CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208742Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	See electronic stamp date
From	Renata Albrecht, MD Division of Transplant and Ophthalmology Products
Subject	Division Director Summary Review
NDA Number	NDA 208742
Related INDs	IND 114720
Applicant Name	Ocular Therapeutix, Inc.
Date of Original Submission **Date of Receipt**	September 24, 2015 September 24, 2015
Review Type:	Standard
PDUFA Goal Date	July 24, 2016 (Sunday)
Proprietary Name / Established (USAN) Name	Dextenza (dexamethasone insert) 0.4mg
Formulation **Use**	Intracanalicular insert 1 insert placed into the canaliculus following the conclusion of (b) (4) surgery
Proposed Indication	Treatment of ocular pain associated with (b) (4) surgery
Action for Application	*Complete Response*

Material Reviewed for this NDA	Names of discipline reviewers
Medical Officer Review	Sonal Wadhwa, Wiley Chambers 7/7/2016
CDTL Review	Bill Boyd, Wiley Chambers 7/18/2016
Statistical Review	Abel Eshete, Yan Wang 6/14/2016
Pharmacology/Toxicology Review	Andrew McDougal, Lori Kotch 7/11/2016
Clinical Pharmacology Review	Abhay Joshi, Philip Colangelo 6/24/2016
Office of Product Quality (OPQ) Drug Substance Drug Product Process Microbiology Facility Biopharmacuetics Regulatory Business Process Manager Application Technical Lead ORA Lead Environmental Assessment	Final dated 6/17/2016 Anamitro Banerjee, ONDP/DNDPI/NDPBII Chunchun Zhang, ONDP/DNDP-I/Branch III Vidya Pai OPF/DIABIII Daniel Schu, OPF/DMA/MABIII Aditi Thakur, Vidya Pai OPF/DIABII, DIABIII Om Anand, ONDP/DB/Branch I Erin Andrews, OPRO/DRBPMI/RBPMBI Chunchun Zhang, ONDP/DNDP-I/Branch III Paul Perdue, ORA/OO/OMPTO/DMPTPO/MDTP Chunchun Zhang, ONDP/DNDP-I/Branch III
OSI/DGCPC	Sharon Gershon, Susan Thompson, Kassa Ayalew 3/10/2016
OSE/DMEPA Proprietary Name Proprietary Name Granted	Michelle Rutledge, Yelena Maslov 1/21/2016 Todd Bridges 1/27/2016
OSE/DMEPA Labeling Review	Michelle Rutledge, Yelena Maslov 6/8/2016
Pediatric Review Committee	Gettie Audain 7/12/2016
OPDP	Meena Ramachandra, 7/5/2016
Project Management	Judit Milstein

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
Office of Program and Regulatory Operations (OPRO)
Office of New Drug Products (ONDP)
Office of Process and Facilities (OPF)
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DMPP =Division of Medical Policy Programs
ODE=Office of Device Evaluation

Table of Contents

1. Benefit-Risk Assessment

I agree with the review team that the applicant submitted clinical studies that demonstrate the safety and efficacy of Dextenza (dexamethasone insert) 0.4 mg, for intracanalicular use for the treatment of ocular pain associated with (b) (4) surgery based on adequate and well controlled studies. The nonclinical data and clinical pharmacology data were considered adequate by the respective disciplines to support approval.

The CMC reviewers determined that sufficient information was presented to conclude the drug product met criteria for identity, strength, quality and purity. However, the Office of Process and Facilities issued a recommendation of "withhold" because a recent inspection of the Ocular Therapeutix, Inc., manufacturing facility, FEI#3008477155, found the facility failed to be compliant with current Good Manufacturing Practices (cGMP).

