

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-818

PHARMACOLOGY REVIEW(S)



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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 50-818
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 6/15/07
PRODUCT: TobraDex ST
INTENDED CLINICAL POPULATION: Patients with steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial infection exists
SPONSOR: Alcon Research, Ltd.
DOCUMENTS REVIEWED: Module 4, volumes 1.1-1.8
REVIEW DIVISION: Division of Anti-Infective and Ophthalmology Drug Products
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Date of review submission to Division File System (DFS): 2/27/08

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

From a nonclinical pharmacology/toxicology standpoint, the proposed drug product is approvable.

B. Recommendation for nonclinical studies

No additional nonclinical studies are recommended.

C. Recommendations on labeling

The nonclinical sections of the proposed labeling are consistent with those in the label of the approved product, Tobradex®. The only recommended change is that animal doses in the descriptions of reproductive and developmental toxicology studies should be expressed in terms of human equivalent dose and multiple of the daily clinical dose for the respective active ingredient.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

In the limited studies performed in rabbits with the proposed new formulation, findings were limited to those commonly seen with corticosteroid treatment in rabbits, including body weight loss and corneal thinning. There was no ocular irritation in rabbit eyes treated with the combination product relative to vehicle control. Findings were comparable to those seen in testing of the original marketed formulation.

B. Pharmacologic activity

Tobramycin is an aminoglycoside antibiotic. Aminoglycosides interfere with bacterial protein synthesis by binding to the bacterial ribosome and are rapidly bacteriocidal. Aminoglycosides have activity primarily against Gram negative organisms, with limited activity against Gram positive organisms and anaerobes.

Dexamethasone is a steroidal anti-inflammatory agent that interferes with prostaglandin biosynthesis and thus inhibits secondary inflammatory mediators. The Sponsor states that dexamethasone 0.1% has only marginal effects on acute ocular inflammatory responses, but is more significant in its inhibition of neutrophil migration into ocular tissue.

C. Nonclinical safety issues relevant to clinical use

The proposed drug product is a new formulation of an existing marketed drug product with the combination of the same two active ingredients. The clinical risks are well known due to a history of use and are described in the label for the approved product TOBRADEX®.

Prolonged use of ophthalmic steroids including dexamethasone can raise IOP, can increase the incidence of cataract, and can suppress the immune response, thereby increasing susceptibility to infection.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW**2.6.1 INTRODUCTION AND DRUG HISTORY**

NDA number: 50-818

Review number: 1

Sequence number/date/type of submission: Original NDA submission, letter date 6/14/07, received 6/15/07.

Information to sponsor: Yes () No (X)

Sponsor and/or agent: Alcon Research, Ltd., Fort Worth, TX

Manufacturer for drug substance: Tobramycin will be manufactured by ∇ and Dexamethasone will be manufactured by ∇

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Reviewer name: Amy C. Nostrandt, D.V.M., Ph.D.

Division name: DAIOP

Review completion date: 2/15/08

Drug:

Trade name: TOBRADEX ST

Generic name: Tobramycin 0.3% / Dexamethasone 0.05% ophthalmic suspension

Code name: AL-1166 (tobramycin), AL-817 (dexamethasone); Tobradex AF

Chemical names:

Tobramycin: D-Streptamine, *O*-3-amino-3-deoxy- α -D-glucopyranosyl-(1 \rightarrow 6)-*O*-[2,6-diamino-2,3,6-trideoxy- α -D-ribo-hexopyranosyl-(1 \rightarrow 4)]-2-deoxy-, or

O-3-Amino-3-deoxy- α -D-glucopyranosyl-(1 \rightarrow 4)-*O*-[2,6-diamino-2,3,6-trideoxy- α -D-ribo-hexopyranosyl-(1 \rightarrow 6)]-2-deoxy-L-streptamine, or

4-[2,6-diamino-2,3,6-trideoxy- α -D-glucopyranosyl]-6-[3-amino-3-deoxy- α -D-glucopyranosyl]-2-D-deoxystreptamine

Dexamethasone: Pregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy-16-methyl-, (11 β , 16 α)-, or

-9-Fluoro-11 β ,17,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione

CAS registry numbers:

Tobramycin: 32986-56-4

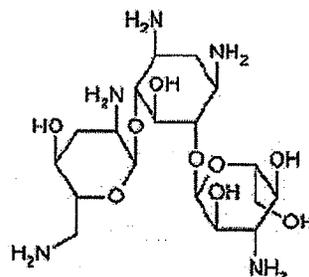
Dexamethasone: 50-02-2

Molecular formulae/molecular weights:

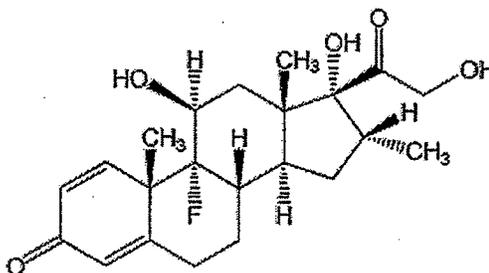
Tobramycin: C₁₈H₃₇N₅O₉; MW = 467.52Dexamethasone: C₂₂H₂₉FO₅; MW = 392.47

Structures:

Tobramycin:



Dexamethasone:



Relevant INDs/NDAs/DMFs: IND 72,063

NDA-50-592 Tobradex® tobramycin 0.3% / dexamethasone 0.1% ophthalmic suspension, Alcon

Drug class: Aminoglycoside antibiotic and corticosteroid

Intended clinical population: For the treatment of steroid-responsive inflammatory ocular conditions for which a steroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

Clinical formulation:

Composition of Tob 0.3% / Dex 0.05% Suspension (FID² 109442)

Component	% w/v	Function	Compendial Status		
Tobramycin	0.3	Active	USP		
Dexamethasone	0.05	Active	USP		
Benzalkonium Chloride	0.01	Preservative	NF		
Edetate Disodium Dihydrate (EDTA)	/	/	USP		
Xanthan Gum			Viscosity agent	NF	
Propylene Glycol			USP		
Sodium Sulfate			USP		
Sodium Chloride			USP		
Tyloxapol			USP		
Sodium Hydroxide and/or Hydrochloric Acid			pH adjuster	NF	
			pH adjuster	NF	
Purified Water			q.s. 100	Vehicle	USP

² FID = Formulation Identification Number

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Tob 0.3% / Dex 0.05% Suspension, available in — 2.5 mL, 5 mL or 10 mL fills, will be packaged in 4, 8 or 10 mL polyethylene natural DROPTAINER fitted with polyethylene dispensing plug and polypropylene cap.

