Food, Drug, and Cosmetic Act/FDCA. This required study is listed below.

3548-1 Safety and Efficacy of DEXTENZA (dexamethasone ophthalmic insert), 0.4 mg for intracanalicular use for the treatment of ocular pain following surgery for childhood cataracts

Final Protocol Submission:	September 2018
Study/Trial Completion:	June 2022
Final Report Submission:	April 2023

Submit the protocol(s) to your IND 114720, with a cross-reference letter to this NDA.

Reports of this required pediatric postmarketing study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM M BOYD
11/30/2018

WILEY A CHAMBERS
11/30/2018

Cross-Discipline Team Leader Review and Division Director Summary Review of NDA 208742 Class 2 Resubmission

Date	July 6, 2017
From	William M. Boyd, M.D. / Renata Albrecht, M.D.
Subject	Cross-Discipline Team Leader Review/Division Director Summary Review
NDA#	NDA 208742
505(b)(2) Application	Yes
Applicant	Ocular Therapeutix
Date of Submission	1/19/2017
PDUFA Goal Date	7/19/2017
Proprietary Name / Established (USAN) names	Dextenza (dexamethasone ophthalmic insert) 0.4 mg
Dosage forms / Strength	0.4 mg intracanalicular insert
Proposed Indication(s)	Treatment of pain associated with (b) (4) surgery
Action:	Complete Response

1. Introduction

Dextenza (dexamethasone ophthalmic insert) 0.4 mg consists of the active ingredient, dexamethasone; and a known polyethylene glycol hydrogel conjugated with fluorescein, (b) (4) (b) (4) Dexamethasone is a corticosteroid.

Dextenza inserts into the inferior punctum, where it is retained in the vertical canaliculus for release of dexamethasone for up to 30 days. Over this time and through hydrolysis, the hydrogel drug product softens, liquefies, and clears through the nasolacrimal duct.

Throughout this review, Dextenza (dexamethasone ophthalmic insert) 0.4 mg is also referred to as OTX-DP.

This application received a Complete Response letter dated 7/21/2016. Per the letter:

> 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.

The Agency had the following comments/recommendations in the 7/21/2016 letter that were 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).

The Applicant's Class 2 resubmission was received January 19, 2017. The NDA was submitted electronically (available internally via \\CDSESUB1\EVSPROD\NDA208742\208742.enx).

2. Background

This is a 505(b)(2) application which references NDA 13-422 Maxidex (dexamethasone ophthalmic suspension) 0.1% and NDA 11-984 Decadron Sterile Ophthalmic Solution (dexamethasone sodium phosphate ophthalmic solution).

Pre-Original Submission regulatory activity included:

5/16/12	PIND 114720 Meeting
9/13/13	EOP2 Meeting
2/11/14	Type C Meeting
8/26/14	pre-NDA CMC Meeting
12/12/14	EOP 2 Meeting (for allergic conjunctivitis indication)
4/14/15	pre-NDA Meeting.

Post-Complete Response letter regulatory activity included:

10/19/16	Type A Meeting.

Currently Available Treatments for the Proposed Indication

NDA	Drug	Indication
22-212	Difluprednate ophthalmic emulsion 0.05% (Durezol)	DUREZOL is a topical corticosteroid that is indicated for the treatment of inflammation and pain associated with (b) (4) surgery. DUREZOL is also indicated for the treatment of endogenous anterior uveitis.
202-872	Loteprednol etabonate ophthalmic gel 0.5% (Lotemax)	LOTEMAX is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.
203-168	Bromfenac ophthalmic solution 0.07% (Prolensa)	PROLENSA is a NSAID indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.
21-664	Bromfenac sodium ophthalmic solution 0.09% (Xibrom)	XIBROM is a NSAID indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.
21-664 201-211 202-030 203-395	Bromfenac sodium ophthalmic solution 0.09% (Bromday)	BROMDAY is a NSAID indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.
21-862	Nepafenac ophthalmic suspension 0.1% (Nevanac)	NEVANAC ophthalmic suspension is a NSAID indicated for the treatment of pain and inflammation associated with cataract surgery.
203-491	Nepafenac ophthalmic suspension 0.3% (Ilevro)	ILEVRO (nepafenac ophthalmic suspension), 0.3% is a NSAID indicated for the treatment of pain and inflammation associated with cataract surgery.
22-427	Ketorolac tromethamine ophthalmic solution 0.45% (Acuvail)	ACUVAIL ophthalmic solution is a NSAID indicated for the treatment of pain and inflammation following cataract surgery.
20-037	Diclofenac sodium ophthalmic solution 0.1% (Voltaren Ophthalmic)	VOLTAREN ophthalmic is indicated for the treatment of post-operative inflammation in patients who have undergone cataract extraction and for the temporary relief of pain and photophobia in patients undergoing corneal refractive surgery.
206-911	BromSite (bromfenac ophthalmic solution) 0.075%	Treatment of post-operative inflammation and prevention of ocular pain in patients undergoing cataract surgery

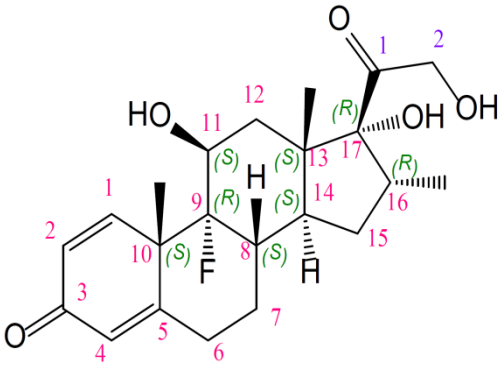
3. CMC

USAN/INN: Dexamethasone
Compendia name: Dexamethasone (USP, EP, JP)
Chemical name(s): Pregna-1,4-diene-3,20-dione, 9- fluoro- 11,17,21-trihydroxy-16- methyl, (11β,16α)-9-Fluoro-11β,17,21-trihydroxy-16α- methylpregna-1,4-diene-3,20-dione

Systematic Chemical Name(s) (IUPAC): (9R,16R,17S)-9-fluoro-17-glycoloyl- 11,17-dihydroxy-10,13,16-trimethyl-6,7,8,9,10,11,12,13,14,15,16,17- dodecahydro-3Hcyclopenta[a]phenanthren-3-one

Chemical Abstracts Service Number: 50-02-2

Structural formula:



Drug Product

Table 1: Composition of DEXTENZA

Ingredient	Nominal Amount	Function	Manufacturer	Specification
Dexamethasone, [redacted] (b) (4) USP	[redacted] (b) (4)	[redacted]	[redacted]	PS 10-2004-002 IC 10-2004-002
4-arm 20K PEG	[redacted]	[redacted]	[redacted]	PS 10-2001-001 IC 10-2001-001
Trilysine Acetate	[redacted]	[redacted]	[redacted]	PS 10-1001-003 IC 10-1001-003

Ingredient	Nominal Amount	Function	Manufacturer	Specification
NHS-Fluorescein	[redacted]	[redacted]	[redacted]	PS 10-2004-005
Sodium Phosphate Dibasic, USP	[redacted]	[redacted]	[redacted]	PS 10-1001-005 IC 10-1001-005
Sodium Phosphate Monobasic, [redacted] USP	[redacted]	[redacted]	[redacted]	PS 10-1001-004 IC 10-1001-004

Source: Module 2.3.P.1

The dexamethasone insert, 0.4 mg appears as [redacted] to yellow [redacted], with no visible foreign particulate matter. The proposed drug product consists of the [redacted] API dexamethasone USP and [redacted] (4-arm polyethylene glycol (PEG) glutarate-trilysine hydrogel conjugated with fluorescein).

Proposed specifications for dexamethasone insert drug product for release and stability testing:

Table 1: Quality Control Specifications

Test	Method	Specification
Appearance	Visual (TM10003)	Drug product appears [redacted] to yellow [redacted], with no visible foreign particulate matter
Dry Dimensions	Calibrated Microscopy (TM10003)	Diameter dimension < [redacted] mm (dry) Length dimension [redacted] mm (dry)
Identity	High Performance Liquid Chromatography (HPLC) (TM60015)	Dexamethasone released from DEXTENZA corresponds to retention time of dexamethasone USP reference standard by HPLC. Dexamethasone is present if the retention time of the drug released from the drug product is within [redacted] minutes of the retention time of the standard
	Fourier Transform Infrared Spectroscopy (FTIR) (TD0325)	Dexamethasone is confirmed if the scan is consistent with the scan from the reference standard by FTIR
Assay	HPLC (TM60015)	Dexamethasone content [redacted] µg per DEXTENZA (90-110% by assay)

Test	Method	Specification
Content Uniformity	HPLC (TM60018)	For 10 DEXTENZA Acceptance Value (AV) is ≤(b) (4). Test additional 20 DEXTENZA if AV is >(b) (4) For the 30 units, AV is ≤(b) (4) and no individual content of any unit is less than [(b) (4) M nor more than [(b) (4)]M where M is the reference value

Source: Module 2.3.P.5.1

Container/Closure

The dexamethasone insert is placed in a foam carrier, sealed within a (b) (4) foil pouch (b) (4) (b) (4). The container closure configuration is provided in Figure 1 below. (b) (4) sensitive to light. (b) (4) protection for the drug product from moisture and light.