See Benefit –Risk Table summary below

Benefit-Risk Summary and Assessment

Dextenza (dexamethasone insert) 0.4%, for intracanalicular use, is a corticosteroid product intended for treatment of pain associated with (b) (4) surgery. It was found to be effective and safe in three randomized, vehicle-controlled clinical trials. Ocular adverse reactions associated with this product are listed below. Because of manufacturing deficiencies at the Ocular Therapeutix, Inc., facility, the application will be issued a Complete Response letter during this review cycle.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Pain following cataract surgery occurs because the surgical procedure involves cutting and manipulating ocular structures while removing the crystalline lens and inserting an artificial intraocular lens. The manipulation of ocular tissues usually results in pain and inflammation.	Pain management following cataract surgery is standard of care.
Current Treatment Options	There are multiple corticosteroid products (difluprednate, loteprednol,) and nonsteroidal anti-inflammatory drugs (bromfenac, nepafenac, ketorolac, diclofenac) approved to treat pain following cataract surgery	Dexamethasone would present another therapeutic option.
Benefit	Dextenza resulted in faster resolution of pain compared to vehicle at Day 1 and Day 8. The treatment difference at Day 8, the primary endpoint, was 49%, 37% and 19% in studies OTX-12-002, OTX-13-002 and OTX-14-003, respectively.	Dextenza was superior to placebo in resolution of pain.
Risk	Dextenza is an intracanalicular insert. In clinical trials the most common reported ocular adverse reactions were: anterior chamber inflammation including iritis, iridocyclitis, anterior chamber cells (9%); intraocular pressure increased (6%); visual acuity reduced (2%); eye pain (2%); cystoid macular edema (1%), corneal edema (1%); and conjunctival hyperemia (1%).	These adverse events are associated with the surgical procedure, and treated with medications.
Risk Management	The benefit of reducing pain appears to outweigh the risks associated with the use of this intracanalicular insert.	This dexamethasone insert provides another option for treatment of post-operative ocular pain.

2. Background

The product was developed under IND 114720, and milestone meetings were held:

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

At the End-of-Phase 2 meeting on September 13, 2013, the applicant proposed to evaluate the primary endpoints of absence of pain and absence of anterior chamber cells at Day (b) (4), but agreed with the Division's recommendation to evaluate pain outcome at Day 1 and Day 8; the Day 8 evaluation was considered as the primary efficacy pain outcome.

At the pre-NDA meeting, the Division advised the applicant to conduct another Phase 3 study to evaluate the anterior chamber cell endpoint at Day 14, because in one of the two Phase 3 studies (OTX-14-003) failed to show statistical superiority of Dextenza over vehicle. Regarding the pain endpoint, both Phase 3 clinical trials and the Phase 2 study showed superiority of Dextenza over vehicle. The Division agreed the NDA could be filed with these studies, but approval would be a review issue.

3. Drug Product Quality & Device Constituent Part

Based on the OPQ review, the quality of the drug substance, drug product, biopharmaceutics and quality microbiology are supported by the information submitted. However, based on the most recent inspection of the drug product manufacturing facility (Ocular Therapeutix, Inc), the Office of Process and Facilities recommended "Withhold" of the application.

Drug Substance
Dexamethasone USP (b) (4) was reviewed under DMF (b) (4), letter of authorization provided by (b) (4), and the DMF was found to be adequate by OPQ.

Drug Product
The dexamethasone intracanalicular insert consists of dexamethasone and 4-arm polyethylene glycol (PEG) glutarate-trilysine hydrogel conjugated with fluorescein. The drug product is (b) (4) yellow (b) (4) with no visible foreign particulate matter. The product contains USP grade excipients: sodium phosphate bibasic, sodium phosphate monobasic (b) (4) water for injection. The specification includes tests for appearance, identification, assay, impurity, dry dimension, content uniformity, expansion, equilibrium diameter, *in vitro* release, water content, visibility, endotoxin and sterility; OPQ found this to be is acceptable. All analytical methods are described in reasonable detail and have been adequately validated. Additionally, all microbiology related issues concerning the drug product have been satisfactorily resolved.