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The Sponsor states that the new formulation with viscosity enhancers is bioequivalent to the currently marketed formulation of TOBRADEX®. Differences between the proposed clinical formulation and that used in the pivotal toxicology study as well as the currently marketed formulation of TOBRADEX® are shown in the following table provided by the sponsor:

Compositions of Tob 0.3% / Dex 0.05%, Tob 0.3% / Dex 0.1% and

TOBRADEX

Ingredient	Composition		
	Current Marketed Product	Pivotal Toxicology Formulation	Clinical Study Formulation
	TOBRADEX (w/v%)	Tob 0.3% / Dex 0.1% (FID 108536) (w/v%)	Tob 0.3% / Dex 0.05% (w/v%)
Tobramycin	0.3	Same	Same
Dexamethasone	0.1	Same	0.05
Benzalkonium Chloride	0.01	Same	Same
Hydroxyethyl Cellulose	/	None	None
Tyloxapol		Same	Same
Disodium Edetate		Same	Same
Sodium Chloride			
Sodium Sulfate			
Xanthan Gum	None		
Propylene Glycol	None		
Sodium Hydroxide	Adjust pH —	Same	Same
Sulfuric Acid	Adjust pH —	None	None
Hydrochloric Acid	None	Adjust pH 5.7	Adjust pH 5.7
Purified Water	q.s. 100	Same	Same

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Route of administration: Topical to the eye

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 50-818 are owned by Alcon Research, Ltd. or are data for which Alcon Research, Ltd. has obtained a written right of reference. Any information or data necessary for approval of NDA 50-818 that Alcon Research, Ltd. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Alcon Research, Ltd. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 50-818.

Studies reviewed within this submission:Pharmacokinetics/Toxicokinetics:

1. Study no. TDOC0002995 (Project No. 31-5707): **Uptake of Dexamethasone Following Topical Ocular Administration of Five Tobramycin/Dexamethasone Formulations to Male New Zealand White Rabbits**
2. Study no. TDOC-0003387 (Project No. 22-5723): **Aqueous Humor Dexamethasone Concentrations Following Topical Ocular Administration of Four Tobradex Formulations to Male New Zealand White Rabbits** – excerpted from Dr. Amy Ellis' review of original IND 72,063

General Toxicology Studies:

1. Study no. TDOC-0003320 (Project No. 22-5723): **Three-Week Topical Ocular Irritation Evaluation of Tobradex Alternate Formula FID 108536 in Rabbits** – excerpted from Dr. Amy Ellis' review of original IND 72,063
2. Technical Report no. 050:30:0502 (Protocol no. N-01-246): **A Three Week Topical Ocular Irritation And Toxicity Study In New Zealand White Rabbits For Evaluation Of Tobramycin And Dexamethasone Degradation Products In Ophthalmic Formulations**

Studies not reviewed within this submission:

Pharmacology/toxicology studies dated prior to 1988 were performed to support applications for the original TOBRADEX® formulation and were submitted and previously reviewed under NDA 50-592. This information is summarized in the appropriate sections below.

2.6.2 PHARMACOLOGY**2.6.2.1 Brief summary**

The proposed drug product is a combination of the aminoglycoside antibiotic, tobramycin, and the steroid, dexamethasone. Activity of these two active ingredients are antibacterial and anti-inflammatory, respectively.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Tobramycin is an aminoglycoside antibiotic. Aminoglycosides interfere with bacterial protein synthesis by binding to the bacterial ribosome and are rapidly bacteriocidal. Aminoglycosides have activity primarily against Gram negative organisms, with limited activity against Gram positive organisms and anaerobes.

Dexamethasone is a steroidal anti-inflammatory agent that interferes with prostaglandin biosynthesis. The Sponsor references work to show that corticosteroids achieve their anti-inflammatory effects through decreased release of arachidonic acid as well as suppression of vascular endothelial cell adhesion molecules, cyclooxygenase, and cytokine expression. They state that this action results in a reduced release of pro-inflammatory mediators and reduced adhesion of circulating leukocytes to the vascular

endothelium, preventing their passage into inflamed ocular tissue. Additionally, decreased expression of cyclooxygenase results in a decreased production of inflammatory prostaglandins, which could cause breakdown of the blood-aqueous barrier and leakage of plasma proteins into the ocular tissue. The Sponsor states that dexamethasone 0.1% has only marginal effects on acute ocular inflammatory responses, but is more significant in its inhibition of neutrophil migration into ocular tissue.

2.6.2.3 Secondary pharmacodynamics

Not applicable

2.6.2.4 Safety pharmacology

The sponsor indicates that safety pharmacology studies are not applicable for this drug product, as it is applied topically to the eye and systemic exposure should be minimal. No safety pharmacology studies were performed. However, it is noted that sufficient systemic concentrations of aminoglycoside antibiotics are ototoxic, can cause neuromuscular blockade, and can be nephrotoxic.

2.6.2.5 Pharmacodynamic drug interactions

Not evaluated

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Alcon has not conducted any nonclinical pharmacology studies with Tobramycin 0.3% / Dexamethasone 0.05% Ophthalmic Suspension. Both active ingredients have a history of clinical use individually (TOBREX and MAXIDEX, respectively) and as a combination product (TOBRADEX) and are well characterized following topical and systemic application.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

The pharmacokinetics of dexamethasone have been characterized in man and laboratory animals. The sponsor has provided the following summary information.

