CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208742Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA:	208742
Submission Type (Code):	New Dosage Form (3)
Brand Name:	Dextenza (proposed)
Drug Name:	Dexamethasone
Submission Date:	09/24/2015
PDUFA Goal Date:	07/24/2016
Priority:	Standard
Proposed Indication:	Treatment of ocular pain associated with the ophthalmic surgery
Dosage Form, Strength and Dosage Regimen:	0.4 mg dexamethasone intracanalicular (b) (4) as a one-time single dose
Applicant:	Ocular Therapeutix Inc.
Clinical Pharmacology Reviewer:	Abhay Joshi, Ph.D.
Clinical Pharmacology Team Leader:	Philip Colangelo Pharm. D., Ph.D.
OCP Division:	Division of Clinical Pharmacology IV (DCP-IV)
OND Division:	DTOP

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1. EXECUTIVE SUMMARY

This submission is a 505b(2) application for the drug product: Dextenza™, which is a single administration sterile dosage form for intracanalicular placement. Dextenza, which is also known as OTX-DP, is postulated to release dexamethasone locally in a sustained and tapered manner for up to 30 days and the proposed indication is treatment of ocular pain associated with the ophthalmic surgery. OTX-DP consists of (b) (4): the active drug substance: 0.4 mg dexamethasone, and the hydrogel delivery vehicle conjugated with fluorescein.

With this submission, the Sponsor has provided 3 clinical study reports, i.e., one Phase 2 study: OTX-12-002 and two Phase 3 studies: OTX-13-002 and OTX-14-003, which assessed the efficacy and safety of the proposed drug product for the treatment of ocular pain and inflammation following cataract surgery. In addition, the submission package also 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.

1.1. Recommendations

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 Reviewer's proposed label changes in Section 3 will be forwarded to the sponsor.

1.2. Phase 4 Commitments

None.

1.3. Summary of Important Clinical Pharmacology Findings

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®.

2. QUESTION BASED REVIEW

This submission is a new dosage form NDA for the topical ophthalmic delivery of dexamethasone. Given the application is for a locally inserted intracanalicular (b) (4) of an already approved drug substance, only relevant questions are addressed below.

2.1. General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to the clinical pharmacology review?

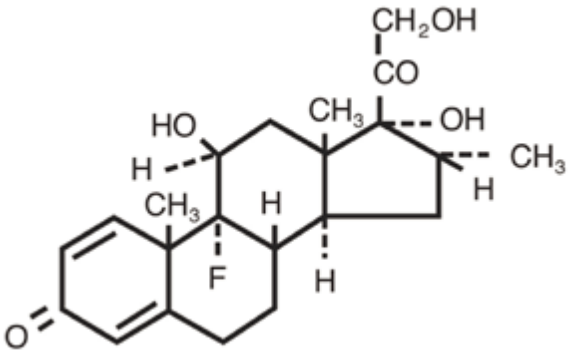
The proposed dosage form is dexamethasone intracanalicular (b) (4) intended to deliver therapeutic levels of dexamethasone continuously for the intended duration of therapy. (b) (4)

Drug substance:

Dexamethasone

Molecular Formula: $C_{22}H_{29}FO_5$

Chemical Structure:



IUPAC chemical name: (8S,9R,10S,11S,13S,14S,16R,17R)-9-fluoro-11,17-dihydroxy-17-(2-hydroxyacetyl)-10,13,16-trimethyl-6,7,8,11,12,14,15,16-octahydrocyclopenta[a]phenanthren-3-one

Molecular Weight: 392.4 (b) (4) g/mol

Solubility: It is practically insoluble in water

Partition coefficient (n-octanol/water): 1.83

Dosage form:

Dextenza (sustained release dexamethasone, 0.4 mg) is a single administration sterile dosage form, which consists of (b) (4) dexamethasone and 4-arm polyethylene glycol (PEG) glutarate-trilysine hydrogel conjugated with fluorescein.

2.1.2. What are the proposed dosage(s) and route(s) of administration?

The proposed drug product is sterile and single use intracanalicular (b) (4) containing 0.4 mg dexamethasone. It is intended to be placed into the inferior vertical canaliculus just below the punctal opening.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Clinical Pharmacology studies:

Study OTX-14-009 was conducted in 16 healthy volunteers, which evaluated the systemic exposures to dexamethasone resulting from a placement/insertion of Dextenza for up to 29 days.

Clinical Studies:

In total, three clinical studies: one Phase 2 study (OTX-12-002) and two Phase 3 studies (OTX-13-002 and OTX-14-003), were conducted to evaluate the efficacy and safety of Dextenza for the treatment of ocular pain and inflammation following cataract surgery. However, with this submission, the Sponsor is only claiming the indication of ocular pain associated with the ophthalmic surgery.

