CLINICAL AND CDTL REVIEW

Application Type	Supplement #13
Application Number(s)	208-742
NDA Type	505(b)(2)
Priority or Standard	Standard
Submit Date(s)	6/28/24
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PDUFA Goal Date	4/28/25
Division/Office	Division of Ophthalmology/Office of Specialty Medicine
Reviewer Name(s)	Sonal D. Wadhwa, MD
Review Completion Date	1/6/25
Established/Proper Name	dexamethasone insert
(Proposed) Trade Name	DEXTENZA (dexamethasone ophthalmic insert) 0.4 mg for intracanalicular use
Applicant	Ocular Therapeutix
Dosage Form(s)	Intracanalicular insert
Applicant Proposed Dosing Regimen(s)	Dextenza is an ophthalmic insert that is inserted in the lower lacrimal punctum and into the canaliculus. A single DEXTENZA releases a 0.4 mg dose of dexamethasone for up to 30 days following insertion
Applicant Proposed Indication(s)/Population(s)	• The treatment of ocular inflammation and pain following ophthalmic surgery • The treatment of ocular itching associated with allergic conjunctivitis
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Patients with ocular pain after ophthalmic surgery or patients with itching due to allergic conjunctivitis

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Glossary

AC	advisory committee
AE	adverse event
BPCA	Best Pharmaceuticals for Children Act
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	clinical study report
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NME	new molecular entity
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PREA	Pediatric Research Equity Act
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment emergent adverse event

Executive Summary

1.1. Product Introduction

DEXTENZA (dexamethasone ophthalmic insert) 0.4 mg for intracanalicular use was first approved for the treatment of ocular pain following ophthalmic surgery in November 2018. Supplemental Application S-001, approved in June 2019, provides for the addition of treatment of ocular inflammation following ophthalmic surgery. Supplemental Application S-007, approved in June 2021, provides for the addition of treatment of ocular itching associated with allergic conjunctivitis.

DEXTENZA is a single administration, sterile dosage form. The drug product consists of two main components: dexamethasone and a (b) (4) polyethylene glycol (PEG) (b) (4) hydrogel conjugated with fluorescein. DEXTENZA is fabricated under controlled environmental conditions. (b) (4)

Dextenza, (dexamethasone ophthalmic insert), 0.4 mg, drug product consists of a (b) (4) fluorescent polyethylene glycol (PEG)-based hydrogel designed to be inserted in the vertical canaliculus to provide dexamethasone to the surface of the eye up to 30 days following insertion.

This Prior Approval Supplement (PAS) includes safety and efficacy data from CLN-Protocol-0050 *"A Randomized, Parallel-Arm, Active Control, Multicenter Study Assessing the Safety and Efficacy of DEXTENZA® for the Treatment of Ocular Pain and Inflammation Following Surgery for Pediatric Cataract"*. This pediatric safety study was conducted to satisfy the requirements governed by the Pediatric Research Equity Act (PREA) and the post-marketing requirement (PMR 3548-1) in the November 3, 2018, Approval letter for the NDA.

> 3548-1 Safety 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

The primary objective of the study was to assess the safety of DEXTENZA compared to an active control, prednisolone acetate suspension 1% (PAS), for the treatment of postoperative pain and inflammation following ocular surgery for pediatric cataract; the 0 to 5 years of age group was

evaluated.

1.2. Conclusions on the Substantial Evidence of Effectiveness

NDA 208742/S-013 DEXTENZA (dexamethasone ophthalmic insert) 0.4 mg for intracanalicular use for the updated pediatric labeling is recommended for approval with the revised labeling identified in this review. One clinical study (Study CLN-Protocol-0050) contained in this submission demonstrated the safe use of DEXTENZA in the pediatric population for the treatment of pain and inflammation following ocular surgery. Extrapolation of safety in the pediatric population for the treatment of itching associated with allergic conjunctivitis was also made.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The data contained in this submission, along with the data which supported the November 2018 original approval of NDA 208742 and June 2019 approval of S-001 and the October 2021 approval of S-007, establishes the safety and efficacy of DEXTENZA (dexamethasone ophthalmic insert) 0.4 mg in the pediatric population for the treatment of pain and inflammation after ocular surgery and treatment of itching associated with allergic conjunctivitis.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Intraocular inflammation and pain, including post-operative inflammation and pain, are consequences of surgical procedures which break the natural skin, conjunctival, and corneal barriers. Allergic responses can be triggered by a variety of stimuli, including environmental insults. Ocular symptoms include itching and redness; together these symptoms constitute the condition of allergic conjunctivitis.	Post-operative pain can be controlled with the use of nonsteroidal or steroid products in the postoperative setting. Itching associated with allergic conjunctivitis can be treated with a variety of medications including steroids, antihistamines, and mast cell inhibitors.
Current Treatment Options	• Currently available treatments for post-operative pain following ophthalmic surgery include the use of steroidal or nonsteroidal anti-inflammatory drug products. • Currently available treatments for itching associated with allergic conjunctivitis include multiple different topical ophthalmic products.	This product 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. This product would provide an alternative treatment for itching, administered as a single dose, into the inferior punctum, where it is

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		retained in the vertical canaliculus until dissolution.
Benefit	• Treatment of post-operative ocular inflammation and pain • Reduction of itching associated with allergic conjunctivitis, as expressed by the patient.	Study CLN-Protocol-0050 supports the safe use of DEXTENZA in the pediatric population for the treat of pain and inflammation following ocular surgery. The safe use in treatment of itching associated with allergic conjunctivitis can be extrapolated.
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 trial 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.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		Section 6.1 Study endpoints
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Intraocular inflammation and pain, including post-operative inflammation and pain, are consequences of surgical procedures which break the natural skin, conjunctival, and corneal barriers.