(b) (4)

Source: Module 2.3.P.7.1

Facilities

Per the ONDQA review #2 dated 7/5/2017:

Drug Substance

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Assessment	Final Recommendation
(b) (4)		Manufacturing, processing, packaging, lot release testing and labelling of Dexamethasone (CSN)	• Low	• Acceptable
		(b) (4) (b) (4) (CTL)	• Low	• Acceptable

All sites supporting the drug substance manufacturing and testing remain acceptable; no new inspections or concerns are noted.

Drug Product

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Assessment	Final Recommendation
Ocular Therapeutix Inc.	3008477155	Manufacturing Release testing, stability testing, Primary and Secondary Packaging, Labeling (NEC)	• High, Withhold on previous Pre-approval Inspection	• Withhold
(b) (4)		DP (b) (4) sterilization (b) (4)	• High, due to sterilization operation	• Acceptable
		DP:Stability Testing (Whole Package Integrity),(CTL)	• Medium	• Acceptable
		DP:Release Testing (Endotoxin Limits) (CTL)	• Medium	• Acceptable
		DP:Release Testing (CTL)	• Low	• Acceptable

DS: Drug Substance; DP: Drug Product

Per the ONDQA review #2 dated 7/5/2017:

The follow up inspection occurred between 4/24/2017 and 5/4/2017 to support preapproval of this NDA. Coverage included a review of the Quality, Production, Materials, Facilities and Equipment, and Laboratory Control Systems, specifically batches manufactured since the last inspection, the firm's training program, roles/responsibilities within the Quality System, change controls, CAPAs/deviations/non-conformances, equipment qualifications, visual inspection, PPQ, in-process analysis and release data. At the close of the inspection a six (6) item Form FDA-483 was issued and included: (1) A failure to properly investigate particulate matter found in the drug product; (2) Production and process controls not followed in that critical parameters for defect action limits have not been set to include defects such as particulate matter; (3) No written procedures for production and process controls to ensure the drug product has the identity, strength, quality and purity they purport; (4) The responsibilities of the QCU are not in writing; (5) Laboratory controls do not include scientifically sound and appropriate specifications and test procedures; (6) Employees lack training required to perform assigned functions.

The initial field recommendation was a withhold for the submission due to insufficient Development Data, Non-Bacterial Contamination, Product/Process Controls indicating the firm is not ready to support commercial manufacturing. The firm's responses were received on 5/24/2017 and 06/22/2017 and were reviewed by New England District Office and by OPF.

The review of the responses received as of 6/28/2017, led to the following conclusions and outstanding concerns:

Observation 1: This observation remains open and highlights multiple concerns a risk to product quality and patient safety. In particular, the firm's investigation report (Attachment -1 – TD 1385, Dextenza Particulate Investigation), is not thorough as –

(b) (4)

Observation 2: This observation remains open and highlights concerns to lack of acceptable quality limits for defects observed during visual inspection.

Observation 3: This observation remains open and highlights the concern that of the 23 lots manufactured only 3 were released for commercial use. Firm will be asked to provide evidence to support that four lots were used for training, as well as investigations and corrective actions for the rejected PPQ lots. There is a concern that firm may not have a robust process and there is no systematic evaluation and documentation to show that the product can consistently meet specifications. Therefore the firm will need to provide additional executed

batches with appropriate in-process control limits and updated AQL limits for defects (yet to be submitted to FDA for review) to demonstrate that firm is ready for commercial manufacturing.

Observation 4: Firm updated their procedure to better define responsibilities for Quality Inspectors and Quality Engineers. QC is responsible for testing and inspection of incoming components (raw materials), containers, closures, labeling, in process material and finished product, and the performance of the manufacturing process to ensure adherence to proper specs/limits and determines the acceptability of each batch for release. QA is responsible for review/approval of all procedures related to production and maintenance, review of associated records, auditing, and evaluating trends. Implementation of these more detailed responsibilities will be reviewed on a future inspection.

Observation 5: While the firm has completed their forced degradation study, their peak purity analysis remains deficient. The firm has not provided mass balance calculations in their force degradation studies for the active ingredient within the finished drug product.

Observation 6: Firm has incorporated updates to their training protocols supporting visual inspection to ensure robustness of training and adequate frequency of requalification. The firm's corrective actions will be reviewed on a future inspection.

Responses to Observation 1, 2, 3, and 5 are not complete and are pending additional updates from the firm. Therefore, the firm is not recommended for approval for the manufacturing operations described in the NDA as they have not demonstrated readiness to commercially manufacture this product. The withhold recommendation is based on Part V of the PAI CGPM 7346.832, Reasons 3, 7, and 8 due to lack of appropriate specifications and concerns identified with the full scale PPQ batches detailed above.

Action Letter Language

Per the ONDQA review #2 dated 7/5/2017:

The following CR statements on the unacceptable status of the manufacturing facility (Ocular Therapeutix Inc.) was recommended and will be included in the CR letter:

> 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.

The following non-CR comments were recommended to be included in the CR letter; however, they will be modified since the particulate issue does not have an expected safety risk. The recommended language was:

1. As yield specifications may be further tightened based on additional batch history and yield improvement initiatives, please tighten yield limits for visual inspection (Percent Actual yield (Step# (b) (4))) and Percent yield for the batch (Step# (b) (4)).

2. Update your visual inspection controls to include risk based defect categorization with related acceptable quality limits (AQL) and justification for the limits.

3. Provide a comprehensive list of manufacturing, equipment and procedural changes and controls put in place since the previous re-submission to address inspectional deficiencies. Provide the updated batch manufacturing instructions and any new production records supporting this NDA for our review.

The non-CR comments will be:

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.

4. Nonclinical Pharmacology/Toxicology

See the original Pharmacology/Toxicology review dated 7/11/2016 in DARRTS for this application.

Per the Pharmacology/Toxicology review dated 6/21/17 in DARRTS for this application:

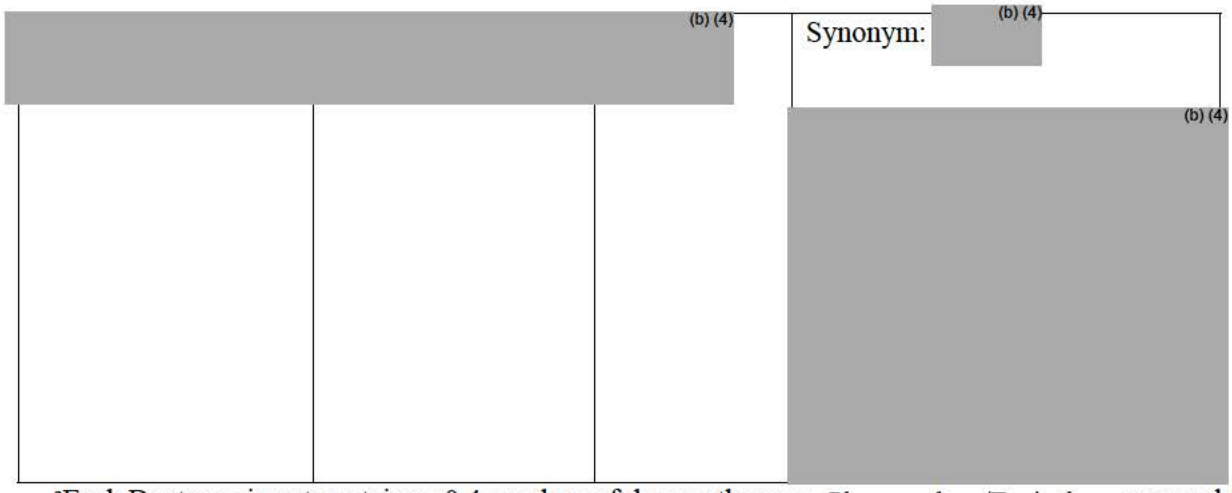
In June 2017, the Quality team alerted Pharmacology/Toxicology to the presence of four specific impurities in the drug substance, (b) (4) with specifications set to not more than (NMT) (b) (4)%. Based on the structures, Quality considered them to be (b) (4), and to be of potential concern.

Table 1: Impurity specifications for the dexamethasone drug substance

Name	Specification (chromatographic purity by HPLC)	Total exposure per 2 inserts[a]	Information from DMF (b) (4) or the published literature
Total impurities	≤ (b) (4)%	≤ (b) (4)µg	
Unspecified impurities	≤ %	≤ µg	
Any individual impurity	≤ %	≤ (b) (4)µg	
(b) (4)	≤ %	(b) (4) µg	Synonyms: (b) (4)

[1] Structures and CAS registry numbers (CASRNs) obtained from Toxnet: US National Institutes of Health (NIH). U.S. National Library of Medicine. Toxnet Toxicology Data Network. Accessed via https://chem.nlm.nih.gov/chemidplus

			(b) (4)
(b) (4)			Synonyms: (b) (4)
			Synonym: (b) (4)



[a]Each Dextenza insert contains a 0.4 mg dose of dexamethasone. Pharmacology/Toxicology assumed placement of inserts in both eyes.

