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APPLICATION NUMBER:

208912Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	208912
Supporting document/s:	SDN001
Applicant's letter date:	4/12/2017
CDER stamp date:	4/12/2017
Product:	Dexycu® (Dexamethasone Suspension for Intraocular Injection, 9%)
Indication:	Treatment of post-operative inflammation (b) (4)
Applicant:	Icon Bioscience Inc. (Sunnyvale, CA)
Review Division:	Division of Transplant and Ophthalmology Products
Reviewer:	Aaron Ruhland, PhD
Supervisor/Team Leader:	Lori Kotch, PhD, DABT
Division Director:	Renata Albrecht, MD
Project Manager:	Diana Willard

Disclaimer

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1 Executive Summary

1.1 Introduction

This NDA application is for Dexycu® (IBI-10090; Dexamethasone Suspension for Intraocular Injection, 9%) for the treatment of post-operative inflammation (b) (4) IBI-10090 (Dexamethasone Suspension for Intraocular Injection 9%), is a biodegradable, controlled release drug-delivery product for single injection resulting in short-term intraocular delivery (2- 3 weeks) of therapeutic levels of dexamethasone in the eye. IBI-10090 is a sterile non-aqueous suspension of (b) (4) dexamethasone formulated with acetyl triethyl citrate (b) (4).

- The NDA was submitted under the 505(b)(2) pathway. The listed drugs (LD) were Decadron® injection (NDA 12-071) and Decadron solution/drops ophthalmic/otic (NDA 11-984).
    - A sufficient bridge to the LD was demonstrated, based on comparison of dose of dexamethasone, as described in Decadron Injection labeling (up to 9 mg/day), and that of the applicant's drug product (0.517 mg/single intraocular injection). The total dose of the dexamethasone following ocular administration of Dexycu® is much lower than that of Decadron at the maximum approved dose. As such, reliance on Decadron for systemic safety (including safety pharmacology and genotoxicity assessment) is scientifically appropriate.
- The Applicant also relied on published studies to support this application, as listed in the *Studies Submitted/Reviewed* section of this review (pg 12-13; asterisk indicates article was necessary for approval). The dose/concentration of API administered to animals in these published papers at least equaled and exceeded the intended clinical dose(s) (on a mg/m^2 basis, on a mg/kg basis). The articles listed provided support for the following nonclinical elements
    - Developmental and Reproductive Toxicity
        - Decadron (0.1%) was listed as the delivered drug in one of these papers (Kasirsky and Lombardi); as such it was included as a listed drug on FORM 356H.
- The Applicant conducted nonclinical ocular toxicity and ocular distribution studies to support the safety the proposed formulation and proposed route of administration.

1.2 Brief Discussion of Nonclinical Findings

The Applicant has proposed a new formulation and route of administration for dexamethasone for the treatment of post-operative inflammation (b) (4) The Applicant has conducted an ocular distribution study and single dose

ocular toxicity study to support these modifications to use. No new ocular toxicity was associated with the formulation or route of administration and the ocular distribution studies confirmed the sustained release of the drug product.

1.3 Recommendations

1.3.1 Approvability: Approvable.

1.3.3 Labeling

1.3.3.1 Applicant's proposed labeling (Sections 8.1, 8.2 and 13 only)

- **See APPENDIX A for current versions of labeling for Decadron® injection and ophthalmic/otic solution [referenced by Applicant in 505(b)(2)]**

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of DEXYCU in pregnant women (b) (4)

In the US general population the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Animal Data

8.2 Lactation

Risk Summary
There (b) (4) the presence of DEXYCU in human milk, the effects on the breastfed infant, or the effects on milk production (b) (4) The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for DEXYCU and any potential adverse effects on the breastfed child from DEXYCU.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

1.3.3.2 FDA's proposed edits to labeling (redline version; Sections 8.1, 8.2 and 13 only)

Reviewer's note: The recommended labeling was edited to harmonize with that of other approved dexamethasone-containing ocular drug products.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
There are no adequate and well-controlled studies with DEXYCU(dexamethasone intraocular suspension) in pregnant women. Topical ocular administration of dexamethasone in mice and rabbits during the period of organogenesis produced cleft palate and embryofetal death in mice and malformations of the abdominal wall/intestines and kidneys in rabbits at doses 7 and 5 times higher than the injected recommended human ophthalmic dose (RHOD) of DEXYCU® (517 micrograms dexamethasone), respectively.