Allergic responses can be triggered by a variety of stimuli, including environmental insults. Ocular symptoms include itching and redness; together these symptoms constitute the condition of allergic conjunctivitis. Since allergic conjunctivitis due to an allergen can only occur after multiple exposures to the allergen, this disease does not occur in patients <2 years old.

2.2. Analysis of Current Treatment Options

Treatment of Pain and Inflammation After Ocular Surgery

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 ocular surgery.
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.
200-738	Loteprednol ophthalmic ointment 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.
20-474	Vexol (rimexelone ophthalmic suspension 1%)	VEXOL is a topical corticosteroid that is indicated for the treatment of post-operative inflammation following ocular surgery.
19-700	Acular (ketorolac)	ACULAR is a NSAID indicated for treatment of inflammation following cataract surgery.

NDA	Drug	Indication
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
218-158	clobetasol propionate ophthalmic suspension. 0.05%	Treatment of post-operative pain and inflammation following ocular surgery

Treatment of Allergic Conjunctivitis

NDA	Brand Name	Indication
21-009	Alocril (nedocromil)	Treatment of itching associated with allergic conjunctivitis
19-700	Acular (ketorolac)	Treatment of itching associated with allergic conjunctivitis
21-127	Optivar (azelastine)	Treatment of itching associated with allergic conjunctivitis
21-079	Alamast (pemirolast)	Treatment of itching associated with allergic conjunctivitis
21-545	Pataday (olopatanol)	Treatment of itching associated with allergic conjunctivitis
22-134	Lastacaft (alcaftadine)	Treatment of itching associated with allergic conjunctivitis
19-700	Acular (ketorolac)	Treatment of itching associated with allergic conjunctivitis
20-803	Alrex (lotemax)	Treatment of signs and symptoms of allergic conjunctivitis
21-565	Elestat (epinastine)	Treatment of itching associated with allergic conjunctivitis

NDA	Brand Name	Indication
22-288	Bepreve (bepotastine)	Treatment of itching associated with allergic conjunctivitis

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Background

- NDA 208-742 submitted on 9/24/15 (SDN-1) for treatment of pain and inflammation after ocular surgery (Studies OTX-12-002, OTX-13-002 and OTX-14-003)
- Original Medical Officer review in DAARTS dated 7/7/16
- CR letter issued for CMC issues on 7/21/16
- Resubmission submitted on 1/19/17 (SDN-33)
- CR letter issued for CMC issues on 7/10/17
- Resubmission submitted on 6/28/18 (SDN-45)
- Approved on 11/30/18 for treatment of pain after ocular surgery and following PMR in approval letter
    - 3548-1 Safety 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
- Supplement #1 submitted 1/10/19 (SDN-57) for indication of treatment of inflammation after ocular surgery
- Medical Officer review in DAARTS dated 3/19/19 (Study OTX-15-003)
- Supplement #1 approved on 6/20/19 for now the indication of treatment of pain and inflammation after ocular surgery
- Supplement #7 submitted on 12/18/20 (SDN-141) for the treatment of allergic conjunctivitis
- Medical Officer review in DAARTS dated 10/4/21 (OTX-14-001, OTX-14-007, OTX-15-002, and CLN-0052)
- Supplement #7 approved on 10/7/21

This current submission contains the pediatric safety study which was conducted to satisfy the requirements governed by PREA and was a post-marketing requirement (PMR 3548-1) per DEXTENZA NDA (208-742) approval. The primary objective was to assess the safety of

DEXTENZA compared to an active control, prednisolone acetate suspension 1%, for the treatment of postoperative pain and inflammation following ocular surgery for pediatric cataract; the 0 to 5 years of age group was evaluated.

The Sponsor submitted this as a Prior Approval Supplement (PAS); however, the Agency determined this would be reviewed as efficacy supplement. This supplement includes safety and efficacy data from CLN-Protocol-0050 "A Randomized, Parallel-Arm, Active Control, Multicenter Study Assessing the Safety and Efficacy of DEXTENZA® for the Treatment of Ocular Pain and Inflammation Following Surgery for Pediatric Cataract". The proposed prescribing information (PI) changes include updates to Section 8 and Section 14 to include the pediatric study information and brief summary of results.

3.2. Summary of Presubmission/Submission Regulatory Activity

Refer to Section 3.1.