Regarding General Qualification Of The Impurities

- Per ICH Q3A[2], the identification threshold is (b) (4)%, and the qualification threshold is (b) (4)%.
- For the 35-day toxicity study of the dexamethasone punctum plug in dogs (report # TR0161) tested drug product lots 02151201 and 02151203, manufactured by the Applicant using drug substance with the same specification (i.e. referenced to (b) (4) DMF (b) (4) Therefore, this reviewer considers the impurities qualified.
    - Note that this determination is made without prejudice to other toxicology studies that may have been conducted using (b) (4) dexamethasone drug substance.

Regarding Potential Mutagenic Potency

- Neither the Applicant nor the referenced DMF identified toxicity information for these impurities. Likewise, a literature search by this reviewer identified no experimental information relevant to genotoxicity or carcinogenicity.
- As the Quality team noted, the presence of (b) (4) moieties raise concern for (b) (4) activity, and therefore genotoxicity. In the absence of additional information, this reviewer presumes each of these four impurities are mutagenic.
- Dextenza is an ophthalmic intracanalicular insert that is inserted in the lower lacrimal punctum and into the canaliculus following ophthalmic surgery. A single Dextenza releases a 0.4 mg dose of dexamethasone for up to 30 days following insertion.
    - Pharmacology/Toxicology assumed Dextenza treatment of both eyes.
- Per ICH M7[3], intake of an individual mutagenic impurity at 120 µg/day for ≤ 1 month is acceptable. Intake of an individual impurity at 1.5 µg/day for a lifetime is acceptable. Therefore, DTOP has no regulatory concerns for the safety of the exposures listed in Table 1 of this review.

[2] CDER/CBER 2008 Guidance for Industry. ICH Q3A Impurities in New Drug Substances. Accessed via: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073385.pdf
[3] CDER/CBER 2015 Guidance for Industry. ICH M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk. Accessed via https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347725.pdf

5. Clinical Pharmacology/Biopharmaceutics

From the original the Clinical Pharmacology review dated 6/14/2016 in DARRTS for this application:

The Clinical Pharmacology information provided by the Applicant in this submission is acceptable, and the Clinical Pharmacology review team recommends that this NDA for Dextenza be approved for the treatment of ocular pain associated with the ophthalmic surgery.

The original submission package contains the clinical study report of a human pharmacokinetic (PK) study, OTX-14-009, which assessed systemic exposures to dexamethasone resulting from a single administration of the proposed drug product in healthy volunteers.

In Study OTX-14-009, the observed systemic exposures to dexamethasone were negligible following the administration of Dextenza. Dexamethasone plasma levels were undetectable (< LLOQ 50 pg/mL) in 5 of the 16 enrolled healthy volunteers (31.3%) at all time-points. In the remaining 11 subjects, dexamethasone plasma concentrations were below the lower limit of quantification (LLOQ) of 50 pg/mL at 1 and 2 hours post-insertion and at the Visits on Day 15, 22 and 29. Overall, plasma concentrations of dexamethasone were detectable in 11% of samples (21 of 187), and ranged from 0.05 ng/mL to 0.81 ng/mL. These observed low systemic exposures to dexamethasone are similar to the reported minimal dexamethasone exposures following intravitreal injection of 0.7 mg dexamethasone, as per the prescribing information for Ozurdex.

6. Clinical Microbiology

Not applicable for this application.

7. Clinical/Statistical- Efficacy

From the original Medical Officer review dated 7/7/2016:

Table of Clinical Studies

Study	Design	Study Control and Drugs	Number of Subjects by Arm Completed Study	Diagnosis/Inclusion Criteria	Primary Endpoint
OTX-12-002 (Phase 2)	Prospective, randomized, double-masked, vehicle-controlled, parallel group	OTX-DP (sustained release dexamethasone 0.4 mg) PVPP (no drug punctum plug)	OTX-DP: 28 PVPP: 29	≥ 21 years who underwent cataract surgery with implantation of an IOL	Absence of anterior chamber cells on Day 8 Absence of ocular pain on Day 8
OTX-13-002	Prospective,	OTX-DP (sustained	OTX-DP: 163	≥ 18 years who	Absence of

(First Phase 3 Study)	randomized, double-masked, vehicle-controlled, parallel group	release dexamethasone 0.4 mg) PVPP (no drug punctum plug)	PVPP: 81	underwent cataract surgery with implantation of an IOL	anterior chamber cells on Day 14 Absence of ocular pain on Day 8
OTX-14-003 (Second Phase 3 Study	Prospective, randomized, double-masked, vehicle-controlled, parallel group	OTX-DP (sustained release dexamethasone 0.4 mg) PVPP (no drug punctum plug)	OTX-DP: 159 PVPP: 76	≥ 18 years who underwent cataract surgery with implantation of an IOL	Absence of anterior chamber cells on Day 14 Absence of ocular pain on Day 8

The primary support for efficacy includes adequate and well-controlled clinical studies (Studies OTX-12-002, OTX-13-002 and C-14-003). The trials were designed to be similar well-controlled studies. The major difference pertained to the Study Schedule; OTX-13-002 had the Day 120 visit as the next visit post-Day 60 and OTX- 14-003 had the Day 90 visit as the next visit post-Day 60. There are no other major differences in study design, inclusion/exclusion criteria, etc. between the two Phase 3 trials.

OTX-12-002 was a prospective, multicenter, randomized, parallel-arm, double-masked, vehicle controlled phase 2 study evaluating the safety and efficacy of OTX-DP for the treatment of ocular inflammation and pain after cataract surgery. The primary endpoints in OTX-12-002 were the proportion of subjects with an absence of cells (i.e. score of "0") in the anterior chamber of the study eye at Day 8, and the proportion of subjects with an absence of pain (i.e. score of "0") in the study eye at Day 8.

The primary efficacy variables in the OTX-13-002 and C-14-003 studies were anterior chamber cells and ocular pain. The primary endpoints were the proportion of subjects with an absence of cells (i.e. score of "0") in the anterior chamber of the study eye at Day 14, and the proportion of subjects with an absence of pain (i.e. score of "0") in the study eye at Day 8. Assessment of anterior chamber cells serves as a hallmark sign of ocular inflammation associated with ophthalmic surgery. Vehicle control was a placebo drug (b) (4) punctum plug.

The primary efficacy analyses in the three studies were conducted based on all randomized subjects (ITT) using a Pearson's chi-square test.

For additional detail, see the Clinical Team Leader Memo dated 7/18/2016 from the original NDA review cycle.

Efficacy Summary Statement

There is evidence from adequate and well-controlled clinical trials that Dextenza is effective in the treatment of pain associated with (b) (4) surgery**.**

At the time of the original submission, there was not sufficient evidence from adequate and well-controlled clinical trials to establish that Dextenza is effective in the treatment of post-surgical inflammation**.** The safety update includes study (OTX-15-003), which upon review may provide the additional confirmatory evidence

needed to support an indication for treating post-surgical inflammation. To date, the applicant has not requested an indication for the treatment of inflammation associated with (b) (4) surgery.

8. Safety

From the original Medical Officer review dated 7/7/2016:

Adequate and well-controlled clinical studies OTX-13-002 and OTX-14-003 were used to evaluate safety. Between the 2 studies there were 324 patients in the safety database who received OTX-DP.

Safety Update

Subsequent to the original submission of NDA 208742 seeking approval of Dextenza (dexamethasone ophthalmic insert), 0.4 mg for intracanalicular use for the treatment of ocular pain occurring after ophthalmic surgery, four additional clinical trials have been completed with the drug product. The trials include one Phase 3 evaluation of the safety and efficacy of Dextenza in the treatment of ocular pain and inflammation following cataract surgery (OTX-15-003), two Phase 3 trials to assess the safety and efficacy of Dextenza for the treatment of allergic conjunctivitis (OTX-14-007 and OTX-15-002), and one feasibility trial to assess the safety and efficacy of Dextenza for the treatment of dry eye (OTX-14-006). An overview of these trials is presented in Module 2 of the 1/19/2017 submission.

No new information contrary to the findings in the original submission was identified in the provided in the 1/19/2017 submission.

Safety Summary Statement

There is evidence from adequate and well-controlled clinical trials that Dextenza is safe in the treatment of pain associated with (b) (4) surgery**.**

The most common ocular adverse events in any treatment group or study were anterior chamber inflammation (described as anterior chamber inflammation, iritis, iridocyclitis, anterior chamber cell, eye inflammation), corneal edema, ocular discomfort, visual acuity reduced, IOP increased, and corneal abrasion.

The most common non-ocular adverse events were headache, nausea, pneumonia and sinusitis.

For additional detail, see the Clinical Team Leader Memo dated 7/18/2016 from the original NDA review cycle.

9. Advisory Committee Meeting

There were no issues raised during the review of this supplemental application that were believed to benefit from discussion at an Advisory Committee meeting.

10. Pediatrics

Safety and effectiveness of Dextenza in pediatric patients below the age of 18 years has not been established.

This application was presented at PeRC on May 11, 2016. Per the agreed Pediatric Study Plan, deferrals (for each or all age groups) were deemed acceptable since the adult studies are completed.