In normal human subjects, the mean oral bioavailability of dexamethasone has been reported to be 78% and 64% in different studies. The mean volume of distribution of dexamethasone in man has been reported as 0.576 to 1.15 L/kg. In animals, corticosteroids, as a class, distribute to muscles, liver, skin, intestine and kidneys. In pregnant rats, dexamethasone crosses the placenta, but fetal plasma levels are below maternal levels. Dexamethasone also distributes into breast milk, but to a small extent. Binding to serum albumin is approximately 77% to 84%. The major elimination route for dexamethasone is liver metabolism. Approximately 60% of the dose in man is found in the urine as 6-(beta)-hydroxydexamethasone, with 6-(beta)-hydroxy-20-dihydrodexamethasone also identified as a significant urinary metabolite. Parent dexamethasone is not found in the urine. The primary P450 isozyme responsible for the biotransformation of dexamethasone is CYP3A4 (27). In humans, plasma clearance of

dexamethasone is 0.111 to 0.225 L/hr/kg. The elimination half-life of dexamethasone is about 3 to 5 hours in man.

To directly support the development of Tobramycin 0.3% / Dexamethasone 0.05% only limited additional nonclinical pharmacokinetic studies, specifically two studies investigating the absorption of dexamethasone into the aqueous humor of rabbit eyes, were performed. Both studies demonstrated higher ocular absorption of dexamethasone from the new formulation containing that ingredient at a concentration of 0.1% relative to the marketed Tobradex formulation also containing 0.1% dexamethasone. Pharmacokinetics of tobramycin were not addressed.

2.6.4.2 Methods of Analysis

For rabbit aqueous humor studies with tobramycin / dexamethasone ophthalmic suspensions, the dexamethasone concentrations were determined using a high performance liquid chromatography tandem mass spectrometry (HPLC/MS/MS) method. The analysis was performed using liquid / liquid extraction followed by electrospray liquid chromatography tandem mass spectrometry (ESI-LC/MS/MS).

2.6.4.3 Absorption

1. Uptake of Dexamethasone Following Topical Ocular Administration of Five Tobramycin/Dexamethasone Formulations to Male New Zealand White Rabbits (TDOC-0002995)

Key study findings: The rank order for both C_{max} and AUC_{0-3h} was FID 108671 > FID 108536 > FID 107738 > TOBRADEX® sterile ophthalmic suspension > TOBRADEX® ophthalmic ointment. The greatest uptake of dexamethasone into aqueous humor following topical ocular administration relative to TOBRADEX® sterile ophthalmic suspension was found following administration of the high-viscosity gel-forming formulations (FID 108671 and FID 108536). FID 108536 is the formulation in this study relevant to the proposed clinical formulation.

Protocol no.: N-05-026

Conducting laboratory and location: Alcon Research Ltd., Fort Worth, TX

Date of study initiation: 3/28/05

GLP compliance: No

QA report: yes () no (X)

Drug, lot #:

Group	Treatment	Lot no.
1	TOBRADEX® Sterile Ophthalmic Suspension (marketed) - 0.3% tobramycin, 0.1% dexamethasone	54191F
2	0.3% Tobradex (CUSI) Ophthalmic Suspension (FID no. 107738 V3) - 0.3% tobramycin, 0.1% dexamethasone	Not provided
3	0.3% Tobradex (Xanthan gum and povidone) Ophthalmic Suspension (FID no. 108671) - 0.3% tobramycin, 0.1% dexamethasone	Not provided

4	0.3% Tobradex (Xanthan gum and BAC) Ophthalmic Suspension (FID no. 108536) - 0.3% tobramycin, 0.1% dexamethasone*	Not provided
5	TOBRADEX® Ophthalmic Ointment - 0.3% tobramycin, 0.1% dexamethasone	450F

*Relevant formulation to the proposed clinical formulation

Methods

Doses: Each animal received a single bilateral dose of 30 µl to each eye

Group	Treatment	Eye Dosed	Number of Animals	Sampling Times
1	TOBRADEX® Sterile Ophthalmic Suspension	OU	3 per time point (12 total)	0.5, 1, 2 and 3 hours
2	Tobramycin/dexamethasone (Alcon Spain) Ophthalmic Suspension (FID 107738)	OU	3 per time point (12 total)	0.5, 1, 2 and 3 hours
3	Tobramycin/dexamethasone (Xanthan Gum and Povidone) Ophthalmic Suspension (FID 108671)	OU	3 per time point (12 total)	0.5, 1, 2 and 3 hours
4	Tobramycin/dexamethasone (Xanthan Gum and BAC) Ophthalmic Suspension (FID 108536)	OU	3 per time point (12 total)	0.5, 1, 2 and 3 hours
5	TOBRADEX® Ophthalmic Ointment	OU	3 per time point (15 total)	0.5, 1, 2, 3 and 6 hours

Species/strain: New Zealand White rabbits

Number/sex/group or time point (main study): 12-15 males per group, 3 (6 eyes) per time point for each treatment

Route, formulation, volume, and infusion rate: 30 µl, applied once to each eye

Age: Not provided

Weight: 2.85 ± 0.09 kg (based on 9 animals weighed prior to dosing)

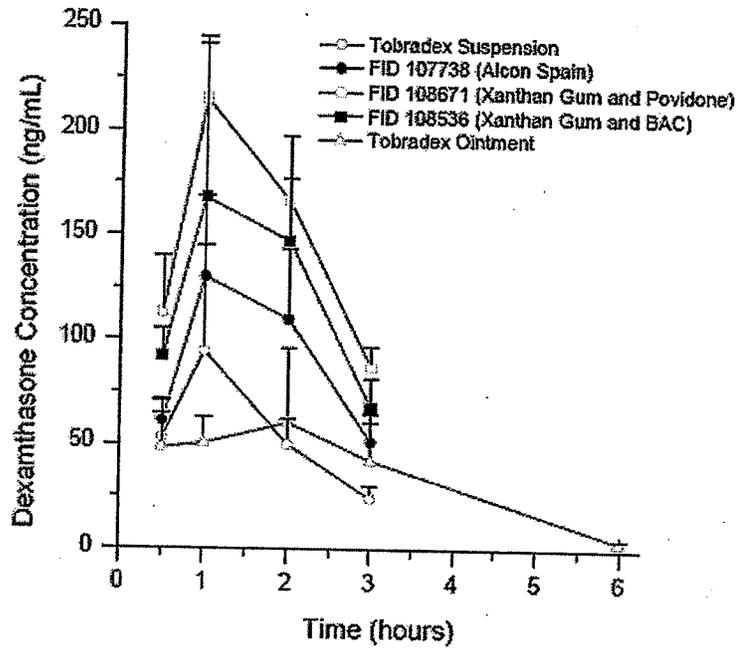
Sampling times for TK: Aqueous humor was collected from both eyes of 3 animals per group at 0.5, 1, 2, and 3 hours after administration for suspension formulations and at 0.5, 1, 2, 3, and 6 hours for the ointment formulation.