3.3. Foreign Regulatory Actions and Marketing History

Dextenza has not yet been approved or marketed in any foreign country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Clinical site integrity was adequately addressed during site inspections during the initial review cycle. OSI was not consulted for this supplement.

4.2. Product Quality

This efficacy supplement does not contain any new CMC information or changes.

4.3. Clinical Microbiology

N/A. This is not an anti-infective.

4.4. Nonclinical Pharmacology/Toxicology

This efficacy supplement does not contain any new Pharm/tox information.

4.5. Clinical Pharmacology

This efficacy supplement does not contain any new Clinical Pharmacology information or changes.

4.6. Devices and Companion Diagnostic Issues

Based on the Genus decision, the Agency determined that the language in 21 CFR 200.50(c) indicating that eye cups, eye droppers, and ophthalmic dispensers are regulated as drugs when packaged with other drugs is now obsolete, as these articles meet the "device" definition. The Agency is now regulating these products including the one which is the subject of this review as drug-led combination products composed of a drug constituent part that provides the primary mode of action (PMOA) and a device constituent part (dispenser). As the drug constituent part provides the PMOA, CDER has primary jurisdiction over these products.

This supplement did not include any changes to the product presentation. A CDRH consult was not deemed necessary for this supplemental NDA.

4.7. Consumer Study Reviews

Not applicable. No consumer studies were conducted.

5. Sources of Clinical Data and Review Strategy

5.1. Review Strategy

Clinical data for one clinical study (CLN-Protocol-0050) was reviewed to support safety and efficacy.

6. Review of Relevant Individual Trials Used to Support Efficacy

Primary Objective
The primary objective was to assess the safety of Dextenza compared to an active control, prednisolone acetate suspension (PAS), for the treatment of postoperative pain and inflammation following ocular surgery for pediatric cataract; the 0 to 5 years of age group was evaluated.

Number of Subjects
Approximately 60 patients were planned to be enrolled.

Description of Study

This was a randomized, parallel-arm, active control, multicenter study. A total of approximately 60 eyes in approximately 60 subjects aged 0 to 5 years were planned to be treated with either Dextenza or prednisolone acetate suspension (PAS). It was expected that only 1 eye per subject would be treated; however, if a subject required bilateral surgery or subsequently required surgery in the contralateral eye during the study (even if the subject was >5 years of age at the time of the second surgery), the study treatment that was not assigned during randomization was used to treat the contralateral eye after the subject completed the last visit (Visit 7, 42 days post-surgery) for the first study eye. Following treatment of the second eye, the subject again completed the full visit schedule through the last visit (Visit 7, 42 days post-surgery). Study duration was approximately 2 to 3 months from screening to the last visit (Visit 7, 42 Days post-surgery).

There were 7 scheduled study visits. Visit 1 was the Screening Visit and occurred up to a maximum of 30 days prior to surgery/treatment. Visit 1 (Screening Visit) and Visit 2 (Day 1) could have been completed on the same day. Visit 2 (Day 1) was on the day of surgery. At the end of surgery on Visit 2, eligibility for enrollment into the study was assessed. Subjects who met eligibility criteria at both Visit 1 (Screening) and Visit 2 (Surgery/Treatment) were randomized to receive Dextenza or PAS. For the eye randomized to receive Dextenza, the Investigator inserted Dextenza into the punctum of the study eye at the conclusion of the cataract surgery if the eye(s) did not experience any protocol-specific procedural exclusion criteria and punctum was successfully dilated. For the eye randomized to be treated with PAS, 1 drop was administered in the lower fornix at the end of surgery by the Investigator. Following that, subject's legally authorized representative (LAR) was instructed to administer 1 PAS drop in the lower fornix QID for a week, followed by TID for the next week, BID for the next week, and QD for the last week. Treated subjects completed post-surgery study Visits 3 through 7 (1, 8, 14, 28, and 42 days post-surgery, respectively).

Inclusion Criteria

- The subject's LAR provided written informed consent, approved by the appropriate IRB, and was able to comply with study requirements and visit schedule.
- Was 0 to 5 years of age (up to the day before the subject turned 6 years of age). In the event that a subject aged 0 to 5 years enrolled in the study and then underwent a second cataract surgery in the contralateral eye during the study period, the subject remained eligible for participation for both eyes, regardless if the second surgery occurred when the subject was >5 years of age).
- Had a cataract and was expected to undergo primary cataract surgery with or without implantation of a posterior chamber intraocular lens.

Exclusion criteria

- Any intraocular inflammation in the study eye present during the screening slit lamp examination.