11. Other Relevant Regulatory Issues

This submission was of sufficient quality to allow for a substantive review without requiring additional clinical information from the applicant. The clinical studies contained in this application were conducted in accordance with International Conference on Harmonization (ICH) guidelines and Good clinical Practice (GCP).

OSI
As part of the original review cycle, the Office of Scientific Investigations completed a Clinical Inspection Summary dated 3/10/2016.

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. The sites chosen for inspection had high enrollment for their respective study.

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.

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.

Financial Disclosures

Ocular Therapeutix has adequately disclosed financial arrangements with the clinical investigators who participated in the development program for adalimumab. There were two (2) investigators who disclosed financial ties to the applicant. A review of these arrangements does not raise questions about the integrity of the results.

(b) (6) (significant equity interest) (b) (6) patients in the OTX-14-003 trial (b) (6) (significant equity interest) only enrolled (b) (6) patients in the OTX-13-002 trial which would be insufficient to alter the trial results.

Biostatistics

Per the original Biostatistics review dated 6/14/2016 in DARRTS for this application:

The primary evidence for the safety and efficacy of Dextenza comes from two prospective, multicenter, randomized, parallel-arm, double-masked, vehicle controlled Phase 3 studies (OTX-13-002 & OTX-14-003). The two primary efficacy endpoints were the proportion of subjects with absence of cells (i.e., score of '0') in the anterior chamber of the study eye at Day 14 and the proportion of subjects with absence of pain (i.e., score of '0') in the study eye at Day 8.

The primary efficacy analyses were conducted based on all randomized subjects (ITT) using a Pearson's chi-square test. A fixed sequence hierarchical testing procedure was used to control the type-I error rate due to the test of two primary efficacy endpoints. The difference in the proportion of subjects with absence of pain at Day 8 was tested only after the difference in the proportion of subjects with absence of anterior chamber cells at Day 14 was statistically significant in favor of Dextenza. The last observation carried forward (LOCF) method was used to impute missing data. Subjects who received a rescue medication prior to the evaluation of the primary efficacy endpoints were set as treatment failures.

StudyOTX-13-002 provided statistically significant evidence in favor of Dextenza for both primary efficacy endpoints. The proportion of subjects with absence of pain at Day 8 (Dextenza vs Vehicle) was [80% vs 43%; diff (95% CI): 37% (24%, 49%)]. Study oxt-14-003 however did not demonstrate the superiority of Dextenza over Vehicle for the proportion of subjects with absence of cells at Day 14. Consequently, because of the pre-specified fixed sequence hierarchical testing procedure, no formal statistical conclusion could be made for the pain outcome in this study. However, in this study, the proportion of subjects with absence of pain at Day 8 in the Dextenza arm was fairly consistent with the result seen in study oxt-13- 002, and the treatment difference was numerically favorable to the Dextenza arm (Table 1).

Table 1: Summary of primary efficacy analysis (ITT: LOCF)

Study	Visit	Proportion of subjects with absence of pain		
		Dextenza	Vehicle	Difference (%) (Asymptotic 95% CI)
Oxt-13-002	Day 8	131/ 164 (80%)	36/83 (43%)	37% (24%, 49%)
Oxt-14-003	Day 8	124/ 161 (77%)	47/80 (59%)	18% (6%, 31%)
Proportion of subjects with absence of anterior chamber cells				
Oxt-13-002	Day 14	54/ 164 (33%)	12/83 (14%)	18% (8%, 29%)
Oxt-14-003	Day 14	63/ 161 (39%)	25/80 (31%)	8% (-5%, 21%)

Source: Adapted from Table 11-2 of the study reports. Subjects who received a rescue therapy were set as treatment failures.

In summary, compared to Vehicle, the Dextenza arm had higher proportion of subjects with absence of pain at Day 8 in all studies and had a relatively favorable risk-benefit profile. However, conclusive inferential claim for the pain outcome could only be made in one study. Therefore, the overall-risk benefits evaluation and the subsequent determination for approval of this product is deferred to the clinical review team.

OPDP
The Office of Prescription Drug Promotion (OPDP) completed a review of the substantially complete label dated in the 7/5/2016 in the original review cycle.

DMEPA
The Division of Medication Error Prevention and Analysis (DMEPA) completed a review this cycle of the substantially complete label on 5/8/2017.

12. Labeling

The Agency will continue to work with the applicant on labeling for this drug product. Draft labeling, with suggested Agency revisions, is attached as an appendix to this review.

The proposed proprietary name, Dextenza, was found to be conditionally acceptable by the Division of Medication Error Prevention and Analysis on 1/27/2016 and 4/12/2017.

13. Regulatory Action/Risk Benefit Assessment

- Regulatory Action

NDA 208742 Dextenza (dexamethasone ophthalmic insert) 0.4 mg is not recommended for approval for the treatment of pain associated with (b) (4) surgery until all manufacturing facilities are found to be incompliance with current Good Manufacturing Practices (cGMPs).

- Risk Benefit Assessment

There is evidence from adequate and well-controlled clinical trials that Dextenza is effective in the treatment of pain associated with (b) (4) surgery by reducing the incidence of ocular pain**.** There is evidence from adequate and well-controlled clinical trials that Dextenza is safe in the treatment of pain associated with (b) (4) surgery**.** The most common ocular adverse events in any treatment group or study were anterior chamber inflammation (described as anterior chamber inflammation, iritis, iridocyclitis, anterior chamber cell), corneal edema, ocular discomfort, visual acuity reduced, eye inflammation, IOP increased, and corneal abrasion. The most common non-ocular adverse events were headache, nausea, pneumonia and sinusitis.

If the drug product which was produced for the clinical trials can be manufactured in a reproducibly consistent manner, the benefits of the product in reducing the incidence of pain following (b) (4) surgery would be expected to outweigh the potential adverse events associated with use of the drug product. Based on pre-approval inspections, the facilities and controls used in the manufacturing of the product have found that the facilities and controls do not comply with current good manufacturing practices and that the product has not been produced in a consistent manner. The product will therefore not be approved until the facility is compliant with current good manufacturing practices.

The following Complete Response statements about the unacceptable manufacturing facility (Ocular Therapeutix Inc) should be included in the CR letter:

1. 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.

The following additional comments should be transmitted as an Information Request:

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.

Appendix

Attached is the Agency's recommended draft labeling with its edits to the applicant's labeling submitted on May 17, 2017. Carton/container labeling should be updated with revisions to product name c/w the attached PI.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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.

/s/

WILLIAM M BOYD
07/10/2017

WILEY A CHAMBERS
07/10/2017

RENATA ALBRECHT
07/10/2017

Cross-Discipline Team Leader Review of NDA 208742

Date	July 13, 2016
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 208742
505(b)(2) Application	Yes
Applicant	Ocular Therapeutix
Date of Submission	9/24/15
PDUFA Goal Date	7/24/16
Proprietary Name / Established (USAN) names	Dextenza (dexamethasone insert) 0.4 mg
Dosage forms / Strength	0.4 mg intracanalicular insert
Proposed Indication(s)	Treatment of pain associated with (b) (4) surgery
Recommended:	Complete Response

1. Introduction

Dextenza (dexamethasone insert) 0.4 mg consists of the active ingredient, dexamethasone; and a known polyethylene glycol hydrogel conjugated with fluorescein, (b) (4) Dexamethasone is a corticosteroid.

Dextenza inserts into the inferior punctum, where it is retained in the vertical canaliculus for release of dexamethasone for up to 30 days. Over this time and through hydrolysis, the hydrogel drug product softens, liquefies, and clears through the nasolacrimal duct.

Throughout this review, Dextenza (dexamethasone insert) 0.4 mg is also referred to as OTX-DP.

2. Background

This is a 505(b)(2) application which references NDA 13-422 Maxidex (dexamethasone ophthalmic suspension) 0.1% and NDA 11-984 Decadron Sterile Ophthalmic Solution (dexamethasone sodium phosphate ophthalmic solution).

Pre-Submission regulatory activity included:

5/16/12	PIND 114720 Meeting
9/13/13	EOP2 Meeting
2/11/14	Type C Meeting
8/26/14	pre-NDA CMC Meeting
12/12/14	EOP 2 Meeting (for allergic conjunctivitis indication)
4/14/15	pre-NDA Meeting.