Aqueous humor samples were placed on dry-ice. Samples were stored at approximately -80°C until sample analysis using a validated LC-MS/MS analytical procedure with a lower limit of quantitation for aqueous humor of 0.500 ng/mL.

Results:

The sponsor's figure below illustrates the time course of dexamethasone concentrations in aqueous humor for each of the tested formulations

Figure 4.-1: Mean (\pm SD, N = 6) Aqueous Humor Dexamethasone Concentration (ng/mL) Following Topical Ocular Administration of Tobramycin/Dexamethasone Ophthalmic Formulations to Male New Zealand White Rabbits.



The sponsor's table below contains maximal aqueous humor concentrations and AUC values for the tested formulations. Maximal aqueous humor concentrations were achieved at 1 hour post dose for all groups treated with suspension formulations and at 2 hours for Group 5, treated with TOBRADEX® ophthalmic ointment.

Table 4-2: Aqueous Humor Dexamethasone C_{max} (ng/mL) and AUC_{0-3h} (ng²h/mL) Study N-05-026

Group	Formulation	C_{max} (ng/mL)		AUC_{0-3h} (ng ² h/mL)	
1	TOBRADEX® Sterile Ophthalmic Suspension	94.5	30.2	160	16
2	Tobramycin/dexamethasone (Alcon Spain) Ophthalmic Suspension (FID 107738)	130	39	264	18
3	Tobramycin/dexamethasone (Xanthan Gum and Povidone) Ophthalmic Suspension (FID 108671)	215	26	427	16
4	Tobramycin/dexamethasone (Xanthan Gum and BAC) Ophthalmic Suspension (FID 108536)	168	77	354	27
5	TOBRADEX® Ophthalmic Ointment	60.7	35.6	144*	16

* AUC_{0-3h} is 213 ± 22 ng²h/mL

TOBRADEX® ophthalmic ointment provided lower aqueous humor Dexamethasone maximal concentrations and AUC_{0-3h} as compared to TOBRADEX® sterile ophthalmic suspension. The rank order for both C_{max} and AUC_{0-3h} was FID 108671 (Xanthan Gum and Povidone) > FID 108536 (Xanthan Gum and BAC) > FID 107738 (Alcon Spain) > TOBRADEX® sterile ophthalmic suspension > TOBRADEX® ophthalmic ointment.

FID 107738 was described as a viscous suspension while FID 108671 and FID 108536 were designed to form high-viscosity gels upon instillation into the eye. Formulation FID 108536 is similar to the proposed clinical formulation that is the subject of this NDA. Greater uptake of dexamethasone into aqueous humor following topical ocular administration was seen with all three new formulations, relative to TOBRADEX® sterile ophthalmic suspension. The greatest uptake of dexamethasone was seen with the two high viscosity gel formulations.

The review of the following study is excerpted from Dr. Amy Ellis' review of the original IND 72,063:

2. Aqueous Humor Dexamethasone Concentrations Following Topical Ocular Administration of Four Tobradex Formulations to Male New Zealand White Rabbits (TDOC-0003387)

Key study findings: A dexamethasone concentration between 0.01% and 0.05% in Tobradex AF would be expected to achieve aqueous humor exposure (based on AUC or C_{max}) similar to that observed following the ocular application of the currently marketed formulation of Tobradex® to male New Zealand White Rabbits.

Protocol no.: N-05-085

Submitted as an amendment to the orig IND (sponsor inadvertently forgot to include it)

Conducting laboratory and location: Alcon Research Ltd., Fort Worth, TX

Date of study initiation: 8/30/05

GLP compliance: No

QA report: yes () no (X)

Drug, lot #: Tobradex AF 0.01% dexamethasone (Batch # 05-41458); Tobradex AF 0.05% dexamethasone (Batch # 05-41457); Tobradex AF 0.1% dexamethasone (Batch #

05-40324) Tobradex® Suspension (marketed product; Lot # 68268F)

Methods

Doses: Each animal received 30 µl of one of the following eye drop formulations into each eye: (1) Tobradex AF 0.01% dexamethasone, (2) Tobradex AF 0.05% dexamethasone, (3) Tobradex AF 0.1% dexamethasone, (4) Tobradex® Suspension (marketed product)

Species/strain: New Zealand White rabbits

Number/sex/group or time point (main study): 20 males per group, for a total of 8 eyes per time point for each treatment

Route, formulation, volume, and infusion rate: 30 µl, applied once to each eye

Age: approximately 5 months

Weight: 2.66 + 0.12 kg

Sampling times for TK: Aqueous humor was collected from both eyes of 4 animals per group at the following time points: 0.5, 0.75, 1, 2, and 3 hours after administration.

Results: The concentration of dexamethasone in the aqueous humor samples was determined using a validated LC-MS/MS method with a lower limit of 0.500 ng/ml. C_{max} was generally achieved 0.75-1 hour after application.