Parameters*	Reference Product (NDA 13422)	Product under Review
Type	Dexamethasone ophthalmic suspension	Dexamethasone insert
Description	Sterile ophthalmic suspension	(b) (4) yellow (b) (4), with no visible foreign particulate matter
Target Weight	5mL	0.4 mg
Dimensions/Size	5mL	Diameter dimension (dry) < 0.55 mm; Length dimension (b) (4) 3 (b) (4) mm (dry)
Container/Closure Design	5 mL plastic DROP-TAINER® dispensers.	One foil pouch containing one dexamethasone insert in foam carrier
Excipients (not in RLD) which require label warning	NA	NA

Container/Closure System

Dexamethasone insert is placed in a foam insert, (b) (4) foil pouch (b) (4)

(b) (4) sensitive to light. (b) (4) .

Figure 1: Dexamethasone Drug Product Packaging Configuration

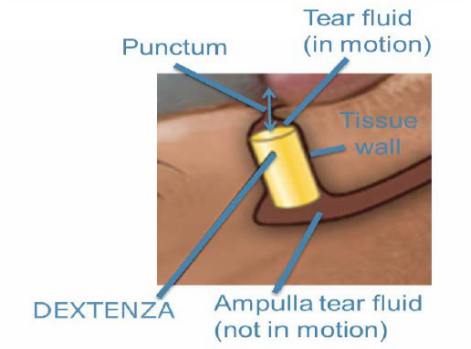
(b) (4)

Eighteen months of stability data for one registration batch and twelve months of stability data for the other two registration batches at long term condition (5°C) are provided at 74% of commercial scale. Expiration Date & Storage Conditions: (b) (4) months with the storage statement of stored 2ºC – 8ºC and a cautionary statement, "protect from light".

Clinical Use

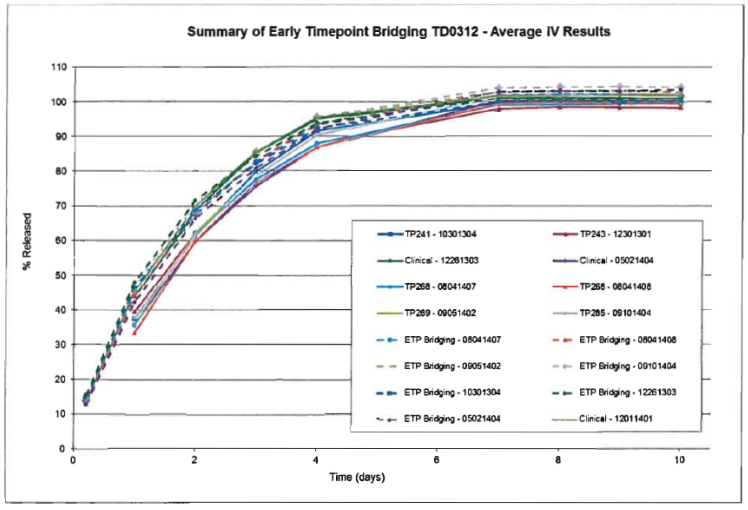
The drug delivery vehicle is designed to remain in the vertical canaliculus for 30 days. Then through hydrolysis, the drug product softens, liquefies and is cleared through the nasolacrimal duct.

Anatomical representation of Dextenza placement



In vitro release

Comparison of the release profiles of various lots, with and without early sampling time points.



Source: CMC review

Facilities inspection

Based on the most recent inspection of the drug product manufacturing facility (Ocular Therapeutix Inc.), the Office of Process and Facilities recommended "Withhold" of the application. The OPQ review includes text for one deficiency and two additional comments (not deficiencies) to be communicated to the applicant.