Currently Available Treatments for the Proposed Indication

NDA	Drug	Indication
22-212	Difluprednate ophthalmic emulsion 0.05% (Durezol)	DUREZOL is a topical corticosteroid that is indicated for the treatment of inflammation and pain associated with (b) (4) surgery. DUREZOL is also indicated for the treatment of endogenous anterior uveitis.
202-872	Loteprednol etabonate ophthalmic gel 0.5% (Lotemax)	LOTEMAX is a corticosteroid indicated for the treatment of post-operative inflammation and pain following (b) (4) surgery.
203-168	Bromfenac ophthalmic solution 0.07% (Prolensa)	PROLENSA is a NSAID indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.
21-664	Bromfenac sodium ophthalmic solution 0.09% (Xibrom)	XIBROM is a NSAID indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.
21-664 201-211 202-030 203-395	Bromfenac sodium ophthalmic solution 0.09% (Bromday)	BROMDAY is a NSAID indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.
21-862	Nepafenac ophthalmic suspension 0.1% (Nevanac)	NEVANAC ophthalmic suspension is a NSAID indicated for the treatment of pain and inflammation associated with cataract surgery.
203-491	Nepafenac ophthalmic suspension 0.3% (Ilevro)	ILEVRO (nepafenac ophthalmic suspension), 0.3% is a NSAID indicated for the treatment of pain and inflammation associated with cataract surgery.
22-427	Ketorolac tromethamine ophthalmic solution 0.45% (Acuvail)	ACUVAIL ophthalmic solution is a NSAID indicated for the treatment of pain and inflammation following cataract surgery.
20-037	Diclofenac sodium ophthalmic solution 0.1% (Voltaren Ophthalmic)	VOLTAREN ophthalmic is indicated for the treatment of post-operative inflammation in patients who have undergone cataract extraction and for the temporary relief of pain and photophobia in patients undergoing corneal refractive surgery.
206-911	BromSite (bromfenac ophthalmic solution) 0.075%	Treatment of post-operative inflammation and prevention of ocular pain in patients undergoing cataract surgery

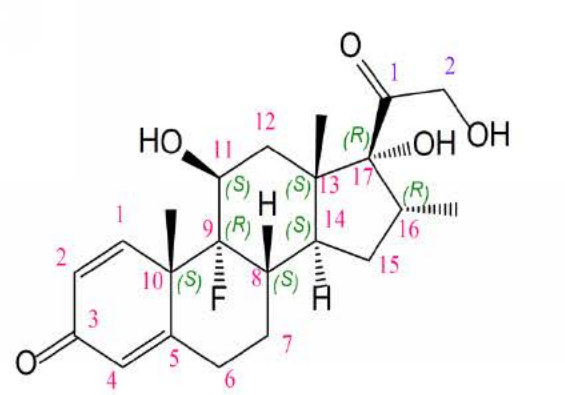
3. CMC

USAN/INN: Dexamethasone
Compendia name: Dexamethasone (USP, EP, JP)
Chemical name(s): Pregna-1,4-diene-3,20-dione, 9- fluoro- 11,17,21-trihydroxy-16-methyl, (11β,16α)-9-Fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione

Systematic Chemical Name(s) (IUPAC): (9R,16R,17S)-9-fluoro-17-glycoloyl- 11,17-dihydroxy-10,13,16-trimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3Hcyclopenta[a]phenanthren-3-one

Chemical Abstracts Service Number: 50-02-2

Structural formula:



Drug Product

Table 1: Composition of DEXTENZA

Ingredient	Nominal Amount	Function	Manufacturer	Specification
Dexamethasone, (b) (4) USP	[redacted]	[redacted]	(b) (4)	PS 10-2004-002 IC 10-2004-002
4-arm 20K PEG	[redacted]	[redacted]	[redacted]	PS 10-2001-001 IC 10-2001-001
Trilysine Acetate	[redacted]	[redacted]	[redacted]	PS 10-1001-003 IC 10-1001-003
NHS-Fluorescein	[redacted]	[redacted]	[redacted]	PS 10-2004-005 IC 10-2004-005

Ingredient	Nominal Amount	Function	Manufacturer	Specification
Sodium Phosphate Dibasic, USP	[redacted]	[redacted]	[redacted]	PS 10-1001-005 IC 10-1001-005
Sodium Phosphate Monobasic, [redacted] USP	[redacted]	[redacted]	[redacted]	PS 10-1001-004 IC 10-1001-004

Source: Module 2.3.P.1

The dexamethasone insert, 0.4 mg appears as [redacted] to yellow [redacted], with no visible foreign particulate matter. The proposed drug product consists of the [redacted] API dexamethasone USP and [redacted] 4-arm polyethylene glycol (PEG) glutarate-trilysine hydrogel conjugated with fluorescein).

Proposed specifications for dexamethasone insert drug product for release and stability testing:

Table 1: Quality Control Specifications

Test	Method	Specification
Appearance	Visual (TM10003)	Drug product appears [redacted] to yellow [redacted], with no visible foreign particulate matter
Dry Dimensions	Calibrated Microscopy (TM10003)	Diameter dimension < [redacted] mm (dry) Length dimension [redacted] mm (dry)
Identity	High Performance Liquid Chromatography (HPLC) (TM60015)	Dexamethasone released from DEXTENZA corresponds to retention time of dexamethasone USP reference standard by HPLC. Dexamethasone is present if the retention time of the drug released from the drug product is within [redacted] minutes of the retention time of the standard
	Fourier Transform Infrared Spectroscopy (FTIR) (TD0325)	Dexamethasone is confirmed if the scan is consistent with the scan from the reference standard by FTIR
Assay	HPLC (TM60015)	Dexamethasone content [redacted] µg per DEXTENZA (90-110% by assay)

Test	Method	Specification
Content Uniformity	HPLC (TM60018)	For 10 DEXTENZA Acceptance Value (AV) is (b) (4). Test additional 20 DEXTENZA if AV is (b) (4). For the 30 units, AV is (b) (4) and no individual content of any unit is less than (b) (4)]M nor more than (b) (4)]M where M is the reference value

Source: Module 2.3.P.5.1

Container/Closure

The dexamethasone insert is placed in a foam carrier, sealed within a (b) (4) foil pouch (b) (4). The container closure configuration is provided in Figure 1 below. (b) (4) are sensitive to light. (b) (4) protection for the drug product from moisture and light.

Source: Module 2.3.P.7.1

Facilities

Drug Substance

Establishment Name	FEI Number	Responsibilities and Profile Codes	Initial Risks Identified	Current Status	Final Recommendation
(b) (4)		Manufacturing, processing, packaging, lot release testing and labelling of Dexamethasone (CSN)	Low	(b) (4) cGMP Inspection VAI	Acceptable based on profile
		(b) (4) (b) (4) (CTL)	Low	(b) (4) cGMP Inspection VAI	Acceptable based on profile

Drug Product

Establishment Name	FEI Number	Responsibilities and Profile Codes	Initial Risks Identified	Current Status	Final Recommendation
Ocular Therapeutix Inc.	3008477155	Manufacturing Release testing, stability testing, Primary and Secondary Packaging, Labeling (NEC); Incoming Release testing.	High, recommended Preapproval inspection	Pre-approval inspection and EIR review: Withhold	Unacceptable, following NWE-DO and EIR review recommendation of withhold
(b) (4)		DP: (b) (4) sterilization (b) (4)	High, due to sterilization operation	1/15/2015 cGMP Inspection NAI	Acceptable, based on District recommendation
		DP:Stability Testing (Whole Package Integrity),(CTL)	Medium	1/10/2014 cGMP Inspection NAI	Acceptable based on profile
		DP:Release Testing (Endotoxin Limits) (CTL)	Medium	9/5/2014 cGMP Inspection NAI	Acceptable based on profile
		DP:Release Testing (CTL)	Low	3/6/2015 cGMP Inspection NAI	Acceptable based on profile

DS: Drug Substance; DP: Drug Product

Ocular Therapeutix Inc., FEI#3008477155, is the applicant and the manufacturer of the new dosage form of dexamethasone. A preapproval inspection was requested on account of high risks related to facility and process identified as part of initial risk assessment.

At the end of the pre-approval inspection, 02/11/2016, a 9-item FDA483 was issued which included issues with quality systems, facility and equipment, manufacturing procedures, in-process controls, and laboratory systems and controls.

Action Letter Language

Per the CMC review dated 6/17/2016 for this application:

The following Complete Response statements about the unacceptable manufacturing facility (Ocular Therapeutix Inc) was recommended to be included in the CR letter:

1. 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.

In addition, the following comments were recommended to be conveyed:

1. The submission 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 submission includes limited 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).

4. Nonclinical Pharmacology/Toxicology

Per the Pharmacology/Toxicology review dated 7/11/2016 in DARRTS for this application:

The nonclinical studies to support this drug product were completed prior to the initial testing of the sustained release dexamethasone intracanalicular depot in patients. This nonclinical P/T review identified no new safety issues related to the dexamethasone drug substance.

The Applicant provided additional nonclinical studies, which support the safety of the vehicle/excipients used in the final drug product. The drug product uses USP dexamethasone, which supports bridging of nonclinical pharmacology and toxicology data.

The Applicant submitted NDA 208742 under the 505(b)(2) pathway, relying on the Agency's findings of safety for two listed drugs approved for topical ocular use: Maxidex (NDA 13-422) and Decadron (NDA 11-984).

At the DTOP Filing Meeting for this NDA, Clinical Pharmacology confirmed that the patient systemic exposure to dexamethasone from Dextenza is lower than the patient systemic exposure from Maxidex 0.1% dexamethasone ophthalmic suspension (Abhay/McDougal, 11/04/2015). Because the systemic exposure of Dextenza is less than Maxidex, the Agency's finding of safety for Maxidex supports the systemic safety of Dextenza. The ocular safety of Dextenza is supported by the Applicant's study # TR0161. For Maxidex, Section 8.1 of the label summarized two papers (Kasirsky and Lombardi 1970, and Ballard et al. 1977).