- Compromised immune system or an autoimmune disease that in the opinion of the Investigator could have affected the quality of the ocular surface.
- Active or chronic/recurrent ocular or systemic disease that was uncontrolled and would likely affect wound healing.
- Currently had suspected or known malignancy or was currently receiving antineoplastic therapy.
- Required use of non-diagnostic topical ophthalmic solutions (other than prophylactic antibiotics or artificial tears for the management of dry eye) in the study eye for the duration of the study (the use of artificial tears was limited to a maximum of 4 times per day).
- Use of the following anti-inflammatory, immunomodulating agents (e.g., cyclosporine), or tumor necrosis factor blockers (e.g., Humira, Enbrel, Simponi, etc.) systemically, or in the study eye, for the duration of the study (excluding inhalants). Washout periods for medications prior to surgery were as follows:
    - Corticosteroid depot in the study eye – 2 months
    - Periocular injection of any corticosteroid solution – 4 weeks
    - Systemic corticosteroids – 2 weeks
    - Topical ocular corticosteroid or cyclosporine – 7 days
    - Topical ocular NSAID – 7 days
- Had ocular hypertension (defined as IOP of >21 mmHg), or glaucoma or was on medications to treat ocular hypertension or glaucoma or had a history of IOP spikes in either eye including steroid-related IOP increases.
- Had a congenital or ocular anomaly including ectropion, entropion, trichiasis, supernumerary puncta and anomalies of the punctum in the study eye.
- Presence of nasolacrimal duct obstruction in the study eye based on assessment by the Investigator
- Active epiphora in the study eye.
- Active or history of chronic or recurrent inflammatory eye disease (e.g., iritis, scleritis, uveitis, iridocyclitis, rubeosis iritis) in the study eye.
- Evidence of acute external ocular infections (bacterial, viral and/or fungal such as vaccinia, varicella, and other viral diseases of the cornea and conjunctiva), tuberculosis of the eye; corneal dystrophies; active corneal ulcers, intraocular infections, dysthyroid ophthalmopathy, active chalazion, or uncontrolled blepharitis in the study eye.
- Current or history of herpes simplex keratitis.
- Retinopathy of prematurity, proliferative or exudative vitreo-retinopathy of any kind, compromised macular function, significant macular disease, clinically significant macular edema, or history of cystoid macular edema in the study eye.
- Corneal or retinal surgery or procedure (laser or incisional) within the past 6 months, or planned to have laser or incisional surgery (except for the non-laser study cataract procedure) or procedure during the study period in the study eye.

- Previous ocular trauma with visible scarring or any deformities due to the trauma in the study eye.
- Known allergy or sensitivity to the IP or its components.
- Previous enrollment in this clinical study or planned to participate in another clinical trial within 30 days prior to entry in this study or during the follow-up period that could confound the treatment or outcomes of this investigation.
- The Investigator determined that the subject should not be included for reasons not already specified (ie. systemic, or other ocular disease/abnormality) if the health of the subject or the validity of the study outcomes may have been compromised by the subject's enrollment.

Procedural Exclusion Criteria

- Required retinal procedure during cataract surgery (planned primary posterior capsulotomy or planned vitrectomy were allowed).
- Had another intra-operative condition that in the opinion of the Investigator precluded further participation in the study (e.g., subjects with intra-operative complications such as posterior capsule rupture, unplanned anterior vitrectomy, torn or ruptured zonules, or torn incisions were excluded).
- Unsuccessful punctal dilation of the study eye (if needed) prior to insertion of Dextenza.

Formulation, Dosage, and Storage of Medication
Subjects were randomized to receive either Dextenza or PAS.

Dextenza
Dextenza consists of 2 main components: dexamethasone (0.4 mg) and a PEG-based hydrogel conjugated with fluorescein. Dexamethasone is an anti-inflammatory 9-fluoro-glucocorticoid (also termed a glucocorticoid agonist). Dextenza is designed to provide a sustained release of therapeutic levels of dexamethasone to the ocular surface for up to 30 days.

The fluorescent PEG hydrogel acts as the delivery platform and is formed as an intracanalicular insert to secure Dextenza in the inferior vertical canaliculus. The intracanalicular insert is designed to stay in the vertical canaliculus for up to 30 days in order to ensure retention through drug delivery. Over this time and through hydrolysis, Dextenza softens, liquefies, and is cleared through the nasolacrimal duct.

The fluorescein in the hydrogel drug delivery vehicle illuminates when excited with a blue light source to provide confirmation of product presence. Dextenza is provided to the Investigator as a (b) (4) intracanalicular insert. The product is packaged in a (b) (6) sealed foil pouch to maintain stability and sterility over time. It is placed into the punctum by the Investigator following punctal dilation using forceps.

Dextenza is supplied as a single use, sterile, ophthalmic insert that is packaged in a foam carrier with a foil laminate pouch. See the package insert for more details.

Prednisolone Acetate Ophthalmic Suspension

PRED FORTE (prednisolone acetate ophthalmic suspension, 1%) was used as the active control. One drop of PAS was administered at the end of surgery, followed by 1 drop QID for a week, TID for the next week, BID for the next week, and once a day for the last week. PAS is FDA-approved (NDA #017011 on 05 May 1973) in the US as a topical anti-inflammatory agent for ophthalmic use.

PAS is supplied in opaque white [redacted] (b) (4) plastic bottles with droppers with white [redacted] (b) (4) caps.

Study Drug Administration

Dextenza contains 0.4 mg of dexamethasone per insert and is designed to provide a sustained release of dexamethasone for up to 30 days. The formulation of Dextenza cannot be adjusted for use in the pediatric population; therefore, the currently approved dose of 0.4 mg of dexamethasone was utilized for this study. Dextenza is single-use, sterile ophthalmic insert, designed to release a 0.4 mg dose of dexamethasone for up to 30 days following insertion.