The following deficiency will be communicated in the Complete Response 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.*

Additional comments (not deficiencies)

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

This is a 505(b)(2) application that relied the applicant's study #TR0161 as well as published literature. The applicant also relied on NDA 13422, Maxidex (dexamethasone ophthalmic suspension) 0.1% and NDA 11984, Decadron Sterile Ophthalmic Solution (dexamethasone sodium phosphate ophthalmic solution) 0.1% for non-clinical information, per Form 356h dated 6/23/2015.

In study #TR0161, dogs received the dexamethasone depot placed into the inferior punctum of the right eye, for up to 35 days. The implants caused ocular discharge, and an increased incidence and severity of reduced pupillary light reflex (PLR). The drug product uses USP dexamethasone, which supports bridging of nonclinical pharmacology and toxicology data, as the exposures are scientifically relevant to the current product.

At the 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 after 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.

The nonclinical P/T review identified no new safety issues related to the dexamethasone drug substance, predicted irritation related to the placement of the depot in the puncta, and also predicted the loss of the implant (presumably dislodged by rubbing the eye; possibly

dissolving enough to enter further into the nasolacrimal duct, away from the surface of the eye). The proposed concentrations of all the excipients are adequately qualified for this drug product, and raise no safety concerns.

From the P/T perspective, P/T recommends approval of the application.

5. Clinical Pharmacology

Dextenza, referred to as OTX during development, is a single administration sterile insert for intracanalicular placement, and is postulated to release dexamethasone locally in a sustained and tapered manner for up to 30 days for the proposed indication.

The application contains the results of a human pharmacokinetic (PK) study, OTX-14-009, in which systemic exposures of dexamethasone resulting from a single administration of the proposed drug product was assessed 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. The Clinical Pharmacology reviewer notes the 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.

Individual Dexamethasone Plasma Concentrations (ng/mL) from PK portion of OTX-14-009

Subject Number	Hours Post-Insertion						Days Post-Insertion					
	0	1	2	4	8	16	2	4	8	15	22	29
S-01 (b) (6)	0	0	0	0	0	0.08	0	0.06	0	0	0	0
S-01	0	0	0	0	0	0	0	0	0.19	0	---	---
S-01	0	0	0	0	0	0	0	0	0.08	0	0	0
S-01	0	0	0	0.81	0.06	0.08	0.06	0.05	0	0	0	0
S-01	0	0	0	0	0.05	0.05	0	0	0	0	0	0
S-01	0	0	0	0	0	0	0	0	0	0	0	0
S-01	0	0	0	0	0.08	0.05	0.07	0.08	0	0	0	0
S-01	0	0	0	0	0.05	0	0	0	0.05	0	0	0
S-01	0	0	0	0	0	0	0	0	0.1	0	0	0
S-01	0	0	0	0	0	0	0	0	0	0	0	0
S-01	0	0	0	0	0	0	0	0	0	0	0	0
S-01	0	0	0	0	0	0	0	0.08	0	0	0	0
S-01	0	0	0	0	0	0	0	0	0	0	0	0
S-01	0	0	0	0.06	0	0	0	0	0	0	0	0
S-01	0	0	0	0	0	0	0	0	0.12	0	---	---
S-01	0	0	0	0	0	0	0	0	---	0	0	0

The Clinical Pharmacology review team recommends that this NDA be approved.

6. Clinical Microbiology

Not Applicable

7. Clinical/Statistical-Efficacy

In support of this NDA, the Applicant submitted the following randomized, controlled, clinical studies. Study OTX-13-002 and Study OTX-14-003 enrolled 241 and 247 subjects respectively each from a total of 16 sites located in the United States (US). Study OXT-12-002 enrolled 60 subjects in 4 sites in the US. Brief summaries for each of these studies are presented below.

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 (dexamethasone implant) 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 (dexamethasone implant) 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 (dexamethasone implant) 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

Ocular Pain Assessment

Ocular pain was assessed by the patient at the screening visit and at each follow-up visit, utilizing a numerical rating scale graded from 0 to 10.