2.2.2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

Response endpoints were absence of anterior chamber cells and absence of ocular pain. Anterior chamber cells were evaluated by slit-lamp biomicroscopy and graded using the SUN Working Group grading scheme. Ocular pain in the study eye was assessed by the subject at screening and at each follow-up visit, utilizing a numeric rating scale graded from 0 to 10.

2.2.3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The systemic exposures to dexamethasone were measured by determining dexamethasone in plasma by utilizing a validated bio-analytical method.

2.2.4. Exposure-Response

For all three Clinical studies i.e., OTX-12-002, OTX-13-002, and OTX-14-003, efficacy was assessed following the same dosage of dexamethasone, i.e., 0.4 mg of dexamethasone delivered by an intracanalicular (b) (4) Therefore, available information is not sufficient to determine the dose-response relationship.

With regard to exposure-response relationship, in Study OTX-14-009, the observed systemic exposures to dexamethasone were minimal. Therefore, due to very low systemic exposures to dexamethasone, the exposure-response relationship cannot be determined.

2.2.5. What are the PK characteristics of the drug and its major metabolite?

Because of the very low systemic exposures to dexamethasone following the administration of 0.4 mg dexamethasone intracanalicular (b) (4) the available pharmacokinetic information is not sufficient to determine complete dexamethasone systemic PK following the administration of Dextenza.

2.3. Analytical Section

Method validation report for Project RBOR2 was submitted separately, which had the information on the bioanalytical method validation for dexamethasone.

2.3.1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The active moiety dexamethasone was detected and quantified in human plasma using a HPLC with MS/MS Detection.

2.3.2. What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The range of the standard curve is 0.05 - 50 ng/mL, which appears to be sensitive enough for the purpose of the clinical study: Study OTX-14-009. The calibration curve was fitted by using a linear least-square regression algorithm with the weight of $1/concentration^2$.

2.3.3. What are the lower and upper limits of quantification (LLOQ/ULOQ)?

Lower and Upper limit of quantification was 0.05 ng/mL and 50 ng/mL, respectively.

2.3.4. What are the accuracy, precision, and selectivity at these limits?

Inter-run assay precision determined by % CV was less than or equal to 6.40%. Inter-run accuracy measured as % different from the theoretical concentration varied between -0.08% and 2.98%.

2.3.5. What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

Freeze-thaw stability was established for 5 cycles at room temperature. Frozen matrix storage stability was determined to be 9 days at -20ºC and -70ºC.

2.3.6. What is the QC sample plan?

The quality control (QC) samples were prepared in human plasma with the concentrations of 0.0500, 0.150, 0.400, 1.50, 6.00, and 38.0 ng/mL.

3. DETAILED LABELING RECOMMENDATIONS

Recommended Clinical Pharmacology changes are provided below with the annotation to the Sponsor's proposed labeling that was submitted with SDN-20 on May 5, 2016:

12.3 Pharmacokinetics

Plasma samples were obtained from 16 healthy volunteers prior to insertion of DEXTENZA and on Day 1 (at 1, 2, 4, 8, 16 hours), 2 (24 hours), 4, 8, 15, 22 and 29 following the insertion of DEXTENZA.

Plasma concentrations of dexamethasone were detectable (above 50 pg/mL, the lower limit of quantification of the assay) in 11% of samples (21 of (b) (4) 189), and ranged from 0.05 ng/mL to 0.81 ng/mL. (b) (4)

4. APPENDICES

4.1. Clinical Pharmacology Individual Study Review

4.1.1. OTX-14-009

Title:

A Single Center Study of the Plasma Pharmacokinetics of OTX-DP (DEXTENZA) in Healthy Volunteers: An Adjunctive Evaluation in Support of the Phase 3 Clinical Program for Treatment of Post-Operative Inflammation and Pain

Sample Analysis Dates: March 27, 2015 to March 28, 2015.

PK Analytical site: (b) (4)

Objectives:

To evaluate the plasma pharmacokinetics (PK) of OTX-DP as a sustained release drug (dexamethasone) (b) (4) when placed in the canaliculus of the eyelid

Formulation & Administration:

OTX-DP drug product has (b) (4) the active ingredient, 0.4 mg dexamethasone, and a polyethylene glycol (PEG) based hydrogel conjugated with fluorescein. The fluorescein in the intracanalicular (b) (4) was used to provide confirmation of test article presence, which was done by illuminating it with a blue light source.

OTX-DP was administered once into the canaliculus by the investigator at the insertion visit on study Day 1.