One drop of PAS was administered at the end of surgery, followed by one drop QID for a week, TID for the next week, BID for the next week, and once daily for the last week.

Study Flow Chart

Study Parameter	Screening/ Baseline (≤ 30 days prior to Surgery)	Surgery and Treatment (Day 1)	1 Day Post-Surgery	8 Days Post-Surgery ± 1 day	14 Days Post-Surgery ± 1 day	28 Days Post-Surgery ± 2 days	42 Days Post-Surgery ± 2 days
Visit	1	2	3	4	5	6	7
Obtain Informed Consent	X						
Demographic Information	X						
Medical/Ophthalmic History	X						
Record Adverse Events		X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
FLACC Pain Assessment	X[1]	X[2]	X[1]	X[1]	X[1]	X[1]	X[1]
Visual Acuity Examination	X[1]		X[1]	X[1]	X[1]	X[1]	X[1]
Slit Lamp Biomicroscopy	X		X	X	X	X	X
Dextenza Presence by Visual Technique			X	X	X	X	X
Punctum Examination	X		X	X	X	X	X
IOP Measurement	X		X	X	X	X	X
Dilated Fundus Examination	X					X	
Eligibility Review	X	X					
Randomization via EDC (prior to surgery)		X					
Punctum Size Assessment (if applicable)		X					
Dextenza Insertion or Administration of Control Drops		X					
Dispense prednisolone acetate suspension drops			X				
Dispense prednisolone acetate suspension dosing diary			X	X	X		
Review Diary				X	X	X	
LAR Survey				X[3]		X[3]	

Abbreviations: EDC = electronic data capture system; FLACC = Face, Legs, Activity, Cry, Consolability; IOP = intraocular pressure; LAR =legally authorized representative.
1. FLACC and visual acuity had to be performed prior to all assessments at all visits.
2. FLACC had to be performed prior to surgery.
3. The LAR Survey was only completed if the subject was randomized to prednisolone.

Safety Plan/Adverse Events

All safety analyses were performed on the Safety population. The safety of Dextenza was primarily assessed by the incidence of adverse events (AEs). An AE was considered a treatment-emergent AE (TEAE) if it occurred or worsened on or after the Dextenza insertion date. An overall summary of AEs is presented including the number of events and the number of subjects with events (along with percentages) by treatment group for AEs in several categories based on location, seriousness, relationship to treatment, and severity. All AEs were coded to SOC and PT using MedDRA. The number of AEs and the number of subjects with any AEs (along with percentages) were tabulated by SOC and PT within each SOC by treatment group and over treatment groups. To count the number of subjects with any AEs, a subject who experienced multiple AEs within the same SOC was counted only once for that SOC (whether or not the AEs were coded to the same PT). A subject who experienced multiple AEs coded to the same PT within the same SOC was counted only once for that particular PT. In the summary, SOC terms were listed in ascending alphabetical order; PTs were listed in order of descending frequency for all subjects within each SOC.

Separate summaries were provided for the following categories of AEs:

- Ocular AEs in the study eye
- Ocular AEs in the non-study eye
- Non-ocular AEs
- Treatment-related ocular AEs in the study eye
- Treatment-related non-ocular AEs
- Serious AEs

FLACC score at each visit and change from baseline was summarized by treatment group. Visual acuity data for the study eye were summarized for each treatment group by visit. IOP was summarized by treatment group separately for the study eye and for the non-study eye. The IOP data were summarized by visit using both continuous and discrete summaries.
Slit lamp biomicroscopy results were summarized for each treatment group for the study eye and non-study eye by visit using discrete summary statistics. Shifts from baseline including normal to abnormal, not clinically significant; abnormal, not clinically significant to abnormal clinically significant; and normal to abnormal, clinically significant were also presented using counts and percentages. Punctum examination results were summarized similarly for the study eye only. Fundus examination results at Screening and Day 28 were summarized similarly, for the study eye and non-study eye separately.

Primary Endpoints

- Absence of pain (i.e., FLACC score of '0') at 8 days post-surgery
- Absence of cells (i.e., score of '0') in anterior chamber of the study eye at 14 days post-surgery

- Absence of pain (i.e., FLACC score of '0') at 1, 14, 28, and 42 days post-surgery
- Anterior chamber cells score in the study eye at 1, 8, 14, and 28 days post-surgery plus 42 days post-surgery
- Need for rescue medication(s) and frequency of daily use

Exploratory Endpoints

- Presence of Dextenza after insertion and at all visits through the Day 28 visit
- Ease of Dextenza use (insertion) as assessed by the Investigator at Visit 2 (Surgery/Treatment)
- Ease of Dextenza visualization at all visits through the Day 28 visit as assessed by the Investigator

Missing Data

The number and percentage of treated eyes who had missing data of efficacy endpoints (FLACC pain score, anterior chamber cells score, and anterior chamber flare score) were categorized by age of subjects as follows: <2 years and ≥2 years and summarized at each assessment visit by treatment group and overall.