Anterior Chamber Cells

Anterior chamber cell count was graded based on the table below.

Grade	Number of Cells in Field
0	0
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50

Efficacy Results

The information on the outcome is summarized in clinical and statistical reviews, and selected tables are presented below:

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=29	**PVPP N=30**	**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=163	**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=160	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.

The statistical reviewer noted that study OTX-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 OTX-14-003 however failed to demonstrate that Dextenza was superior to vehicle for 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, the treatment difference in pain at Day 8 favored the Dextenza arm in Study OTX-14-003, and was similar to the significant treatment difference in Study OTX-13- 002. These findings were also seen in Phase 2 Study OTX-12-002.

I agree with the conclusion reached by the reviewers that there is evidence from adequate and well-controlled clinical trials that Dextenza is effective in the treatment of pain associated with ocular surgery; however, there is lack of consistent evidence from adequate and well-controlled clinical trials to establish that Dextenza is effective in the treatment of post-surgical inflammation**.**

8. Safety

The safety of Dextenza was evaluated in three randomized studies, vehicle-controlled trials. There were 351 patients enrolled, the mean age of the population was 67 years (range 19 to 93 years), 57% were female, and 83% were white. Forty-five percent had brown iris color and 30% had blue iris color. Additional safety information was obtained from a Phase 2 study and Phase 1 PK study.

Product Visualization

Subjects in all four studies were followed until the product was either removed (Study OTX-14-009) or could no longer be confirmed to be present in the canaliculus (Studies OTX-12-

002, OTX-13-002, OTX-14-003). The applicant therefore used product visualization as a measure of exposure to Dextenza or vehicle. Summary of product visualization/exposure in the four studies is presented below. A total of 367 subjects were administered Dextenza, of which 325 were exposed to Dextenza for the intended duration of therapy of at least 30 days. The number of subjects in whom Dextenza could be visualized decreased to 191 by the Day 60 Visit.

Summary of product visualization/exposure (Safety population)

	OTX-14-009	**OTX-12-002**		**OTX-13-002**		**OTX-14-003**	
	Dextenza (N=16)	Dextenza (N=30)	Vehicle (N=30)	Dextenza (N=162)	Vehicle (N=84)	Dextenza (N=160)	Vehicle (N=80)
Day 2	16 (100%)	29 (96.7%)	29 (96.7%)	162 (100.0%)	81 (96.4%)	160 (100.0%)	80 (100.0%)
Day 4	16 (100%)	29 (96.7%)	29 (96.7%)	162 (100.0%)	79 (94.0%)	159 (99.4%)	80 (100.0%)
Day 8	16 (100%)	29 (96.7%)	29 (96.7%)	162 (100.0%)	79 (94.0%)	160 (100.0%)	80 (100.0%)
Day 14	15 (93.7%)	29 (96.7%)	29 (96.7%)	161 (99.4%)	78 (92.8%)	159 (99.4%)	80 (100.0%)
Day 30	12 (85.7%)	28 (93.3%)	27 (93.1%)	143 (88.3%)	72 (85.7%)	142 (88.7%)	70 (87.5%)
Day 60	N/A	20 (66.7%)	21 (91.3%)	100 (61.7%)	47 (55.9%)	71 (44.4%)	31 (38.7%)

Source: Statistical Review Adapted from Table 14.2.4.1 in CSR OTX-12-002; Table 14.3.10 in CSR OTX-13-002 and Table 14.3.10 in CSR OTX-14-003.

Adverse Reactions

The most common ocular adverse reactions reported by patients treated with Dextenza were: anterior chamber inflammation including iritis, iridocyclitis, anterior chamber cell (9%); intraocular pressure increased (6%); visual acuity reduced (2%); eye pain (2%); cystoid macular edema (1%), corneal edema (1%); and conjunctival hyperemia (1%).