Study Design:

This was an open-label study to evaluate the systemic exposures to dexamethasone from the OTX-DP drug product. In total 16 healthy volunteers were enrolled and 14 subjects completed the study. One subject exited the study at Day 15 due to loss of OTX-DP and, an additional subject exited the study at the Day 15 due to the adverse event of increased intraocular pressure. Demographics and other baseline characteristics of the enrolled subjects are given in Table 1.

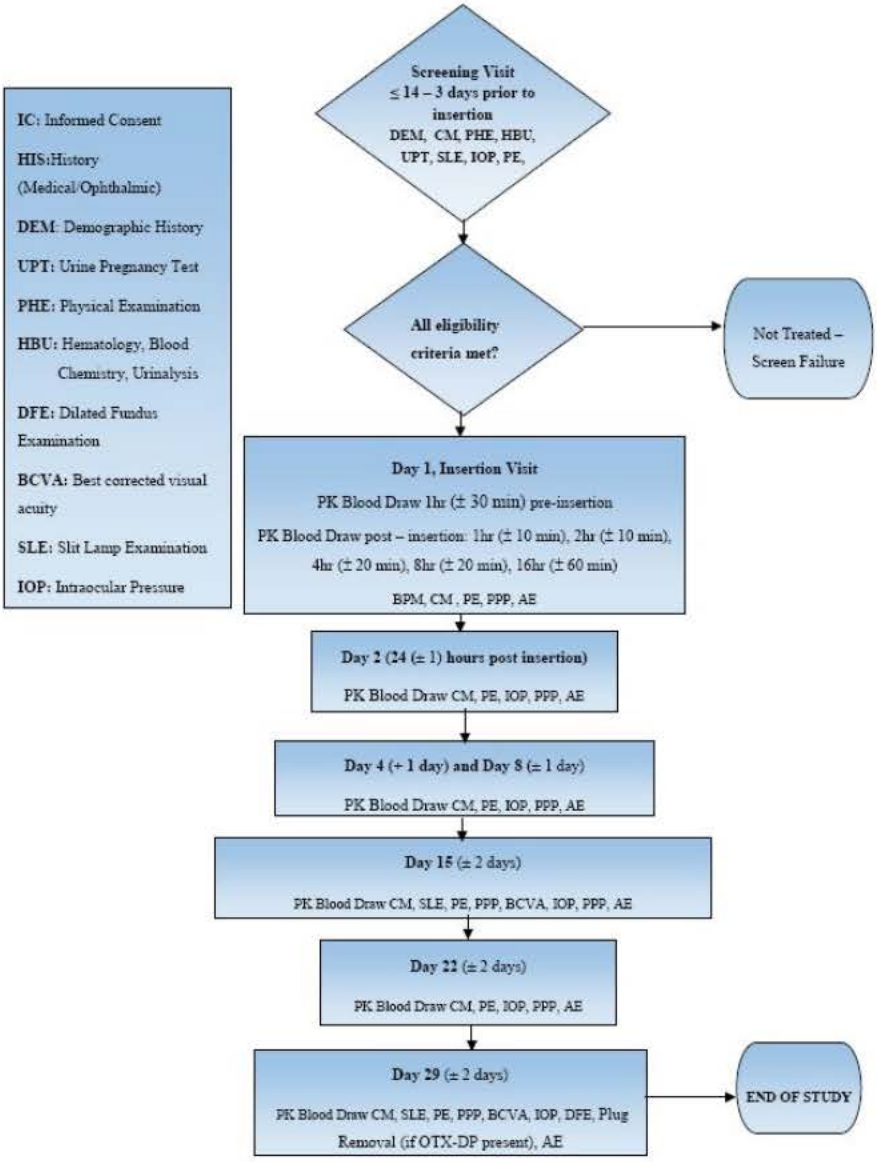
Table 1: Demographic and Other Baseline Characteristics

		N (%)
Age (years)	N	16
	Mean	31.7
	Median	27
	Min, Max	19, 55
Gender	Male	5 (31.3%)
	Female	11 (68.7%)
Height (inches)	N	16
	Mean	65.7
	Median	65
	Min, Max	59, 74
Weight (pounds)	N	16
	Mean	143.4
	Median	145
	Min, Max	108, 170
BMI	Mean	23.35
	Median	23.5
	Min, Max	19.47, 26.26
Race	Caucasian	7 (43.7%)
	American Indian or Alaskan Native	0
	Asian	0
	Black or African American	5 (31.3%)
	Native Hawaiian or Other Pacific Islander	0
	Other [a]	4 (25.0%)
	Multi-racial	0

a Subjects with race "other" self-identified as being Mexican or Mexican/American