5. Clinical Pharmacology/Biopharmaceutics

Per the Clinical Pharmacology review dated 6/14/2016 in DARRTS for this application:

The Clinical Pharmacology information provided by the Applicant in this submission is acceptable, and the Clinical Pharmacology review team recommends that this NDA for Dextenza be approved for the treatment of ocular pain associated with the ophthalmic surgery.

The submission package contains the clinical study report of a human pharmacokinetic (PK) study, OTX-14-009, which assessed systemic exposures to dexamethasone resulting from a single administration of the proposed drug product in healthy volunteers.

In Study OTX-14-009, the observed systemic exposures to dexamethasone were negligible following the administration of Dextenza. Dexamethasone plasma levels were undetectable (< LLOQ 50 pg/mL) in 5 of the 16 enrolled healthy volunteers (31.3%) at all time-points. In the remaining 11 subjects, dexamethasone plasma concentrations were below the lower limit of quantification (LLOQ) of 50 pg/mL at 1 and 2 hours post-insertion and at the Visits on Day 15, 22 and 29. Overall, plasma concentrations of dexamethasone were detectable in 11% of samples (21 of 187), and ranged from 0.05 ng/mL to 0.81 ng/mL. These observed low

systemic exposures to dexamethasone are similar to the reported minimal dexamethasone exposures following intravitreal injection of 0.7 mg dexamethasone, as per the prescribing information for Ozurdex.

6. Clinical Microbiology

Not applicable for this application.

7. Clinical/Statistical- Efficacy

Table of Clinical Studies

Study	Design	Study Control and Drugs	Number of Subjects by Arm Completed Study	Diagnosis/Inclusion Criteria	Primary Endpoint
OTX-12-002 (Phase 2)	Prospective, randomized, double-masked, vehicle-controlled, parallel group	OTX-DP (sustained release dexamethasone 0.4 mg) PVPP (no drug punctum plug)	OTX-DP: 28 PVPP: 29	≥ 21 years who underwent cataract surgery with implantation of an IOL	Absence of anterior chamber cells on Day 8 Absence of ocular pain on Day 8
OTX-13-002 (First Phase 3 Study)	Prospective, randomized, double-masked, vehicle-controlled, parallel group	OTX-DP (sustained release dexamethasone 0.4 mg) PVPP (no drug punctum plug)	OTX-DP: 163 PVPP: 81	≥ 18 years who underwent cataract surgery with implantation of an IOL	Absence of anterior chamber cells on Day 14 Absence of ocular pain on Day 8
OTX-14-003 (Second Phase 3 Study	Prospective, randomized, double-masked, vehicle-controlled, parallel group	OTX-DP (sustained release dexamethasone 0.4 mg) PVPP (no drug punctum plug)	OTX-DP: 159 PVPP: 76	≥ 18 years who underwent cataract surgery with implantation of an IOL	Absence of anterior chamber cells on Day 14 Absence of ocular pain on Day 8

The primary support for efficacy includes adequate and well-controlled clinical studies (Studies OTX-12-002, OTX-13-002 and C-14-003). The trials were designed to be similar well-controlled studies. The major difference pertained to the Study Schedule; OTX-13-002 had the Day 120 visit as the next visit post-Day 60 and OTX- 14-003 had the Day 90 visit as the next visit post-Day 60. There are no other major differences in study design, inclusion/exclusion criteria, etc. between the two Phase 3 trials.

OTX-12-002 was a prospective, multicenter, randomized, parallel-arm, double-masked, vehicle controlled phase 2 study evaluating the safety and efficacy of OTX-DP for the treatment of ocular inflammation and pain after cataract surgery. The primary endpoints in

OTX-12-002 were the proportion of subjects with an absence of cells (i.e. score of "0") in the anterior chamber of the study eye at Day 8, and the proportion of subjects with an absence of pain (i.e. score of "0") in the study eye at Day 8.

The primary efficacy variables in the OTX-13-002 and C-14-003 studies were anterior chamber cells and ocular pain. The primary endpoints were the proportion of subjects with an absence of cells (i.e. score of "0") in the anterior chamber of the study eye at Day 14, and the proportion of subjects with an absence of pain (i.e. score of "0") in the study eye at Day 8. Assessment of anterior chamber cells serves as a hallmark sign of ocular inflammation associated with ophthalmic surgery. Vehicle control was a placebo drug (b) (4) punctum plug.

The primary efficacy analyses in the three studies were conducted based on all randomized subjects (ITT) using a Pearson's chi-square test.

Analysis of Primary Endpoint(s)

Study OTX-12-002: Absence of Anterior Chamber Cells at Day 8 and Ocular Pain at Day 8, Intent-to-Treat Population with LOCF (Last Observation Carried Forward)

	OTX-DP N=164	**PVPP N=83**	**Difference-DP-PVPP Estimate**	**Difference-DP-PVPP P-value**
Absence of Anterior Chamber Cells at Day 14				
Yes	6 (20.7%)	3 (10%)	10.7%	0.1495
No	23 (79.3%)	27 (90.0%)		
Absence of Pain at Day 8				
Yes	23 (79.3%)	9 (30.0%)	49.3%	<0.0001
No	6 (20.7%)	21 (70.0%		

Study OTX-12-002 did not demonstrate the superiority of Dextenza over vehicle for the proportion of subjects with absence of anterior chamber cells at Day 14. However, a significantly higher proportion of subjects in the Dextenza arm reported no pain at Day 8 compared with the vehicle arm.

Study OTX-13-002: Absence of Anterior Chamber Cells at Day 14 and Ocular Pain at Day 8, Intent-to-Treat Population with LOCF (Last Observation Carried Forward)

	OTX-DP N=164	**PVPP N=83**	**Difference-DP-PVPP Estimate**	**Difference-DP-PVPP P-value**
Absence of Anterior Chamber Cells at Day 14				
Yes	54 (33.1%)	12 (14.5%)	18.7%	0.0018
No	109 (66.9%)	71 (85.5%)		
Absence of Pain at Day 8				
Yes	131 (80.4%)	36 (43.4%)	37.0%	<0.0001
No	32 (19.6%)	47 (56.6%)		

Study OTX-13-002 demonstrated superiority of Dextenza over vehicle in both primary efficacy endpoints. The proportion of subjects with no anterior chamber cells at day 14 in the Dextenza arm was significantly higher compared with the vehicle arm. Similarly, a significantly higher proportion of subjects in the Dextenza arm reported no pain at Day 8 compared with the vehicle arm.

Study OTX-14-003: Absence of Anterior Chamber Cells at Day 14 and Ocular Pain at Day 8, Intent-to-Treat Population with LOCF (Last Observation Carried Forward)

	OTX-DP N=161	**PVPP N=80**	**Difference-DP-PVPP Estimate**	**Difference-DP-PVPP P-value**
Absence of Anterior Chamber Cells at Day 14				
Yes	63 (39.4%)	25 (31.3%)	8.1%	0.2182
No	97 (60.6%)	55 (68.8%)		
Absence of Pain at Day 8				
Yes	124 (77.5%)	47 (58.8%)	18.8%	0.0025
No	36 (22.5%)	33 (41.3%)		

Study OTX-14-003 did not demonstrate the superiority of Dextenza over vehicle for the proportion of subjects with absence of anterior chamber cells at Day 14. A significantly higher proportion of subjects in the Dextenza arm reported no pain at Day 8 compared with the vehicle arm.

Analysis of Secondary Endpoints(s)

Study OTX-12-002: Absence of Anterior Chamber Cells and Ocular Pain by Visit (ITT Population)

	OTX-DP N=161	**PVPP N=80**	**Difference-DP-PVPP Estimate**	**Difference-DP-PVPP P-value**
Day 1				
Absence of AC Cells	0	0		
Absence of Pain	18 (62.1%)	5 (17.2%)	44.8%	0.0002
Day 4				
Absence of AC Cells	2 (6.9%)	0	6.9%	0.1186
Absence of Pain	24 (82.8%)	7 (23.3%)	59.4%	<0.0001
Day 8				
Absence of AC Cells	6 (20.7%)	3 (10.3%)	10.3%	0.2351
Absence of Pain	23 (79.3%)	9 (31.0%)	48.3%	0.0001
Day 11				
Absence of AC Cells	6 (20.7%)	2 (6.9%)	13.8%	0.1265
Absence of Pain	23 (79.3%)	7 (24.1%)	55.2%	<0.0001
Day 14				
Absence of AC Cells	10 (34.5%)	1 (3.4%)	31.0%	0.0027
Absence of Pain	23 (79.3%)	7 (24.1%)	55.2%	<0.0001
Day 30				
Absence of AC Cells	18 (62.1%)	4 (13.8%)	48.3%	0.0002
Absence of Pain	23 (79.3%)	21 (72.4%)	51.7%	<0.0001

Study OTX-13-002: Absence of Anterior Chamber Cells and Ocular Pain by Visit (ITT Population)

	OTX-DP N=164	**PVPP N=83**	**Difference-DP-PVPP Estimate**	**Difference-DP-PVPP P-value**
Day 2				
Absence of AC Cells	4 (2.5%)	2 (2.4%)	0	0.9830
Absence of Pain	116 (71.22%)	38 (45.8%)	25.4%	0.0001
Day 4				
Absence of AC Cells	15 (9.2%)	6 (7.3%)	1.9%	0.6189
Absence of Pain	127 (77.9%)	43 (52.4%)	25.5%	0.0001
Day 8				
Absence of AC Cells	22 (13.5%)	9 (11.0)	2.5%	0.5754
Absence of Pain	131 (80.4%)	35 (42.7%)	37.7%	<0.0001