In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Animal Data

Topical ocular administration of 0.15% dexamethasone (0.75 mg/kg/day) on gestational days 10 to 13 produced embryofetal lethality and a high incidence of cleft palate in mice. A dose of 0.75 mg/kg/day in the mouse is approximately 7-times the injected RHOD of DEXYCU®, on a mg/m^2 basis. In rabbits, topical ocular administration of 0.1% dexamethasone throughout organogenesis (0.20 mg/kg/day on gestational day 6, followed by 0.13 mg/kg/day on gestational days 7-18) produced intestinal anomalies, intestinal aplasia, gastroschisis and hypoplastic kidneys. A dose of 0.13 mg/kg/day in the rabbit is approximately 5-times the injected RHOD of DEXYCU®, on a mg/m^2 basis. A no-observed-adverse-effect-level (NOAEL) was not identified in the mouse or rabbit studies.

(b) (4) Lactation

Systemically administered corticosteroids are present in human milk and can suppress growth, interfere with endogenous corticosteroid production or cause other unwanted effects. There is no information regarding the presence of injected DEXYCU® in human milk, the effects on the breastfed infants, or the effects on milk production to inform risk of DEXYCU® to an infant during lactation. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for DEXYCU® and any potential adverse effects on the breastfed child from DEXYCU®.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Animal studies have not been conducted to determine whether DEXYCU® has the potential for carcinogenesis or mutagenesis. Fertility studies have not been conducted in animals.

2 Drug Information

2.1 Drug

CAS Registry Number: 50-02-2

Generic Name: Dexamethasone Suspension for Intraocular Injection, 9%

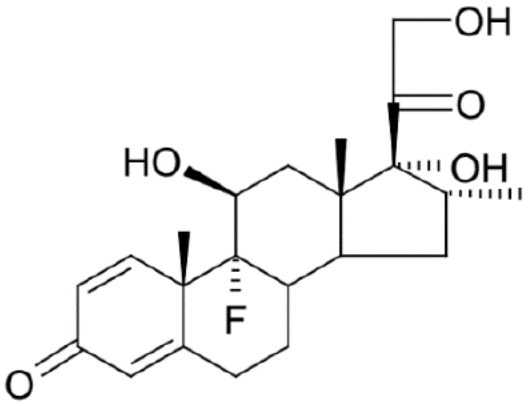
Code Name: Dexycu®, IBI-10090

Chemical Name:

- Pregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy-16-methyl, (11β,16α)-9-Fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione
- (9R,16R,17S)-9-fluoro-17-glycoloyl-11,17-dihydroxy-10,13,16-trimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-3-one

Molecular Formula/Molecular Weight

Structure:



Pharmacologic Class: Corticosteroid

2.2 Relevant INDs, NDAs, BLAs and DMFs

- IND 105,562: Dexamethasone (IBI-10090), Icon Bioscience Inc
- NDA 12071: Decadron® injection (referenced on Form 356h)
  - Date approved: 10-6-1959
  - Maximum recommended daily dose: Initial doses of up to 9 mg/day are recommended, though the labeling states higher doses may be necessary
- NDA 11-984: Decadron® solution/drops ophthalmic/otic (referenced on Form 356h)
  - Date approved: 9-2-1959
  - Concentration: 0.1% Solution
  - Maximum recommended frequency of dosing: an initial dose of one or two drops every hour during the day and every two hours at night. Following a positive response, the dose should be decreased to one drop every four hours with further tapering to one drop three or four times daily.
- DMF (b) (4) (b) (4) (b) (4) authorization provided)

2.3 Drug Formulation

Ingredient	Function	Quality Standard	Amount (g/0.575g Vial Fill Weight)[a]	Amount (µg per 5 µL Intraocular Injection, DDS)[a,c]	Amount (wt %)
Formulation:					
Dexamethasone (b) (4)	Drug substance	USP	0.0517	517	9.0
Acetyl Triethyl Citrate (ATEC)	(b) (4)	NF	(b) (4)		

2.4 Comments on Novel Excipients

Acetyl triethyl citrate is a novel excipient not qualified for intraocular administration. The Applicant conducted a 6-month ocular toxicity study in rabbits using the excipient at concentrations up to 99% content. There was no toxicity associated with vehicle (containing the excipient), and therefore the excipient is considered qualified for anterior segment intraocular administration at the concentration proposed.