OTX-DP was inserted unilaterally into the inferior vertical canaliculus during the Insertion Visit for all subjects. On the day of insertion, blood samples where obtained at 60 ± 30 min pre-insertion and at 60 ± 10 min, 120 ± 10 min, 240 ± 20 min, 480 ± 20 min, 960 ± 60 min. Blood samples were also withdrawn during follow-up visits on Days 2 (24 (± 1) hours post-insertion), 4, 8, 15, 22 and 29. These blood samples were utilized for the pharmacokinetic analysis. If OTX-DP could not be visualized at any visit, the subject was to be exited from the study at the completion of that visit. If OTX-DP was still confirmed to be present at the Day 29 Visit, it was to be removed via saline irrigation or application of manual pressure. Overall study design is illustrated in Figure 1.

Figure 1: Study Design



Assay Method:

Dexamethasone plasma concentrations were determined using a HPLC-MS/MS method. The lower limit of quantification was (LLOQ) 0.05 ng/mL and the validated analytical range was 0.05 ng/ml to 50 ng/mL.

Results:

Pharmacokinetic

Dexamethasone plasma levels were below the LLOQ at all time-points in 5 (31.3%) of the 16 subjects was. Additionally, in the remaining 11 subjects, dexamethasone plasma concentrations were below LLOQ at 1 and 2 hours post-insertion and at the Day 15, 22 and 29 Visits. Individual dexamethasone plasma concentrations are reported in Table 2 and the pharmacokinetic parameters (C_{max}, T_{max}, $AUC_{0\text{-}last}$) are presented in Table 3. For subjects with quantifiable plasma concentrations, C_{max} was less than 1 ng/mL (Range: From 0.05 to 0.81 ng/mL), $AUC_{0\text{-}last}$ ranged from 0.13 to 7.18 h*ng/mL, and T_{max} ranged from 4.0 to 163.0 hours.

Table 2: Individual Dexamethasone Plasma Concentrations (ng/mL)

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

Ease of insertion, Ease of Visualization, Ease of removal, and Retention of OTX-DP

OTX-DP was considered easy to insert in 15 of 16 (93.7%) of eyes, and moderate in the one remaining eye. Visualization of OTX-DP was rated by the Investigator as being easy or moderate in the vast majority of subjects. OTX-DP was visualized in all 16 subjects through the Day 8 Visit (Table 4). At the Day 15 Visit, the drug product could not be visualized in one subject, and it was removed from one subject following the Day 15 Visit due to an AE. OTX-DP could be visualized in 12 (85.7%) of the remaining 14 subjects at the final study visit. Removal of OTX-DP was easy or moderate in all eyes from which it was removed at the Day 29 Visit.

Table 3: Pharmacokinetic Parameter Estimates

Subject	Gender	Age (yr)	BMI	Race	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (h*ng/mL)	T_{max} (h)
S-01 (b) (6)	Female	52	25.02	Black/Afr Amer	0.082	6.373	16.567
S-01	Female	26	24.3	Black/Afr Amer	0.185	4.462	143.583
S-01	Female	23	25.75	Caucsian	0.081	3.906	166.500
S-01	Male	27	21.83	Black/Afr Amer	0.808	4.370	4.017
S-01	Female	25	23.81	Other[a]	0.052	0.495	15.333
S-01	Female	43	23.96	Caucasian	0.000	0.000	Not calculated
S-01	Female	46	23.17	Caucasian	0.078	6.337	8.017
S-01	Female	55	19.47	Black/Afr Amer	0.053	7.179	142.300
S-01	Female	25	24.46	Black/Afr Amer	0.100	3.606	139.867
S-01	Female	39	21.81	Other[a]	0.000	0.000	Not calculated
S-01	Female	19	26.26	Other[a]	0.000	0.000	Not calculated
S-01	Male	20	21.95	Other[a]	0.083	3.305	103.883
S-01	Female	27	22.24	Caucasian	0.000	0.000	Not calculated
S-01	Male	27	22.43	Caucasian	0.064	0.123	7.733
S-01	Male	26	25.85	Caucasian	0.120	3.798	163.900
S-01	Male	27	21.24	Caucasian	0.000	0.000	Not calculated

[a] Subjects with race "other" self-identified as being Mexican or Mexican/American

Table 4: OTX-DP Presence by Visualization

		OTX-DP (N=16)
		n (%)
Day 2	OTX-DP Visualized	16/16 (100.0%)
Day 4	OTX-DP Visualized	16/16 (100.0%)
Day 8	OTX-DP Visualized	16/16 (100.0%)
Day 15	OTX-DP Visualized	15/16 (93.7%)
Day 22	OTX-DP Visualized	14/14* (100.0%)
Day 29	OTX-DP Visualized	12/14 (85.7%)