Summary of adverse events in the study eye (Safety population)

Adverse event (AE)	Treatment: N (%)	
	Dextenza N=367	Vehicle N=194
Any AE	141 (38.4%)	95 (49.0%)
Any serious AE (SAE)	5 (1.4%)	8 (4.1%)
Any ocular AE	101 (27.5%)	78(40.2%)
Intraocular Pressure Increased	22 (6.0%)	8 (4.1%)
Anterior Chamber	19 (5.2%)	13 (6.7%)
Iritis	13 (3.5%)	16 (8.2%)
Corneal Oedema	5 (1.4%)	12 (6.2%)
Visual Acuity Reduced[1]	7 (1.9%)	7 (3.6%)
Conjunctival Hyperaemia	4 (1.1%)	6 (3.1%)
Cystoid Macular Oedema	5 (1.4%)	3 (1.5%)
Ocular Discomfort	3 (0.8%)	4 (2.1%)
Eye Pain	5 (1.4%)	2 (1.0%)
Eye Inflammation	0 (0.0%)	5 (2.6%)
Corneal Abrasion	1 (0.3%)	1 (0.3%)

Source: Statistical Review, Tables 3 and 5 of ISS. [1] visual acuity reduced from the previous visit not from baseline.

Lid apposition, punctal appearance and tear meniscus was evaluated at screening and all subsequent visits in Study OTX-13-002 and OTX -14-003. Study eyes were judged to have no clinical significant abnormal finding, with the exception of one patient (b) (6)) who

experienced dacryocanaliculitis and tear meniscus described as "contains pus consistent with canaliculitis Dx".

Labeling will include information on contraindication of use in patients with active or suspected infection. Warnings will be included about the increase in intraocular pressure and glaucoma, and occurrence of cataract, seen with prolonged steroid use; risk of bacterial, viral and fungal infection due to immune suppression with prolonged use; delayed wound healing.

The most common non ocular adverse reaction reported by patients treated with Dextenza was headache (1%).

9. Advisory Committee Meeting

This application did not raise any scientific issues that would benefit from discussion at an Advisory Committee meeting.

10. Pediatrics

This product triggers PREA as a new dosage form and route of administration. The sponsor was seeking approval for both pain and inflammation associated with ocular surgery, but the sponsor failed to demonstrate efficacy for treatment of inflammation. Thus the applicant was granted a deferral for studies (pain indication) in pediatric patients from 0 to <18 years of age.

11. Other Relevant Regulatory Issues

505(b)(2) Application
This is a 505(b)(2) application that relied on published literature and NDA 13422 Maxidex (dexamethasone ophthalmic suspension) 0.1% and NDA 11-984 Decadron Sterile Ophthalmic Solution (dexamethasone sodium phosphate ophthalmic solution) for non-clinical information, per 356h dated 6/23/2015. The "bridge" between the current product and the relied on information will be reviewed again by the 505(b)(2) committee before the application can be approved.

OSI Inspection of Clinical Data
Inspection of the studies was conducted and no data integrity issues that would preclude reliance on the data were identified. Three sites (#1, #2 and #4) were inspected based on relatively large enrollment at these sites, and all three were classified as NAI.

Financial Disclosure
As provided under 21 CFR 54.2, there were no disclosed financial interests/arrangements nor evidence to suggest that the results of the study were impacted by any financial payments.

12. Labeling

Package Insert
Preliminary review completed, final labeling deferred until resolution of the GMP deficiency.

Carton and Container
Preliminary review completed, final labeling deferred until resolution of the GMP deficiency.

Trade Name
DMEPA concluded that the proposed proprietary names Dextenza was acceptable on 1/27/2016.

13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies (REMS)

Not applicable, no issues were identified during the review that would rise to the level of a REMS.

- Other Postmarketing Requirements (PMR) and Commitments (PMC)

Not applicable, no issues were identified during the review qualified as PMRs or PMCs.

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

/s/

RENATA ALBRECHT
07/21/2016