2.5 Comments on Impurities/Degradants of Concern

There are three major degradants associated with dexamethasone (Dex): (b) (4)

ICH Q3B(R2) guidance for the qualification of impurities in new drugs is either 1.0% or 50 µg, whichever is lower, therefore the qualification threshold for the degradants is 1.0% would be 5.17 µg

Related Substance	IBI-10090 Drug Product Acceptance Criteria	LOD[a] (µg/mL)	LOQ[a] (µg/mL)	ICH Q3B(R2)[b] Reporting Threshold	ICH Q3B(R2)[b] Identification & Qualification Thresholds
(b) (4)					1.0% or 5.17 µg
					1.0% or 5.17 µg
					1.0% or 5.17 µg
Unspecified impurity (any other single impurity)	(b) (4)	NA	NA	(b) (4)	1.0% or 5.17 µg
Total	NMT (b) (4)	NA	NA	NA	NA

a (b) (4)

b Threshold limits according to ICH Q3B(R2) Impurities in New Drug Products for a maximum daily dose (MDD) of dexamethasone (b) (4)

c Limit equivalent to (b) (4)

NA = not applicable

The Applicant justifies the safety of (b) (4) and (b) (4) based on various considerations including:

- stability data
- impurities levels that have been qualified based on pre-clinical and clinical studies

Table 6 **Intraocular Doses of Dexamethasone and Level of Exposure to (b) (4) in Pre-Clinical (Tox) and Clinical Studies**

Clinical Study Number[a]	Batch Number	Intraocular Dose (µg)	(b) (4)
PC0904 (Tox post dosing analysis)	001/09A001 (4.5%)	513	
	002/09A001 (6%)	684	
	002/09A001 (6%)	1368[c]	
C09-01 Phase 2 Clinical Study	001/09A001 (4.5%)	513	
	002/09A001 (6%)	684	
C10-01 Phase 2 Clinical Study	002/10E001 (6%)	513	
	005/10E001 (9%)	776	
	006/10E001 (12%)	1046	
C11-01 Phase 2 Clinical Study	002/10E001 (6%)	342	
	005/10E001 (9%)	517	
	006/10E001 (12%)	697	
C13-04 Phase 3 Clinical Study	002-13I001 (6%)	342	
	005-13J001 (9%)	517	
C15-01 Phase 3 Clinical Study	504-501-003 (9%)	517	

[a] Impurity results transcribed from stability long-term storage for up to (b) (4) (b) (4) that were used during the duration of pre-clinical and clinical studies

[b] Values in bold indicate the highest exposure of animals and humans to (b) (4) in pre-clinical and clinical studies

[c] (b) (4)

- (b) (4)

- Given the release characteristics of the formulation *in situ* following administration (aqueous humor), dose sequestration of dexamethasone and its degradants will occur due to slow rate release from the delivery platform as opposed to immediate dose.
    - The adjusted *in vitro* results per day indicates that the sequestered dose brings down the daily impurity exposure below the qualification threshold with a maximum exposure of (b) (4) per day

	Nonclinical Study PC094	P3 Clinical Study C13-04	P3 Clinical Study C15-01
Batch	001-09A001 001-09A001	002-13I001 005-13J001	504-501-003
Manufacturing site	Clinical manufacturing site	Clinical manufacturing site	Commercial manufacturing site
Degradation products			
[redacted] (b) (4)			
Unspecified Degradation products	ND	ND	<QL
Total Degradation Products	[redacted] (b) (4)		

P3=Phase 3; ND=not detected; QL=quantifiable level

Reviewer's note: It was agreed with the CMC discipline that the Applicant's justification is sufficient and the specifications should be considered qualified.

2.6 Proposed Clinical Population and Dosing Regimen

The intended clinical regimen is a single 5 µL intraocular injection of Dexycu (dexamethasone 9%), containing 517 µg dexamethasone, into the [redacted] (b) (4) of the eye inferiorly behind the iris, immediately after completion of cataract surgery.

Reviewer's note: The Applicant provides original nonclinical data to support ocular safety and relies on an LD (Decadron) to support systemic safety.
ese data were consistent with safety profiles of other dexamethasone-containing approved products, indicating that there was sufficient safety data to support initiation of pivotal clinical trials.

- Dexamethasone is a widely-used corticosteroid for a variety of conditions and systemic exposure, even to the entire intraocular dose at once, is not a significant systemic safety concern, given approved LD doses.