The following tables from the sponsor's report summarize the results of this experiment:

Mean (± SD) Aqueous Humor Concentration (ng/mL) of Dexamethasone

Time (h)	TOBRADEX		TOBRADEX AF (0.01% Dex.)		TOBRADEX AF (0.05% Dex.)		TOBRADEX AF (0.1% Dex.)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0.5	46.7	19.2	41.7	18.4	61.5	24.0	97.8	40.1
0.75	48.6	17.0	45.6	16.6	106	19	120	46
1	69.4	21.6	44.3	16.5	92.4	19.3	129	36
2	36.6	9.0	41.8	21.6	68.0	22.6	117	26
3	16.5	7.6	13.7	3.3	31.5	8.9	53.3	20.6

Aqueous Humor Dexamethasone C_{max} (ng/mL) and AUC_{0-3h} (ng*h/mL)

Formulation	C _{max} (ng/mL)	AUC _{0-3h} (ng*h/mL)
TOBRADEX	69.4 ±21.6	118 ±6
TOBRADEX AF (0.01% Dexamethasone)	45.6 ±16.6	103 ±9
TOBRADEX AF (0.05% Dexamethasone)	106 ±19	191 ±10
TOBRADEX AF (0.1% Dexamethasone)	129 ±36	291 ±14

The increases in AUC and C_{max} observed in the 0.01-0.1% dexamethasone Tobradex AF groups were linear with an approximately 2.8-fold increase between the low and high concentrations. The report notes that the concentration of dexamethasone 0.75 hr after Tobradex (marketed formulation) application was lower than expected. The sponsor calculated AUC_{0-3 h} without the 0.75 hr time point to be 126 + 8 ng*h/ml. Using

linear regression, the investigators calculated that a Tobradex AF with 0.02-0.03% dexamethasone would be expected to provide an aqueous humor dexamethasone level similar to that achieved following application of the marketed Tobradex®.

2.6.4.4 Distribution

No additional nonclinical distribution studies specific to the development of Tobramycin 0.3% / Dexamethasone 0.05% were conducted.

The sponsor does state that, in animal studies, glucocorticoids as a class distribute to muscle, liver, skin, intestines and kidney. Plasma protein binding is 84.7% in rats, 72.7% in dogs, 73.8% in cattle, and 77.4% in man. In pregnant rats, fetal plasma levels are 4-6 times less than maternal levels. Dexamethasone is distributed into milk.

2.6.4.5 Metabolism

Dexamethasone is extensively metabolized to 6-(beta)-hydroxydexamethasone or 6-(beta)-hydroxy-20-dihydrodexamethasone, with 60% and 5-10% of the dose excreted in the urine, respectively. Parent dexamethasone is not found in the urine. The primary P450 isozyme responsible for the biotransformation of dexamethasone is CYP3A4. No additional nonclinical metabolism studies specific to the development of Tobramycin 0.3% / Dexamethasone 0.05% were conducted.

2.6.4.6 Excretion

Dexamethasone is metabolized and excreted in the urine. The plasma half life is 2.4-7.4 hours. No additional nonclinical excretion studies specific to the development of Tobramycin 0.3% / Dexamethasone 0.05% were conducted.

Pharmacokinetic drug interactions

The Sponsor has provided the following information regarding drug interactions with dexamethasone. No information regarding tobramycin is provided. Dexamethasone metabolism is subject to induction by anticonvulsants. Clearance of dexamethasone is increased by 87% by phenobarbital and by 140% by phenytoin. Additionally, both ephedrine and cyclophosphamide induce metabolism by about 40%.

Metabolism of dexamethasone is inhibited by certain antibiotics. Isoniazid has been shown to reduce clearance by approximately 27%. The primary P450 metabolizing isozyme for dexamethasone is CYP3A. Concomitant administration of potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole) may result in an increase in systemic levels of dexamethasone.

No additional nonclinical pharmacokinetic drug interaction studies specific to the development of Tobramycin 0.3% / Dexamethasone 0.05% were conducted.

2.6.4.8 Other Pharmacokinetic Studies

None

2.6.4.9 Discussion and Conclusions

The Sponsor states that nonclinical pharmacokinetic studies in rabbits indicate that the projected daily exposure to dexamethasone following topical ocular administration of

Tobramycin 0.3% / Dexamethasone 0.05% is equivalent to that using the marketed TOBRADEX formulation and that this was confirmed in clinical studies.

The Sponsor does not address the pharmacokinetics of tobramycin.

2.6.4.10 Tables and figures to include comparative TK summary

Table 2.6.5.3(1)

Pharmacokinetics: Absorption After a Single Dose

Test Article : Tobramycin / Dexamethasone
 Location in CTD: Module 4, Section 4.2.2.2, Vol. 1
 Study No.: N-05-026
 Study Report: TDOC-0002995

Species	Rabbit	Rabbit
Gender (M/F)/Number of animals	M/12	M/12
Feeding condition	fed	fed
Vehicle/Formulation	TOBRADEX	Tob 0.3% / Dex 0.1%
Method of Administration	Topical ocular	Topical ocular
Dose (mg)	0.03	0.03
Sample (e.g., whole blood, plasma, serum)	Aqueous humor	Aqueous humor
Analyte	dexamethasone	dexamethasone
Assay	HPLC-MS/MS	HPLC-MS/MS
PK parameters		
C _{max} (ng/mL)	94.5 ± 50.2	168 ± 77
AUC ₀₋₂₄ (ng ² h/mL)	160 ± 16	354 ± 27

Table 2.6.5.3(2)

Pharmacokinetics: Absorption After a Single Dose

Test Article : tobramycin / dexamethasone
 Location in CTD: Module 4, Section 4.2.2.2, Vol. 1
 Study No.: N-05-085
 Study Report: TDOC-0003387

Species	Rabbit, NZW	Rabbit, NZW	Rabbit, NZW	Rabbit, NZW
Gender (M/F)/Number of animals	M/20	M/10	M/20	M/20
Feeding condition	fed	fed	fed	fed
Vehicle/Formulation	TOBRADEX	Tob 0.3% / Dex 0.01%	Tob 0.3% / Dex 0.05%	Tob 0.3% / Dex 0.1%
Method of Administration	Topical Ocular	Topical Ocular	Topical Ocular	Topical Ocular
Dose (mg)	0.03	0.003 mg	0.015	0.03
Sample (e.g., whole blood, plasma, serum)	Aqueous humor	Aqueous humor	Aqueous humor	Aqueous humor
Analyte	dexamethasone	dexamethasone	dexamethasone	dexamethasone
Assay	HPLC-MS/MS	HPLC-MS/MS	HPLC-MS/MS	HPLC-MS/MS
PK Parameters				
C _{max} (ng/mL)	69.4 ± 21.6	45.6 ± 16.6	106 ± 19	129 ± 36
AUC ₀₋₂₄ (ng ² h/mL)	118 ± 6	103 ± 9	191 ± 10	291 ± 14