	OTX-DP N=164	PVPP N=83	Difference-DP-PVPP Estimate	Difference-DP-PVPP P-value
Day 14				
Absence of AC Cells	54 (33.3%)	12 (14.5%)	18.9%	0.0016
Absence of Pain	129 (79.6%)	33 (39.8%)	39.9%	<0.0001
Day 30				
Absence of AC Cells	101 (62.0%)	22 (28.4%)	33.6%	<0.0001
Absence of Pain	135 (83.3%)	38 (46.9%)	36.4%	<0.0001
Day 60				
Absence of AC Cells	103 (71.0%)	31 (39.2%)	31.8%	<0.0001
Absence of Pain	116 (80.0%)	41 (51.9%)	31.9%	<0.0001

Study OTX-14-003: Absence of Anterior Chamber Cells and Ocular Pain by Visit (ITT Population)

	OTX-DP N=161	PVPP N=80	Difference-DP-PVPP Estimate	Difference-DP-PVPP P-value
Day 2				
Absence of AC Cells	9 (5.6%	4 (5.1%)	0.6%	0.8571
Absence of Pain	105 (65.6%)	32 (40.0%)	25.6%	0.0002
Day 4				
Absence of AC Cells	22 (13.8%)	9 (11.4%)	2.4%	0.5978
Absence of Pain	117 (73.6%)	39 (48.8%)	24.8%	0.0001
Day 8				
Absence of AC Cells	36 (22.5%)	11 (13.8%)	8.8%	0.1073
Absence of Pain	123 (77.4%)	47 (58.8%)	18.6%	0.0027
Day 14				
Absence of AC Cells	63 (39.4%)	25 (31.3%)	8.1%	0.2182
Absence of Pain	123 (76.9%)	46 (57.5%)	19.4%	0.0019
Day 30				
Absence of AC Cells	97 (61.4%)	37 (48.1%)	13.3%	0.0525
Absence of Pain	61 (38.6%)	40 (51.9%)	13.3%	0.0015
Day 60				
Absence of AC Cells	103 (73.0%)	36 (50.7%)	22.3%	0.0012
Absence of Pain	111 (78.7%)	41 (57.7%)	21.0%	0.0014

The absence of ocular pain results are consistent for each trial.

Efficacy Summary Statement

There is evidence from adequate and well-controlled clinical trials that Dextenza is effective in the treatment of pain associated with (b) (4) surgery**.**

There is not sufficient evidence from adequate and well-controlled clinical trials to establish that Dextenza is effective in the treatment of post-surgical inflammation**.**

8. Safety

Adequate and well-controlled clinical studies OTX-13-002 and OTX-14-003 were used to evaluate safety. Between the 2 studies there were 324 patients in the safety database who received OTX-DP.

Exposure/Implant Visualization

OTX-13-002: Extent of Exposure-Number of Patients Subjects with Product Visualized (Safety Population)

	OTX-DP N=162	**PVPP N=84**
Day 2	N=162	N=81
Product Visualized	162 (100%)	81 (100%)
Day 4	N=162	N=80
Product Visualized	162 (100%)	79 (98.8%)
Day 8	N=162	N=80
Product Visualized	162 (100%)	79 (98.8%)
Day 14	N=161	N=79
Product Visualized	161 (100%)	78 (98.7%)
Day 30	N=161	N=78
Product Visualized	143 (88.8%)	72 (92.3%)
Day 60	N=142	N=72
Product Visualized	142 (100%)	47 (65.3%)

On Day 60, 100% of subjects in the OTX-DP safety group were able to have their insert visualized.

OTX-14-003: Extent of Exposure-Number of Patients Subjects With Product Visualized (Safety Population)

	OTX-DP N=160	**PVPP N=80**
Day 2	N=160	N=80
Product Visualized	160 (100%)	80 (100%)
Day 4	N=159	N=80
Product Visualized	159 (100%)	80 (100%)
Day 8	N=160	N=80
Product Visualized	160 (100%)	870 (100%)

	OTX-DP N=160	**PVPP N=80**
Day 14	N=160	N=80
Product Visualized	159 (99.4%)	80 (100%)
Day 30	N=158	N=77
Product Visualized	142 (89.9%)	70 (90.9%)
Day 60	N=140	N=67
Product Visualized	71 (50.7%)	31 (46.3%)

On Day 60, 51% of subjects in the OTX-DP safety group were able to have their insert visualized.

Deaths

OTX-13-002: There were no deaths in the study.
OTX-14-003: One death from cardiac failure congestive occurred in the study:

Nonfatal Serious Adverse Events

Eight SAEs were reported for five subjects in the study.

Study OTX-13-002: Serious Adverse Events

Subject	**Group**	**SAE**
(b) (6)	PVPP	Hypopyon
	OTX-DP	Retroperitoneal Bleed
	OTX-DP	Dehydration and Gout
	PVPP	Lumbar Stenosis and Hydronephrosis
	PVPP	Developmental Hip Dysplasia and Medical Device Complication

Study OTX-14-003: Serious Adverse Events (Safety Population)

Subject	**Group**	**SAE**
(b) (6)	OTX-DP	Colon Cancer
	PVPP	CHF
	PVPP	Mental Disorder (Nervous Breakdown)
	PVPP	Angina Pectoris
	OTX-DP	Peripheral Arterial Occlusive Disease

Common Adverse Events

Study OTX-13-002: Ocular AE in the Study Eye (Safety Population)

	OTX-DP N=162	**PVPP N=84**
Any ocular AE	62	43
Eye disorders	47	38
IOP increased	13	3
AC inflammation	10	7
Corneal edema	2	5
Ocular discomfort	3	4
Visual acuity reduced	3	3
Eye inflammation	0	5
Iritis	1	4
Conjunctival hyperemia	3	1
Cystoid macular edema	4	0
Conjunctivitis	2	1
Lacrimation increased	2	1
Posterior capsular opacification	2	1
Corneal disorder	1	1
Eye pain	2	0
Eye pruritus	2	0
Conjunctival edema	0	1
Diabetic retinal edema	1	0
Eye discharge	1	0
Eye irritation	1	0
Eyelid irritation	1	0
Hypotony	1	0
Iridocyclitis	0	1
Macular edema	1	0
Ocular ischemic neuropathy	1	0
Photophobia	1	0
Punctate keratitis	0	1
Pupillary disorder	1	0
Refraction disorder	0	1
Trichiasis	1	0
Vitreous Floaters	0	1
Injury		
Corneal abrasion	0	1
Incision site edema	1	0
Infections		
Hypopyon	0	1
Neoplasms		
Benign neoplasm of eyelid	1	0

Study OTX-14-003: Ocular AE in the Study Eye (Safety Population)

	OTX-DP N=160	**PVPP N=80**
Any ocular AE	46	31
Eye disorders		
Iritis	12	11
AC inflammation	9	5
IOP increased	7	4
Corneal edema	3	4
Eye pain	2	2
Conjunctival hyperemia	1	2
Cystoid macular edema	1	2
Ciliary hyperemia	1	1
Eye irritation	1	1
Keratitis	2	0
Visual acuity reduced	2	0
AC cell	0	1
Conjunctivitis allergic	1	0
Conjunctivochalasis	1	0
Corneal disorder	1	0
Diplopia	1	0
Dry eye	1	0
Eye hemorrhage	0	1
FBS	1	0
Hypotony	1	0
Lacrimation increased	1	0
Photophobia	1	0
Pinguecula	1	0
Vitreous disorder	1	0
Injury		
Corneal abrasion	1	3
Infections		
Dacrocanaliculitis	0	1
Hordeolum	1	0

The most common ocular adverse events in any treatment group or study were anterior chamber inflammation (described as anterior chamber inflammation, iritis, iridocyclitis, anterior chamber cell), corneal edema, ocular discomfort, visual acuity reduced, eye inflammation, IOP increased, and corneal abrasion.