2.7 Regulatory Background

- IND 105,562 (Dexamethasone (IBI-10090), Icon Bioscience Inc.)
  - Pre-IND (SDN001/002)
    - Pharmacology/Toxicology review by Maria Rivera, PhD; dated 7/20/2009. The reviewer:

- Agreed that no new pharmacology studies are needed
- Agreed that no systemic toxicology studies are needed Agreed that no new studies of carcinogenicity, mutagenicity, or reproductive toxicity are needed
- Agreed that the design of ocular pharmacokinetic study was adequate
- Agreed that a single dose toxicity study in rabbits appeared sufficient to support a Phase 2 study and NDA submission if no new issues arise that warrant additional nonclinical studies

- IND 105,562 submission (SDN003; received 11/25/2009)
  - Pharmacology/Toxicology review by Maria Rivera, PhD; dated 7/19/2010. The reviewer concluded that:
    - Acetyltriethyl citrate (ATEC) was qualified for intraocular injection into the anterior chamber after review of a single-dose toxicology study with the clinical formulation.
    - No ocular adverse effects were observed in New Zealand White rabbits at single Dexycu doses up to 1368 µg.

3 Studies Submitted

3.1 Studies Reviewed

- Study #PC0902: Pharmacokinetics of Intraocular 10090 in the Aqueous Humor of Rabbits
- Study #PC0903: Pharmacokinetics of intraocular IBI-10090 in the aqueous humor of rabbits
- Study #PC1002: Pharmacokinetics study of IBI-10090 in the anterior chamber of rabbits
- Study #PC1301: Pharmacokinetics study of IBI-10090 in the anterior chamber of rabbits
- Study#PC0904: The toxicity potential of placebo 10090-003, low dose 10090-001, high dose 10090-002 and extra high dose 2x 10090-002 following intraocular administration
- *Ballard, P., *et* al, 1977, “Comparative teratogenicity of selected glucocorticoids applied ocularly in mice”, *Teratology*, 16(2): 175 – 180.
- *Kasirsky, G., and L. Lombardi,1970, “Comparative teratogenic study of various corticoid ophthalmics”, *Toxicol Appl Pharmacol*, 16(3): 773 – 778.
- *Jerome, C., and A. Hendrickx,1988, “Comparative teratogenicity of triamcinolone acetonide and dexamethasone in the rhesus monkey (Macaca mulatta)”, *J Med Primatol*, 17(4): 195 – 203.

*publications referenced by Applicant which support Developmental and Reproductive Toxicity safety assessment and labeling.

3.3 Previous Reviews Referenced

- Pharmacology/Toxicology review
  - Author: Maria Rivera
  - Dated 7-19-2010
  - Original IND review (IND 105,562)

4 Pharmacology

4.1 Primary Pharmacology

Dexamethasone is a synthetic derivative of the glucocorticoid hydrocortisone with anti-inflammatory activity. There is extensive nonclinical and clinical efficacy and safety information on local and systemic exposure to dexamethasone in the published scientific literature. Dexamethasone is approved for use by various routes of administration including oral tablets, intravenous injection, ophthalmic/otic solution, inhalation, dermal, and ocular suspension.

4.3 Safety Pharmacology

Systemic exposure, even to the entire intraocular dose at once, is not a significant safety pharmacology concern, given approved LD doses.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Study #PC0902: Pharmacokinetics of Intraocular 10090 in the Aqueous Humor of Rabbits

from Dr. Rivera's review (IND 105,562 dated 7-19-2010):

> IBI-10090 at the 3 intended clinical concentrations was injected into the anterior chamber of rabbits. Aqueous humor (AH) samples from the eyes of 3 rabbits/timepoint were collected on Days 1, 3, 8, 15, and 29 postdose with 10090-001 (**513** µg/10 µL) and 10090-002 (684 µg/10 µL), and on Days 1, 2, 4, and 5 after dosing with 10090-004 (114 µg/10 µL). After a single injection of 1000-004 (114 µg/10 µL), dexamethasone levels in the anterior chamber were maintained for 1 day with no dexamethasone detected at Day 5. After a single injection of 1000-001 (513 µg/10 µL), dexamethasone levels in the anterior chamber were maintained for 15 days with no dexamethasone detected at Day 22. After a single injection of 1000-002 (684 µg/10 µL), dexamethasone levels in the anterior chamber were maintained for 22 days with no dexamethasone detected at Day 29. The AH levels at Day 1 were 1.03, 6.56, and 8.76 µg/mL, respectively.