Data observed after subjects received rescue medications were included in the efficacy summary. Presence of test article and product use and visualization data were summarized using observed data only. Safety data were analyzed using all observed data.

Interim Analysis

None.

Statistical Analysis Plan

This study was not designed to show statistical significance; therefore, there was no formal statistical testing. All summaries were descriptive. All descriptive statistical analyses were performed using SAS statistical software unless otherwise noted. Summaries for continuous and ordinal variables included the number of observations (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum. Minima and maxima were reported with the same precision as the raw values; means and medians were presented to 1 additional decimal place than reported in the raw values. SDs were presented to 2 additional decimal places than reported in the raw values. Summaries for discrete variables included counts and percentages. All percentages were rounded to 1 decimal place. Differences between treatment groups were calculated as Dextenza minus PAS drops and change from baseline was calculated as follow-up visit minus baseline. The 95% confidence interval of the difference was calculated. The baseline visit was defined as the last non-missing measure prior to initiation of investigational treatment. All safety and efficacy summaries were presented by treatment group and overall, where appropriate, for each study visit. Listings were sorted by treatment group, subject number, study visit, and parameter, as applicable. No multiplicity adjustments were made

since there were no formal hypothesis tests.

6.1.1. Study Results

Compliance with Good Clinical Practices

This submission was of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

Financial Disclosure

See Section 13.2 for the financial disclosure template.

Protocol Violations/Deviations

Study CLN-Protocol-0050: Protocol Deviations

	Dextenza N=37	PAS N=32
At Least One Protocol Deviation	29	29
At Least One Important Protocol Deviation	5	4
Investigational Product	1	2
Missed Procedure	1	1
ICF	1	0
Inclusion/Exclusion Criteria	0	1
Other	2	0
At Least One Not Important Protocol Deviation	29	29
Missed Procedure	18	17
Study Visit Schedule	8	12
Investigational Product	0	19
ICF	7	8
Concomitant Medication	1	0
Order of Assessments	1	0
Other	22	18

Table of Demographic Characteristics

Study CLN-Protocol-0050: Demographics

	Dextenza N=37	PAS N=32
Age		
Mean (sd)	1.2 (1.4)	1.4 (1.6)
Min, max	0, 4	0, 4
Gender		
Male	25	18
Female	12	14
Ethnicity		
Hispanic or Latino	4	4
Not Hispanic or Latino	33	28
Race		
American Indian	0	0
Asian	1	0
African American	1	2
Native Hawaiian	0	0
White	33	27
Other	2	1
Multiple	0	1
Unknown	0	1
Iris Color		
Blue	23	16
Brown	11	12
Green	1	2
Gray	1	0
Hazel	1	2

Study CLN-Protocol-0050: Subject Disposition

	Dextenza	PAS
Number of randomized subjects	34	33
Treated Eyes-Total	37	32
Treated Eyes-Initial Treatment	34	31
Treated as Randomized	33	31
Treated not as Randomized	1	0
Treated Eyes-Second eye Treatment	3	1
Safety Analysis Population	37	32
Study completed	37	32
Discontinued	0	0

Treatment Compliance, Concomitant Medications, and Rescue Medication Use
The need for rescue medication in study eyes that received Dextenza was 6/37 (16.2%) receiving rescue medication 28 days post-surgery, which was comparable to the PAS control group 4/32 (12.5%).

Efficacy Results – Primary Endpoint
This study was not designed to show statistical significance; therefore, there was no formal statistical testing. All results are descriptive in nature.

Primary Endpoints

- Absence of pain (i.e., FLACC score of '0') at 8 days post-surgery
- Absence of cells (i.e., score of '0') in anterior chamber of the study eye at 14 days post-surgery
- Absence of pain (i.e., FLACC score of '0') at 1, 14, 28, and 42 days post-surgery
- Anterior chamber cells score in the study eye at 1, 8, 14, and 28 days post-surgery plus 42 days post-surgery
- Need for rescue medication(s) and frequency of daily use

Study CLN-Protocol-0050: Summary of Ocular Pain FLACC Scores and Mean Change From Baseline (Safety Population)

	Dextenza N=37	PAS N=32
Baseline		
FLACC Score 0	36	30
Mean (sd)	0.2 (1.3)	0.4 (1.9)
Visit 3 (POD#1)		
FLACC Score 0	32 (86.5)	26 (81.3)
Mean (sd)	0.4 (1.1)	0.7 (1.5)
Change From Baseline to Visit 3	0.2 (1.8)	0.3 (2.3)
Visit 4 (POD#8)		
FLACC Score 0	35	27
Mean (sd)	0.1 (0.3)	0.2 (0.8)
Change From Baseline to Visit 8	-0.2 (1.4)	-0.3 (2.2)
Visit 5 (POD#14)		
FLACC Score 0	35	31
Mean (sd)	0.1 (0.4)	0.2 (0.9)
Change From Baseline to Visit 5	-0.1 (1.4)	-0.3 (2.1)
Visit 6 (POD#28)		
FLACC Score 0	35	29
Mean (sd)	0.2 (0.9)	0.2 (0.8)
Change From Baseline to Visit 6	0.0 (1.6)	-0.3 (2.1)
Visit #7 (POD#42)		
FLACC Score 0	36 (97.3)	32 (100)
Mean (sd)	0.1 (0.7)	0.0 (0.0)
Change From Baseline to Visit 7	-0.1 (1.5)	-0.4 (1.9)