Study OTX-13-002: Non-Ocular AE (Safety Population)

	OTX-DP N=162	**PVPP N=84**
Any Non-Ocular AE	24	12
Infections		
Body tinea	1	0
External ear cellulitis	1	0
Viral gastroenteritis	1	0
Nasopharyngitis	1	0
Sinusitis	1	0
Skin bacterial infection	0	1
Tooth infection	1	0
Upper respiratory tract infection	0	1
GI disorders		
Constipation	1	0
Oral pain	1	0
Retroperitoneal hemorrhage	1	0
Vomiting	1	0
Injury, Poisoning, and Procedural Complications		
Arthropod bite	1	0
Thermal burn	0	1
Tooth fracture	1	0
Neoplasms		
Basal cell carcinoma	1	0
Malignant melanoma	0	1
Prostate cancer	0	1
Nervous system disorder		
Headache	1	1
Sinus headache	1	0
General disorders		
Medical device complication	0	1
Peripheral edema	1	0
Musculoskeletal disorders		
Arthralgia	0	1
Lumbar spinal stenosis	0	1
Muscle spasms	0	1
Respiratory disorders		
Nasal congestion	1	0
Upper airway cough syndrome	1	0
Vascular disorders		
HTN	1	0
Peripheral vascular disorder	1	0

	OTX-DP N=162	PVPP N=84
Congenital, Familial, and Genetic Disorders		
Developmental hip dysplasia	0	1
Ear Disorders		
Vertigo	1	0
Metabolism Disorders		
Hydronephrosis	0	1
Skin disorders		
Rash	1	0

Study OTX-14-003: Non-Ocular AE (Safety Population)

	OTX-DP N=160	PVPP N=80
Any Non-Ocular AE	**10**	**6**
Infections		
Atypical pneumonia	0	1
Cystitis	0	1
Sinusitis	1	0
Urinary tract infection	1	0
Nervous system disorders		
Headache	2	0
Dizziness	0	1
Cardiac disorders		
Angina	0	1
CHF	0	1
GI disorders		
Nausea	2	0
Injury, Poisoning, and Procedural Complications		
Contusion	1	0
Lower limb fracture	1	0
Investigations		
Blood pressure increased	1	0
ECG abnormal	1	0
Neoplasms		
Colon CA	1	0
Psychiatric disorders		
Mental disorder	0	1

	OTX-DP N=160	PVPP N=80
Skin disorders		
Diabetic ulcer	1	0
Vascular disorders		
Peripheral arterial occlusive disease	1	0

The most common non-ocular adverse events were headache, nausea, pneumonia and sinusitis.

Safety Summary Statement

There is evidence from adequate and well-controlled clinical trials that Dextenza is safe in the treatment of pain associated with (b) (4) surgery**.**

The most common ocular adverse events in any treatment group or study were anterior chamber inflammation (described as anterior chamber inflammation, iritis, iridocyclitis, anterior chamber cell, eye inflammation), corneal edema, ocular discomfort, visual acuity reduced, IOP increased, and corneal abrasion.

The most common non-ocular adverse events were headache, nausea, pneumonia and sinusitis.

9. Advisory Committee Meeting

There were no issues raised during the review of this supplemental application that were believed to benefit from discussion at an Advisory Committee meeting.

10. Pediatrics

Safety and effectiveness of Dextenza in pediatric patients below the age of 18 years has not been established.

This application was presented at PeRC on May 11, 2016. Per the agreed Pediatric Study Plan, deferrals (for each or all age groups) were deemed acceptable since the adult studies are completed.

11. Other Relevant Regulatory Issues

This submission was of sufficient quality to allow for a substantive review without requiring additional clinical information from the applicant. The clinical studies contained in this application were conducted in accordance with International Conference on Harmonization (ICH) guidelines and Good clinical Practice (GCP).

OSI
The Office of Scientific Investigations completed a Clinical Inspection Summary dated 3/10/2016.

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. The sites chosen for inspection had high enrollment for their respective study.

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.

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.

Financial Disclosures
Ocular Therapeutix has adequately disclosed financial arrangements with the clinical investigators who participated in the development program for adalimumab. There were two (2) investigators who disclosed financial ties to the applicant. A review of these arrangements does not raise questions about the integrity of the results.

(b) (6) (significant equity interest) (b) (6) patients in the OTX-14-003 trial (b) (6) (significant equity interest) only enrolled (b) (6) patients in the OTX-13-002 trial which would be insufficient to alter the trial results.

Biostatistics

Per the Biostatistics review dated 6/14/2016 in DARRTS for this application:

The primary evidence for the safety and efficacy of Dextenza comes from two prospective, multicenter, randomized, parallel-arm, double-masked, vehicle controlled Phase 3 studies (OTX-13-002 & OTX-14-003). The two primary efficacy endpoints were the proportion of subjects with absence of cells (i.e., score of '0') in the anterior chamber of the study eye at Day 14 and the proportion of subjects with absence of pain (i.e., score of '0') in the study eye at Day 8.

The primary efficacy analyses were conducted based on all randomized subjects (ITT) using a Pearson's chi-square test. A fixed sequence hierarchical testing procedure was used to control the type-I error rate due to the test of two primary efficacy endpoints. The difference in the proportion of subjects with absence of pain at Day 8 was tested only after the difference in the proportion of subjects with absence of anterior chamber cells at Day 14 was statistically significant in favor of Dextenza. The last observation carried forward (LOCF) method was used to impute missing data. Subjects who received a rescue medication prior to the evaluation of the primary efficacy endpoints were set as treatment failures.

StudyOTX-13-002 provided statistically significant evidence in favor of Dextenza for both primary efficacy endpoints. The proportion of subjects with absence of pain at Day 8 (Dextenza vs Vehicle) was [80% vs 43%; diff (95% CI): 37% (24%, 49%)]. Study oxt-14-003 however did not demonstrate the superiority of Dextenza over Vehicle for the proportion of subjects with absence of cells at Day 14. Consequently, because of the pre-specified fixed sequence hierarchical testing procedure, no formal statistical conclusion could be made for the pain outcome in this study. However, in this study, the proportion of subjects with absence of pain at Day 8 in the Dextenza arm was fairly consistent with the result seen in study oxt-13-002, and the treatment difference was numerically favorable to the Dextenza arm (Table 1).

Table 1: Summary of primary efficacy analysis (ITT: LOCF)

		Proportion of subjects with absence of pain		
Study	**Visit**	**Dextenza**	**Vehicle**	**Difference (%) (Asymptotic 95% CI)**
Oxt-13-002	Day 8	131/ 164 (80%)	36/83 (43%)	37% (24%, 49%)
Oxt-14-003	Day 8	124/ 161 (77%)	47/80 (59%)	18% (6%, 31%)
Proportion of subjects with absence of anterior chamber cells				
Oxt-13-002	Day 14	54/ 164 (33%)	12/83 (14%)	18% (8%, 29%)
Oxt-14-003	Day 14	63/ 161 (39%)	25/80 (31%)	8% (-5%, 21%)

Source: Adapted from Table 11-2 of the study reports. Subjects who received a rescue therapy were set as treatment failures.

In summary, compared to Vehicle, the Dextenza arm had higher proportion of subjects with absence of pain at Day 8 in all studies and had a relatively favorable risk-benefit profile.

However, conclusive inferential claim for the pain outcome could only be made in one study. Therefore, the overall-risk benefits evaluation and the subsequent determination for approval of this product is deferred to the clinical review team.

12. Labeling

The Office of Prescription Drug Promotion (OPDP) completed a review of the substantially complete label dated 7/5/2016.

The Division of Medication Error Prevention and Analysis (DMEPA) did not complete a review this cycle of the substantially complete label but did provide email comments.

NDA 208742 Dextenza (dexamethasone insert) 0.4 mg is not recommended for approval for the treatment of pain associated with (b) (4) surgery until all manufacturing facilities are found to be incompliance with current Good Manufacturing Practices (cGMPs).

The Agency will continue to work with the applicant on labeling for this drug product. Draft labeling, with suggested Agency revisions, is attached as an appendix to this review.

The proposed proprietary name, Dextenza, was found to be conditionally acceptable by the Division of Medication Error Prevention and Analysis on 1/27/2016.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

NDA 208742 Dextenza (dexamethasone insert) 0.4 mg is not recommended for approval for the treatment of pain associated with (b) (4) surgery until all manufacturing facilities are found to be incompliance with current Good Manufacturing Practices (cGMPs).

- Risk Benefit Assessment

NDA 208742 Dextenza (dexamethasone insert) 0.4 mg is not recommended for approval for the treatment of pain associated with (b) (4) surgery until all manufacturing facilities are found to be incompliance with current Good Manufacturing Practices (cGMPs).

There is evidence from adequate and well-controlled clinical trials that Dextenza is effective in the treatment of pain associated with (b) (4) surgery**.** There is not sufficient evidence from adequate and well-controlled clinical trials that Dextenza is effective in the treatment of post-surgical inflammation**.**

There is evidence from adequate and well-controlled clinical trials that Dextenza is safe in the treatment of pain associated with (b) (4) surgery**.**

The most common ocular adverse events in any treatment group or study were anterior chamber inflammation (described as anterior chamber inflammation, iritis, iridocyclitis, anterior chamber cell), corneal edema, ocular discomfort, visual acuity reduced, eye inflammation, IOP increased, and corneal abrasion. The most common non-ocular adverse events were headache, nausea, pneumonia and sinusitis.

The following Complete Response statements about the unacceptable manufacturing facility (Ocular Therapeutix Inc) should be included in the CR letter:

1. 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.

The following additional comments should be transmitted as an Information Request:

1. The submission 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 submission includes limited 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).

Appendix

NDA 208742 Dextenza (dexamethasone insert) 0.4 mg is not recommended for approval for the treatment of pain associated with (b) (4) surgery until all manufacturing facilities are found to be incompliance with current Good Manufacturing Practices (cGMPs).

The Agency will continue to work with the applicant on labeling for this drug product. Draft labeling, with suggested Agency revisions, is attached here.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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.

/s/

WILLIAM M BOYD
07/18/2016

WILEY A CHAMBERS
07/18/2016