Reviewer comment: For reference, a dose of 517 µg administered in 5 µL is the intended marketed recommended human ocular dose.

Study #PC0903: Pharmacokinetics of intraocular IBI-10090 in the aqueous humor of rabbits

New Zealand white rabbits (n= 3/time point; minimum weight of 2.5 kg) were assigned to one of three groups: extra-low dose (10090-004; 114µg/10µL), low dose (10090-001; **513** µg/10µL) or high dose (10090-002; 684 µg/10µL. Aqueous humor was collected at sacrifice and analyzed for dexamethasone concentration using HPLC.

Day	10090-001 (513 µg/10 µL)	10090-001 (**513 µg**/10 µL)	10090-002 (684 µg/10 µL)
	Mean Dexamethasone Concentration, µg/mL		
1	1.03 ± 0.5	6.56 ± 2.1	8.76 ± 2.1
3	0.03 ± 0	2.53 ± 0.2	3.69 ± 1.2
8	0	0.51 ± 0.1	1.81 ± 0.5
15	0	0.15 ± 0.2	0.17 ± 0.1
22	0	0	0.05 ± 0
29	0	0	0

In the rabbit eyes, after single injection of 10090-004 (114 µg/10 µL), the dexamethasone levels in the anterior chamber were maintained for one day. There was no dexamethasone detectable in the aqueous humors of rabbit eyes at Day 5.
After a single injection of 10090-001 (**513** µg/10 µL), the dexamethasone levels in the anterior chamber were detectable for a period of 15 days. There was no dexamethasone detectable in the aqueous humor of rabbit eyes at Day 22 and 29.
In the rabbit eyes, after single injection of 10090-002 (684 µg/10 µL), the dexamethasone levels in the anterior chamber were detectable for a period of 22 days. There was no dexamethasone detectable in the aqueous humors of rabbit eyes at Day 29.

Study #PC1002: Pharmacokinetics study of IBI-10090 in the anterior chamber of rabbits

Fifteen New Zealand White rabbits (minimum weight 3kg) were assigned to receive a single intraocular injection (7.5 µL injection volume) with 10090-002 (**513** µg/7.5 µL, dexamethasone), 10090-005 (776 µg/7.5 µL), or 10090-006 (1046 µg/7.5 µL). Aqueous humor was collected at sacrifice and analyzed for dexamethasone concentration using HPLC. The study was not designed to determine systemic exposure.

Day	10090-004 (**513** µg/10 µL)	10090-005 (776 µg/10 µL)	10090-006 (1046 µg/10 µL)
	Mean Dexamethasone Concentration, µg/mL		
1	6.44 ± 4.4	8.59 ± 1.6	14.06 ± 5.0
3	4.63 ± 2.9	4.18 ± 1.9	5.68 ± 0.7
8	0.68 ± 0.3	1.90 ± 2.1	2.27 ± 2.1
14	0.09 ± 0 (Day 11)	0.37 ± 0.3	1.16 ± 0.8
21	0	0.22 ± 0.3	0.11 ± 0.1
28	0	0	0

After a single injection of 10090-002 (513 µg/7.5 µL), the dexamethasone levels in the anterior chamber were maintained for a period of 11 days. There was no dexamethasone detectable in the aqueous humor of rabbit eyes on Day 14.
After a single injection of 10090-005 (776 µg/7.5 µL, Dex) or 10090-065 (1046 µg/7.5 µL, Dex), dexamethasone levels in the anterior chamber were maintained for a period of 21 days. There was no dexamethasone detectable in the aqueous humor of rabbit eyes on Day 28.

Study #PC1301: Pharmacokinetics study of IBI-10090 in the anterior chamber of rabbits

Fifteen New Zealand White rabbits (minimum weight 3kg) were assigned to receive a single intraocular injection (5 µL injection volume) with 10090-002 (342 µg5 µL, Dex), or 10090-005 (517 µg5 µL, Dex), or 10090-006 (697 µg/5 µL). Aqueous humor was collected at sacrifice and analyzed for dexamethasone concentration using HPLC. The study was not designed to determine systemic exposure.