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Table 2.6.5.1
Overview of Pharmacokinetics Studies

Study Description	Species (Strain)	Route of Administration and Dose	Findings	Testing Facility	Report No. / Location in Module 4 / Volume No.
Absorption					
Ocular absorption of dexamethasone	Rabbit (New Zealand White)	Topical Ocular	At equal concentrations of dexamethasone, Tob 0.3% / Dex 0.1% demonstrated greater absorption than TOBRADEX	Alcon Research, Ltd.	TDOC-0002995 / Section 4.2.2.2 / Vol. 1
Ocular absorption of dexamethasone	Rabbit (New Zealand White)	Topical Ocular	Dexamethasone aqueous humor levels increase in proportion to the dexamethasone concentration in the Tobramycin / Dexamethasone Ophthalmic Suspension	Alcon Research, Ltd.	TDOC-0003587 / Section 4.2.2.2 / Vol. 1

2.6.6 TOXICOLOGY

The proposed drug product represents a formulation change of an approved and marketed product, TOBRADEX®. The formulation changes involve inactive ingredients, including one to enhance retention in the eye, and a reduction of the dexamethasone concentration. The concentration of the active ingredient tobramycin is not changed. The pivotal toxicology study in rabbits was conducted with a formulation that contained Tobramycin 0.3% and Dexamethasone 0.1%, or containing twice the concentration of dexamethasone of the formulation used in the clinical trials.

2.6.6.1 Overall toxicology summary

Information below includes summaries of studies performed and submitted to this application, summary data provided by the sponsor, and summary information for the active ingredients from the original IND review.

General toxicology:

In sufficient amounts, aminoglycoside antibiotics, including tobramycin, are known to damage the kidneys, cochlear hair cells (which can lead to hearing loss and/or vestibular toxicity), and 8th cranial nerve. These toxicities are unlikely to be relevant to the topical ophthalmic use of tobramycin.

Topical corticosteroids can suppress the HPA axis and cause thinning of the skin. The sponsor notes that systemic exposure to corticosteroids also can suppress the HPA axis, result in fluid and electrolyte disturbances, and result in behavioral disturbances. There has also been association of corticosteroids with increased susceptibility to infection and posterior subcapsular cataracts. Ophthalmic corticosteroids can raise intraocular pressure.

Studies performed by the sponsor to support the original TOBRADEX® formulation:

The sponsor describes in summary a one month topical ocular toxicology study performed in NZW rabbits and a 3-month topical ocular toxicology study performed in cynomolgus monkeys to support the original TOBRADEX® formulation.

In the rabbit, the sponsor concluded that tobramycin-dexamethasone ophthalmic suspension did not possess ocular irritation potential and should not present a systemic hazard and under normal prescribed clinical use conditions. The systemic changes observed in this study (i.e., depressed growth curves, changes in clinical chemistries, significant differences in liver, kidney and adrenal weights, histopathological changes in the liver and adrenals) were limited to those treatment groups containing a steroid and were attributed to the systemic absorption and pharmacological effects of the corticosteroid component. The sponsor states that those changes have been previously reported by other investigators in that species.

In monkeys, the sponsor again concluded that the original TOBRADEX® suspension did not possess ocular irritation potential in monkeys under the anticipated clinical dosage regimen and should not present an ocular hazard to humans under a similar regimen.

Studies performed by the sponsor to support the currently proposed formulation:

A three-week topical ocular toxicology study of the Tobradex "alternate formula" was performed in NZW rabbits to support the proposed new clinical formulation that is the subject of this application. No ocular irritation was noted in the rabbits when Tobradex AF was applied 4 times daily to the eyes for 21 days. Systemic findings were limited to decreased body weights and corneal thinning in the treated eye and the untreated contralateral eye in animals treated with either the original or the new Tobradex formulations. The sponsor states that these are expected findings in rabbits treated with corticosteroids.

A second three-week topical ocular toxicology study in NZW Rabbits was performed in order to evaluate the effects of the new formulation containing degradation products that had been detected during stability testing of the drug product in order to support the safety of the proposed product specifications. A number of the dexamethasone-related degradation products and _____ (degradation product of tobramycin) were added to the final marketed TOBRADEX® formulation at levels of approximately three to five times of that observed in stability testing. Each treated rabbit received the test article four times per day, one drop to the right eye (OD). Findings were limited to rabbits treated with a dexamethasone-containing formulation, and were consistent with known effects of corticosteroids in that species. These included decreased body weights, decreased corneal thickness, increased liver weights, and decreased adrenal gland, brain, pituitary, and spleen weights.

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Genetic toxicology:

Referenced data indicate that tobramycin was negative in the Ames test, the mouse lymphoma forward mutation assay, the chromosomal aberrations test in Chinese hamster ovary cells, and an *in vivo* mouse micronucleus test.

The sponsor has not provided genetic toxicity testing data for dexamethasone. However, the reviewer of the original IND cited data to indicate that dexamethasone was negative in the Ames *Salmonella* reversion assay, but it induced sister chromatid exchange and chromosome aberrations in cultured human lymphocytes. *In vivo*, dexamethasone was positive in a mouse micronucleus test and it also induced sister chromatid exchange in mouse bone marrow cells.

Carcinogenicity:

The sponsor has not provided carcinogenicity data relevant to the proposed drug product. The reviewer of the IND for this product stated in her review that a rat inhalation carcinogenicity study performed with TOBI® showed no evidence of treatment-related neoplasms. Serum concentrations measured in the rats following dosing demonstrated that significant systemic exposure to tobramycin occurred in this study. This information has not yet been included in the TOBI® label. Carcinogenicity studies have not been conducted with dexamethasone or with Tobradex (original or ST).