* OTX-DP was removed from one subject due to an AE following the Day 15 Visit

Safety

The Safety Population consisted of 16 subjects (5 male and 11 female healthy volunteers). In total, 4 subjects (25%) experienced one treatment related adverse event (AE) each, out of which 3 subjects (18.7%) had increased intraocular pressure. In each case, the event was considered of mild severity, and resolved upon removal of OTX-DP. One subject was withdrawn from study due to the ocular event. One additional subject (6.3%) experienced a non-ocular AE (nasopharyngitis) which was not considered to be treatment related, of mild severity, and did not result in subject withdrawal from study.

No serious AEs were reported in the study. Additional safety assessments including slit lamp biomicroscopy parameters, dilated fundus examination parameters, visual acuity, and punctum examination did not raise any safety concerns.

Sponsor's conclusions:

Based on these results, the Sponsor concludes that the systemic exposures to dexamethasone resulting from OTX-DP are negligible, with the majority of samples being below the LLOQ. The safety profile of OTX-DP was determined to be consistent with that reported previously with the ocular administration of dexamethasone.

Reviewer's Assessment:

The Sponsor's conclusion of minimal systemic exposure following the administration is valid. However, given the observed minimal systemic exposures to dexamethasone, the reported PK parameter estimates have limited utility.

4.2. Cover Sheet and OCBP Filing/Review Form

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	208742	**SDN**	1
Applicant	Ocular Therapeutix Inc.	**Submission Date**	09/24/2015
Generic Name	Dexamethasone	**Brand Name**	DEXTENZA (proposed)
Drug Class	Corticosteroid		
Indication	Ocular pain associated with the ophthalmic surgery		
Dosage Regimen	One time insertion		
Dosage Form	0.4 mg sustained release dexamethasone intracanalicular (b) (4)	**Route of Administration**	For insertion and retention into the vertical canaliculus
OCP Division	IV	**OND Division**	DTOP

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Abhay Joshi, Ph.D.	Philip Colangelo Pharm. D., Ph.D.
Pharmacometrics	-	
Genomics	-	

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	9/24/2015	**74-Day Letter Date**	12/7/2015
Review Due Date	6/19/2016	**PDUFA Goal Date**	7/24/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		

☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose	1	OTX-14-009 Adjunctive study to Phase 3 Clinical program (Study overview in the note section below)
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☐ Multiple Dose		
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
☐ QT			
Pharmacometrics			
☐ Population Pharmacokinetics			
☐ Exposure-Efficacy			
☐ Exposure-Safety			

Total Number of Studies	**In Vitro**		**In Vivo**	3
Total Number of Studies to be Reviewed				1

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	Refer to the note section below (Bioequivalence Waiver section)
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	OTX-14-009, Pharmacokinetic study in healthy subjects
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	Refer to the note section below (Bioequivalence Waiver section)
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	OTX-14-009, Method for quantitation of dexamethasone in human plasma
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☐Yes ☐No ☑N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	Sponsor requested Pediatric Study Plan deferral (SDN:2)
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

***Note*:**

OTX-14-009 study overview excerpt

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects (Randomized Subjects)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Human Pharmacokinetic Studies									
Plasma PK	OTX-14-009	5.3.3.1	Plasma pharmacokinetics of DEXTENZA	Prospective, single-center, open-label, uncontrolled	**DEXTENZA**: 0.4 mg dexamethasone; intracanalicular	N=16	Healthy subjects	29 days	Complete Full, final

Bioequivalence Waiver

Given that the Dexamethasone (b) (4) (DEXTENZA) is a novel drug delivery system of dexamethasone, FDA recommended evaluation of systemic PK exposure to dexamethasone following insertion of the to-be-marketed product in Humans. Current review submission (SDN: 1) includes the study report OTX-14-009 (Plasma pharmacokinetics of DEXTENZA in 16 healthy subjects) addressing the aforementioned recommendation. The sponsor also submitted a "Waiver of Evidence of *in vivo* Bioavailability or Bioeqivalence" (SDN: 2) on October 16th, 2015 citing "self-evident" criteria (21 CFR 320.22); and from Clinical Pharmacology perspective, this request is acceptable.

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/s/

ABHAY JOSHI
11/09/2015

PHILIP M COLANGELO
11/09/2015

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/s/

ABHAY JOSHI
06/24/2016

PHILIP M COLANGELO
06/24/2016