Day	10090-004 (342 µg/5 µL)	10090-005 (517 µg/5 µL)	10090-006 (697 µg/5 µL)
	Mean Dexamethasone Concentration, µg/mL		
1	3.33 ± 0.84	3.70 ± 1.63	9.77 ± 3.48
3	1.53 ± 0.25	4.12 ± 1.9	4.65 ± 0.53
8	0.27 ± 0.45	0.79 ± 0.41	0.55 ± 0.20
15	0.01 ± 0.02 (Day 11)	0.00 ± 0	0.10 ± 0.17
22	0 (Day 15)	0.01 ± 0.02	0
29	0	0	0

After a single injection of 10090-002 (342 µg/5 µL), dexamethasone levels in the anterior chamber were maintained for a period of 11 days. There was no

dexamethasone detectable in the aqueous humor of rabbit eyes on Day 15. After single injection of 10090-005 (517 µg/5 µL), the dexamethasone levels in the anterior chamber were maintained for a period of 22 days. There was no dexamethasone detectable in the aqueous humor of rabbit eyes on Day 29. After single injection of 10090-006 (697 µg/5 µL), the dexamethasone levels in the anterior chamber were maintained for a period of 15 days. There was no dexamethasone detectable in the aqueous humor of rabbit eyes on Day 22.

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: The toxicity potential of placebo 10090-003, low dose 10090-001, high dose 10090-002 and extra high dose 2x 10090-002 following intraocular administration

Study no.:	PC0904
Study report location:	eCTD0001: Section 4.2.3.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	3-18-2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	10090-001 and 10090-002, lot # 09A001, >99% pure (based on reported % total degradation products of (b) (4) %)

Key Study Findings

- Originally reviewed by Dr. Maria Rivera for IND 105,562 (see Nonclinical review dated 7-19-2010)
- Reexamination of the data by this reviewer found no new conclusions or discrepancies with the conclusions of Dr. Rivera in her review
- The NOAEL after a single ocular administration of IBI-10090 was 1368 µg.

Methods

Doses:	Group 1: placebo Group 2: 513 µg Group 3: 684 µg Group 4: 1368 µg
Frequency of dosing:	Single dose; right eye
Route of administration:	Intraocular injection into anterior chamber
Dose volume:	Groups 1, 2, 3: 0.01 mL Group 4: 0.02 mL
Formulation/Vehicle:	Clinical formulation
Species/Strain:	Rabbit; New Zealand White
Number/Sex/Group:	Placebo: 2M/3F Low dose: 3M/2F High dose: 3M/2F Extra high dose: 2M/3F
Age:	Adult (actual age not specified)
Weight:	3.5 – 4.1 kg

Observations and Results

Mortality

- No animals died on study or were sacrificed before schedule

Clinical Signs (daily)

- No changes in clinical signs were considered related to the test article

Body Weights (prior to dosing and weekly)

- No changes in body weights were attributed to the test article

Ophthalmoscopy (Day 0 (prior to dose), 2, 9, 16, 23, 30, and 37 including gross examination of the eye (lids and conjunctiva), IOP measurements, slit lamp examination of the cornea, anterior chamber, iris, and lens)

- No changes in ophthalmic observations were attributed to the test article

Histopathology (Sacrifice/necropsy conducted on Study Day 37)

Adequate Battery: Both eyes with optic nerves. Pathology report is signed.

Peer Review: No

Histological Findings:

- No histopathological changes were considered related to the test article

Dosing Solution Analysis

- Analysis showed that the dosing solutions were within the acceptable range of potency at the time of administration

7 Genetic Toxicology, Carcinogenicity and Reproductive and Developmental Toxicology

Because dexamethasone has a long history of use, the Division agreed during the Pre-IND meeting held on July 27, 2009 that Icon Bioscience does not need to perform new studies to investigate the carcinogenicity, mutagenicity, or reproductive effects of IBI-10090. Accordingly, the label will report that there are no adequate nonclinical data to inform risk for carcinogenicity or mutagenicity.

The Sponsor references the following published articles [redacted] (b) (4)

- Ballard, P., *et* al, 1977, "Comparative teratogenicity of selected glucocorticoids applied ocularly in mice", *Teratology*, 16(2): 175 – 180.
- Kasirsky, G., and L. Lombardi,1970, "Comparative teratogenic study of various corticoid ophthalmics", *Toxicol Appl Pharmacol*, 16(3): 773 – 778.
- Jerome, C., and A. Hendrickx,1988, "Comparative teratogenicity of triamcinolone acetonide and dexamethasone in the rhesus monkey (Macaca mulatta)", *J Med Primatol*, 17(4): 195 – 203.