Reproductive toxicology:

Alcon has not conducted reproductive or developmental toxicology studies with the proposed formulation. They cite published findings for tobramycin. Clinical findings suggest that high doses of aminoglycosides administered during pregnancy may result in adverse congenital effects. These effects are generally related to the recognized toxicity of this class of antibiotic, e.g. congenital deafness. In nonclinical studies, subcutaneous administration of up to 100 mg/kg of tobramycin did not affect mating behavior or cause impairment of fertility in male or female rats. Doses of 20 and 40 mg/kg tobramycin given subcutaneously to rabbits on Days 6 through 18 of gestation resulted in maternal toxicity, but no teratogenic effects. Studies conducted in rats with tobramycin administered subcutaneously at doses of 50 or 100 mg/kg/day on Days 6 through 15 of gestation revealed no evidence of an effect on fetal development or viability. Significant systemic exposure to tobramycin may be unlikely following topical ophthalmic application.

The sponsor states that dexamethasone is reported to be teratogenic in rabbits and mice following topical ocular administration in multiples of the therapeutic dose. Corticosteroids produce fetal resorptions and a specific abnormality, cleft palate, in the mouse. In the rabbit, corticosteroids have produced fetal resorptions and abnormalities involving the head, ears, limbs, and palate. Ocular administration of 0.1% dexamethasone resulted in 15.6% and 32.3% incidence of fetal anomalies in two groups of pregnant rabbits. Fetal growth retardation and increased mortality rates have been observed in rats with chronic dexamethasone therapy.

Special toxicology:

Technical reports for six toxicology studies related to container materials were submitted. The studies were negative for *in vitro* cytotoxicity of the container and polyethylene plugs and for *in vivo* acute systemic toxicity in mice, dermal irritation in rabbits and ocular irritation in rabbits.

2.6.6.2 Single-dose toxicity

The sponsor has provided the following summary information:

The oral LD₅₀ in mice for tobramycin is > 11,500 mg/kg; the intravenous LD₅₀ is 104 mg/kg in the rat and 73 mg/kg in the mouse.

For dexamethasone, the intraperitoneal LD₅₀ of dexamethasone was determined to be 410 mg/kg and 54 mg/kg in the mouse and rat, respectively. The oral LD₅₀ of dexamethasone in rats is >3 g/kg.

2.6.6.3 Repeat-dose toxicity

1. Three-Week Topical Ocular Irritation Evaluation of Tobradex Alternate Formula FID 108536 in Rabbits (TDOC-0003320) (excerpted from Dr. Amy Ellis' review of original IND 72,063)

Key study findings: Tobradex AF (0.3% tobramycin and 0.1% dexamethasone) did not cause eye irritation in New Zealand White rabbits when applied 4 times daily for 21 days.

Protocol no.: N-05-053

Vol. 4, p. 971

Conducting laboratory and location: Alcon Research Ltd., Fort Worth, TX

Date of study initiation: 6/1/05

GLP compliance: U.S. GLP

QA report: yes (x) no ()

Drug, lot #: Tobradex AF (Lot # 05-40324-1); Tobradex® Suspension (marketed product; Lot # 5AGK1A); Tobradex AF vehicle (Lot # 05-40334-1). Both Tobradex formulations contained 0.3% tobramycin and 0.1% dexamethasone.

Methods

Doses: Each animal received one of the following eye drop formulations 4 times each day: (1) Tobradex AF vehicle control, (2) Tobradex AF Ophthalmic Suspension, (3) Tobradex® marketed product

Species/strain: New Zealand White rabbits

Number/sex/group or time point (main study): 5/sex/group

Route, formulation, volume, and infusion rate: One drop, applied to right eye (superior corneoscleral junction) 4 times each day for 21 days. The left eye served as an untreated control.

Satellite groups used for toxicokinetics or recovery: No

Age: approximately 5 months

Weight: 3.6-4.1 kg

Sampling times for TK: N/A

Unique study design or methodology (if any): None

Results:

Mortality: Rabbits were checked for viability twice daily. No unscheduled deaths occurred.

Clinical signs: Twice daily observation; unremarkable.

Body weights: Measured prior to randomization, weekly during the treatment period, and during the final week of the study. The animals that received dexamethasone lost weight and the vehicle controls did not. This is known to occur in rabbits that are exposed to corticosteroids.

Food consumption: Not measured.

Water consumption: Not measured.

Ophthalmoscopy: Indirect ophthalmologic examinations were performed before the rabbits were placed on study and during the final week of treatment. Ultrasound pachymetry was used to measure corneal thickness before the initiation of dosing and during the final week of treatment. Intraocular pressure was measured before the initiation of dosing and weekly during the treatment period.

Examination using a biomicroscopic slit lamp revealed no changes in the conjunctiva, iris, lens, or cornea associated with any treatment. Flare, fluorescein uptake, and neovascularization were not observed in any animal and the pupil reflexes were normal. Indirect ophthalmic examination revealed no differences between the treatment groups or between the control and treated eyes.

Pachymetry showed that the corneas of animals treated with dexamethasone were thinner than those in the vehicle group; this was true for both the eye where drug was administered and the contralateral eye. The difference between mean corneal thickness in vehicle and control animals was statistically significant in the males treated with the marketed Tobradex® suspension. Corticosteroid administration is known to cause corneal thinning in rabbits, so the finding was not unexpected.

There was no drug-related effect on intraocular pressure.

ECG: Not done.

Hematology: Not done.

Clinical chemistry: Not done.

Urinalysis: Not done.

Organ weights: Not measured.

Histopathology: The eyes and adnexa were excised from all animals, fixed in Davidson's fixative, preserved in 10% neutral buffered formalin and examined microscopically by a board-certified veterinary pathologist. The pathologist examined sections containing eyes, eyelids, nictitating membranes, Harderian glands, and lachrymal glands (as possible for each specimen). There were no treatment-related microscopic changes. Minimal to mild mononuclear cell infiltrates were seen in various ocular tissues, regardless of treatment.

Toxicokinetics: Not done.