Study CLN-Protocol-0050: Summary of AC Cell Scores (Safety Population)

	Dextenza N=37	PAS N=32
Visit 1 (Baseline)		
N	33	31
Grade 0	33 (100%)	31 (100%)
Visit 3 (POD#1)		
N	28	26
Grade 0	18 (64.3%)	13 (50.0%)
Visit 4 (POD#8)		
N	29	26
Grade 0	18 (62.1%)	17 (65.4%)
Visit 5 (POD#14)		
N	31	26
Grade 0	25 (80.6%)	19 (73.1%)
Visit 6 (POD#28)		
N	30	27
Grade 0	30 (100%)	25 (92.6%)
Visit #7 (POD#42)		
N	32	27
Grade 0	30 (93.8%)	26 (96.3%)

Study CLN-Protocol-0050: Rescue Medication in the Study Eye By Duration (Safety Population)

	Dextenza N=37	PAS N=32
Visit 1 (Baseline)		
N	37	32
Used Rescue Medication	0	0
Did Not Use Rescue Medication	37	32
Visit 3 (POD#1)		
N	37	32
Used Rescue Medication	3	3
Did Not Use Rescue Medication	34	29
Visit 4 (POD#8)		
N	37	32
Used Rescue Medication	5	4
Did Not Use Rescue Medication	32	28
Visit 5 (POD#14)		
N	37	32
Used Rescue Medication	5	4
Did Not Use Rescue Medication	32	28
Visit 6 (POD#28)		
N	37	32
Used Rescue Medication	6	4
Did Not Use Rescue Medication	31	28

Reviewer's Comment:

Although the study was not powered to achieve statistical significance, treatment with Dextenza in the study eyes showed control of ocular inflammation and pain at 8, 14, 28, and 42 days post-surgery. Additionally, most study eyes treated with Dextenza had an absence of anterior chamber cells at 14 days post-surgery (25/31 [80.6%]), which was similar to the proportion in the PAS control group (19/26 [73.1%]). Further, the need for rescue medication in

study eyes that received Dextenza was relatively low, with only 6/37 (16.2%) receiving rescue medication 28 days post-surgery, which was comparable to the PAS control group (4/32 [12.5%]).

There is a high rate of missing data (in particular regarding the anterior chamber cell count which was conducted via slit lamp examination and was difficult to obtain due to the nature of the young pediatric population). Similar proportions of anterior chamber cell data were missing 14 days post-surgery in the treatment groups, with 31/37 study eyes in the Dextenza group and 26/32 study eyes in the PAS control group. The median age of subjects was 1 year old in this study, with 43/65 treated subjects aged 1 year or younger, and therefore it was difficult to perform these examinations at each scheduled visit on this age group.

Data Quality and Integrity
OSI was not consulted for this supplement.

Efficacy Results – Secondary and other relevant endpoints
Only descriptive statistics.

Dose/Dose Response
Only one dose studied. One insert lasts 30 days.

7. Integrated Review of Effectiveness

Previous Efficacy Trials
Medical Officer review in DAARTS dated 7/7/16 (Studies OTX-12-002, OTX-13-002 and OTX-14-003)-support treatment of pain after ocular surgery.

Medical Officer review in DAARTS dated 3/19/19-support treatment of inflammation after ocular surgery (Study OTX-15-003).

Medical Officer review in DAARTS dated 10/4/21 (OTX-14-001, OTX-14-007, OTX-15-002, and CLN-0052)-support treatment of ocular itching due to allergic conjunctivitis.

This supplement supports safety of Dextenza in pediatrics for treatment of ocular pain and inflammation following cataract surgery in all pediatric age patients and for treatment of itching associated with allergic conjunctivitis for children >2 years old.

8. Review of Safety

8.1. Safety Review Approach

Study CLN-Protocol-0050 was reviewed to assess the safety of Dextenza in the pediatric population.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Study CLN-Protocol-0050: Extent of Exposure (Safety Population)

	Dextenza N=37	PAS N=32
Mean (sd)	34.1 (11.3)	28.5 (4.8)
Min, Max	5.5, 45.0	7.0, 42.0

Reviewer's Comment:
Study eyes treated with Dextenza and PAS had a mean (SD) exposure of 34.2 (11.3) days and 28.5 (4.8) days, respectively.

8.2.2. Relevant characteristics of the safety population:

The safety population is representative of the population that the drug product is intended to treat.

8.2.3. Adequacy of the safety database:

The safety database is adequate with respect to size, duration of exposure, duration of treatment, and patient demographics.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

This submission was of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

8.3.2. Categorization of Adverse Events

MedDRA version 25.0 was used to classify adverse events.