Labeling for IBI-10090 will rely on most relevant data (ocular-route), [redacted] (b) (4) The provided ocular-route published studies conducted by Ballard (1977; mouse data) and Kasirsky (1970; rabbit data) [redacted] (b) (4) have been submitted to support labeling of multiple approved dexamethasone-containing ocular products over the years, and these labels are publicly available. This reviewer will utilize this information to harmonize Applicant's labeling with that of other ocular formulations of dexamethasone.

The key study findings for the Ballard (1977) and Kasirsky (1970) papers are presented below:

Ballard (1977)

Title:	Comparative Teratogenicity of Selected Glucocorticoids Applied Ocularly in Mice
Journal:	Teratology, 16: 175-180 (1977)
Authors:	Paul D. Ballard, Elaine F. Hearney and Marvin B. Smith

Key Study Findings:

Dexamethasone acetate or Dexamethasone alcohol were administered to pregnant mice via bilateral topical ocular administration from GD 10-13. Females were C-sectioned on GD 18. Endpoint analyses included fetal body weights, implantation sites, fetal viability, fetal gross exams and fetal soft tissue evaluations. A significant decrease in the number of surviving fetuses in dexamethasone-treated mice was reported. Additionally, there was a significant increase in the incidence cleft palate in all dose groups.

Methods

Concentrations:	0, 0.15%, 0.75% and 1.5% [1]
Frequency of dosing:	5 drops per day
Dose volume:	1uL
Route of administration:	Topical ocular (applied directly to cornea)
Formulation/Vehicle:	Dexamethasone/0.9% Sterile Saline
Species/Strain:	CD-1 mice
Number/Sex/Group:	Not reported (group size assumed to be equal across doses)
Satellite groups:	none
Study design:	C-sectioned on Day 18

[1]At concentrations of 0.15%, 0.75% and 1.5%, 10 drops (1uL) per day for 2 eyes, and an average mouse weight of 0.02 kilograms, daily doses were 0.75 mg/kg/day, 3.75 mg/kg/day, 7.50 mg/kg/day, respectively, assuming 100% absorption. HEDs are 0.0608 mg/kg/day (or 3.65 mg per 60 kg adult), 0.304 mg/kg/day (18.2 mg per 60kg adult) and 0.6081 mg/kg/day (or 36.5 mg per 60 kg adult), respectively, based on BSA scaling.

Results:

- No treatment-related changes in fetal body weights were reported.
- Cleft Palate at LOAEL (0.15% Dexamethasone):
    - Dexamethasone acetate: 84% of liveborn fetuses
    - Dexamethasone alcohol: 40% of liveborn fetuses

  (At 0.75% and 1.5% Dexamethasone 97-100% of liveborn fetuses had cleft palate)

Embryofetal lethality:

- Dexamethasone acetate: The number of surviving fetuses was 55%, 34%, 47% of controls at 0.15%, 0.75% and 1.5%, respectively.
- Dexamethasone alcohol: The number of surviving fetuses was 61%, 22%, 48% of controls at 0.15%, 0.75% and 1.5%, respectively.

Malpositioned gonad at LOAEL (0.75% Dexamethasone):

- Dexamethasone acetate: 25% of liveborn fetuses
- Dexamethasone alcohol: 13% of liveborn fetuses

  (At 1.5% Dexamethasone 19-27% of liveborn fetuses had malpositioned gonads).

- *Reviewer comment:* Malpositioned gonads were often present unilaterally, and the anomaly did not appear dose-responsive. The gonad was not reported to be abnormal in morphology. It is unclear if the anomaly represents a persistent defect or a developmental delay. The anomaly is not reported in other systemic-route toxicology studies in the mouse or in other species, using considerably higher doses.

Kasirsky (1970)

Title: Comparative Teratogenic Study of Various Corticoid Ophthalmics

Journal: Toxicology and Applied Pharmacology 16, 773-778 (1970)

Authors: Gilbert Kasirsky and Lorraine Lombardi

Key Study Findings:

Pregnant New Zealand white rabbits (10/group) were administered 0.1% dexamethasone (Decadron® 0.1%) from GD 6-18 (0.36 mg/day on GD 6 and 0.24 mg/day on GD 7-18). Half of the females were allowed to deliver and the other half were C-sectioned on GD29 (~12-24 hours prior to expected delivery). Two third of the animals were processed for soft tissue evaluation (Wilson's technique), and one third for skeletal evaluation (Staples technique). Ocular administration of 0.1% dexamethasone (0.13 mg/kg/day) in rabbits throughout embryogenesis produced intestinal anomalies,

intestinal aplasia, gastroschisis and hypoplastic kidneys in 25% of total dexamethasone-treated offspring.