8.3.3. Routine Clinical Tests

Not performed.

8.4. Safety Results

8.4.1. Deaths

No deaths occurred.

8.4.2. Serious Adverse Events

There was 1 serious ocular TEAE of iritis, which was reported in the PAS control group. The event was severe and considered related to the study procedure (cataract surgery). The dose of PAS was subsequently increased, and the event resolved 34 days later.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

There were no discontinuations.

8.4.4. Significant Adverse Events

See Section 8.4.2.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Study CLN-Protocol-0050: Ocular Treatment Emergent AE in the Study Eye (Safety Population)

	Dextenza N=37	PAS N=32
Subjects With at Least 1 TEAE	18	10
Eye disorders	11	8
Anterior capsule contraction	2	1
Anterior chamber inflammation	1	1
Conjunctival hyperemia	0	2
Iritis	1	1
Ocular hyperemia	1	1
AC cell	1	0
AC flare	1	0
Choroidal effusion	1	0
Corectopia	1	0
Corneal edema	0	1
Eye inflammation	1	0
Eye irritation	0	1

	Dextenza N=37	PAS N=32
Eye pain	0	1
Lenticular pigmentation	0	1
Posterior capsular opacification	1	0
Retinal detachment	0	1
Strabismus	1	0
Swelling of eyelid	0	1
Uveitis	1	0
Vitreous hemorrhage	0	1
Investigations		
IOP increased	7	3
Injury		
Corneal abrasion	1	0
Iris tear	1	0
Congenital disorders		
Persistent pupillary membrane	0	1
Infections		
Eye abscess	0	1
Nervous system disorders		
Nystagmus	0	1

Study CLN-Protocol-0050: Non-Ocular Treatment Emergent AE in the Study Eye (Safety Population)

	Dextenza N=37	PAS N=32
Subjects With at Least 1 TEAE	11	6
General disorders		
Pyrexia	4	3
Infections		
COVID-19	1	0
Candida infection	1	0
Croup infections	0	1
Ear infection	1	0
Upper respiratory tract infection	0	1
UTI	1	0

	Dextenza N=37	PAS N=32
Respiratory disorders		
Cough	0	1
Nasal congestion	1	0
Oropharyngeal pain	0	01
Seasonal allergy	1	0
Upper airway cough syndrome	0	1
GI disorders		
Vomiting	1	1
Diarrhea	0	1
Skin disorders		
Rash	0	1

8.4.6. Laboratory Findings

Not performed.

8.4.7. Vital Signs

Not performed.

8.4.8. Electrocardiograms (ECGs)

Not performed.

8.4.9. QT

N/A.

8.4.10. Immunogenicity

N/A.

8.5. Analysis of Submission-Specific Safety Issues

N/A.

8.6. Safety Analyses by Demographic Subgroups

N/A.

8.7. Specific Safety Studies/Clinical Trials

N/A.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

N/A.

8.8.2. Human Reproduction and Pregnancy

This drug has not been tested in pregnant women.

8.8.3. Pediatrics and Assessment of Effects on Growth

This pediatric safety study was conducted to satisfy the requirements governed by the Pediatric Research Equity Act (PREA) and the post-marketing requirement (PMR 3548-1) in the November 3, 2018, Approval letter for the NDA.

3548-1 Safety 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

The primary objective of the study was to assess the safety of DEXTENZA compared to an active control, prednisolone acetate suspension 1% (PAS), for the treatment of postoperative pain and inflammation following ocular surgery for pediatric cataract; the 0 to 5 years of age group was evaluated.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

N/A.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

N/A.

8.9.2. Expectations on Safety in the Postmarket Setting

No risk management activities are recommended beyond the routine monitoring and reporting of all adverse events.

8.9.3. Additional Safety Issues From Other Disciplines

N/A.

8.10. Integrated Assessment of Safety

This supplement supports safety of Dextenza in pediatrics for treatment of ocular pain and inflammation following cataract surgery in all pediatric age patients and for treatment of itching associated with allergic conjunctivitis for children >2 years old.

9. Advisory Committee Meeting and Other External Consultations

There were no issues identified in the review of the application that were thought to benefit from an Advisory Committee discussion.

10. Labeling Recommendations

See Appendix 13.3.

11. Risk Evaluation and Mitigation Strategies (REMS)

No risk management activities are recommended beyond the routine monitoring and reporting of all adverse events.

12. Postmarketing Requirements and Commitments

There are other outstanding Post-marketing Requirements or Phase 4 Commitments.

13. Appendices

13.1. References

No additional literature references were identified that were contrary to the literature refences submitted in the application.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study CLN-Protocol-0050

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 0		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 15		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Labeling

The Pediatric Review Committee (PeRC), the Division of Pediatrics and Maternal Health (DPMH), and the Office of Prescription Drug Promotion (OPDP) were consulted to review the applicant-proposed Prescribing Information submitted on June 28, 2024.

Following is the agreed Prescribing Information submitted on March 14, 2025, which incorporates the Division's recommended revisions based on this review.

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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SONAL D WADHWA
04/02/2025 09:09:01 AM

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