Methods

Doses:	0.36 mg/day on gestational day (GD) 6 and 0.24 mg/day on GD 7-18[1]
Frequency of dosing:	6 drops per day on GD 6, 4 drops per day on GD7-19
Dose volume:	60 µL
Route of administration:	Topical Ocular (into conjunctival sac); unilateral administration is presumed given calculations in the paper
Formulation/Vehicle:	0.1% Dexamethasone/saline
Species/Strain:	New Zealand white rabbits
Number/Sex/Group:	10
Satellite groups:	none
Study design:	5/group C-sectioned, 5/group natural delivery

[1]*Assuming an average rabbit weight of 1.8 kg, administration of 0.36 mg/day and 0.24 mg/day would result in doses of 0.20 mg/kg/day and 0.13 mg/kg/day, respectively. HEDs are 0.0648 mg/kg/day (or 3.89 mg/day in a 60-kg adult) and 0.0421 mg/kg/day (or 2.53 mg/day in a 60-kg adult), respectively, based on BSA scaling.*

Results:

The following anomalies were reported in the dexamethasone treated group:

Hypoplastic Kidneys:	7/61 liveborn (11%)
Gastroschisis (herniated abdominal viscera):	2/61 liveborn (3%)
Intestinal aplasia:	2/61 liveborn (3%)
Intestinal disorders:	4/61 liveborn (7%)
Total Malformations:	15/61 (25%)
Dead offspring:	2/63 (3%)

Dead offspring were present in controls at an incidence of 2%, and herniated abdominal viscera at 0.3%. No other malformations were reported in a total of 308 control fetuses.

11 Integrated Summary and Safety Evaluation

The Applicant has proposed a new formulation and route of administration for dexamethasone for the treatment of post-operative inflammation (b) (4) Dexycu® will be administered by intracameral injection. Dexamethasone is currently approved as a topical drop and intravitreal implant. The Applicant has conducted an ocular distribution study and single dose ocular toxicity study to support this application. The ocular distribution studies confirmed the sustained release of the drug product, and the submitted ocular toxicity study conducted using the Applicant's formulation and proposed route of administration was considered acceptable to provide

support for this application. The publications submitted to support reproductive and developmental toxicity allowed substantive labeling.

12 Appendix/Attachments

APPENDIX A: Formerly approved labeling for Decadron Injection (NDA 012071) and Decadron Ophthalmic/Otic Solution (NDA 11-984); nonclinical sections only

Decadron Injection (NDA 012071)

> Usage in Pregnancy
> Since adequate human reproduction studies have not been done with corticosteroids, use of these drugs in pregnancy or in women of childbearing potential requires that the anticipated benefits be weighed against the possible hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.
>
> Corticosteroids appear in breast milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects. Mothers taking pharmacologic doses of corticosteroids should be advised not to nurse.

Decadron Ophthalmic/Otic Solution (NDA 11-984; drug discontinued and the labeling is no longer available.

Pregnancy: Pregnancy Category C: Dexamethasone has been shown to be teratogenic in mice and rabbits following topical ophthalmic application in multiples of the therapeutic dose. In the mouse, corticosteroids produce fetal resorptions and a specific abnormality, cleft palate. In the rabbit, corticosteroids have produced fetal resorptions and multiple abnormalities involving the head, ears, limbs, palate, etc.

There are no adequate or well-controlled studies in pregnant women. Ophthalmic Solution DECADRON Phosphate should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be observed carefully for signs of hypoadrenalism.

Nursing Mothers: Topically applied steroids are absorbed systemically. Therefore, because of the potential for serious adverse reactions in nursing infants from dexamethasone sodium phosphate, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Reviewer's note: Both drug products have been discontinued for reasons other than lack of safety or efficacy (NDA 012071: withdrawal acknowledged 4-18-2003; NDA 011984, withdrawal acknowledged 9-16-2004).

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/s/

AARON M RUHLAND
01/19/2018

LORI E KOTCH
01/19/2018