2. Study title: A Three Week Topical Ocular Irritation And Toxicity Study In New Zealand White Rabbits For Evaluation Of Tobramycin And Dexamethasone Degradation Products In Ophthalmic Formulations

Key study findings: Degradation products of tobramycin and dexamethasone did not result in ocular irritation or ocular toxicity in the rabbit when the drug product with these added products were administered to one eye four times per day for 21 days. Effects typically seen with dexamethasone topical ocular administration in this species were seen, but there was no difference between treatment groups. The Sponsor concluded that the presence of exaggerated levels of dexamethasone-related degradation products or the tobramycin degradation product, ~~_____~~ does not pose a safety concern. The study was used to justify specifications for these degradation products in the drug product.

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Study no.: Technical Report no. 050:30:0502 (Protocol no. N-01-246)
 Volume and page #: Module 4, Volume 4, no continuous pagination
 Conducting laboratory and location: Alcon Research, Ltd., Fort Worth, TX
 Date of study initiation: 4/11/02
 GLP compliance: Yes
 QA report: yes (X) no ()
 Drug, lot #, and % purity:

Test/Control Articles	Lot Number(s)	Expiration Date
TOBRADEX Ophthalmic Suspension Vehicle	02-30991	9-19-02
TOBRADEX Ophthalmic Suspension + degradation products	02-30990	9-19-02
TOBEX Ophthalmic Solution Vehicle	02-30993	9-13-02
TOBEX Ophthalmic Solution + degradation product	02-30992	9-13-02
MAXIDEX Ophthalmic Suspension	62083P	6-02

Methods

- Doses: Group 1 – TOBRADEX vehicle
- Group 2 – TOBRADEX ophthalmic suspension with added degradation products
- Group 3 – TOBEX vehicle
- Group 4 – TOBEX with added degradation products
- Group 5 – MAXIDEX ophthalmic suspension

Ingredient	TOBRADEX Ophthalmic Suspension Vehicle	TOBRADEX Ophthalmic Suspension + Degradation Products	TOBEX Ophthalmic Solution Vehicle	TOBEX Ophthalmic Solution + Degradation Product	MAXIDEX Ophthalmic Suspension
Tobramycin, USP, Ph.Eur.	NA	0.3	NA	0.3	NA
	NA	0.009	NA	0.044	NA
Dexamethasone, Ph.Eur., USP	NA	0.1	NA	NA	0.1
	NA	0.002	NA	NA	NA
	NA	0.002	NA	NA	NA
	NA	0.001	NA	NA	NA
	NA	0.002	NA	NA	NA
	NA	0.002	NA	NA	NA
	NA	0.001	NA	NA	NA
	NA	0.001	NA	NA	NA
Benzalkonium chloride, NF, Ph.Eur.	0.01	0.01	0.01	0.01	0.01
Hydroxyethyl cellulose (intrinsic 250 HR), NF, Ph.Eur.	0.25	0.25	NA	NA	NA
Tyloxapol, USP	0.05	0.05	0.1	0.1	NA
Polyvinylpyrrolidone 30, NF	NA	NA	NA	NA	0.05
Sodium phosphate, dibasic - anhydrous, USP	NA	NA	NA	NA	0.2
Hydroxypropyl methylcellulose (2%), USP	NA	NA	NA	NA	0.5

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Ingredient	TOBRADEX Ophthalmic Suspension Vehicle	TOBRADEX Ophthalmic Suspension + Degradation Products	TOBREX Ophthalmic Solution Vehicle	TOBREX Ophthalmic Solution + Degradation Product	MAXIDEX Ophthalmic Suspension
Dipotassium EDTA (Edestate Dipotassium), USP, Ph.Eur.	0.01	0.01	NA	NA	0.01 (dihydrate)
Sodium chloride, USP, Ph.Eur.	0.3	0.5	0.278	0.278	0.7
Sodium sulfate (Anhydrous), Ph.Eur., USP or NCC	1.2	1.2	0.152	0.152	NA
Sodium citrate, monohydrate, USP	NA	NA	NA	NA	Adjust pH
Boric acid, NF, Ph.Eur.	NA	NA	1.24	1.24	NA
Sulfuric acid, NF, BP	pH adjust	pH adjust	pH adjust	pH adjust	NA
Sodium hydroxide, NF, Ph.Eur.	pH adjust	pH adjust	pH adjust	pH adjust	pH adjust
Purified water, USP, Ph.Eur.	QS to 100%	Vehicle	Vehicle	Vehicle	Q.S.

^aDegradation product of tobramycin.
^bDegradation product of dexamethasone.
 N = not applicable

Species/strain: New Zealand White rabbits

Number/sex/group or time point (main study): 4

Route, formulation, volume, and infusion rate: One drop (36 µL) to right eye (OD) four times per day for 21 days

Satellite groups used for toxicokinetics or recovery: None

Age: Approximately 4 months

Weight: 2.8-3.2 kg

Unique study design or methodology (if any): Dexamethasone-related degradation products were synthesized and added to the final market formulation of Tobradex at 3-5x the amount seen in stability testing. (degradation product of tobramycin) was also added to the final market formulation at 3-5x the concentration seen in stability testing

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Observation and Times:

Clinical signs: Twice daily for mortality /morbidity and overt signs of toxicity. Detailed observations were made twice weekly.

Body weights: Pre-treatment and weekly

Food consumption: Not evaluated

Ophthalmoscopy: Slit lamp biomicroscopy and pachymetry were performed prior to the first treatment day. During the study, slit-lamp exams were performed once weekly and prior to necropsy. Corneal pachymetry was repeated prior to necropsy.

EKG: Not evaluated

Hematology / Clinical chemistry / Urinalysis: Not evaluated

Gross pathology: All study animals were euthanized and subjected to necropsy on Day 22. Weighed organs were observed grossly and abnormalities were described.

Organ weights: Liver, adrenal glands, pituitary gland, spleen, heart, brain, testes, ovaries, and kidneys

Histopathology: Weighed tissues were collected, fixed, and saved for possible future evaluation. Ocular tissues (eyes and adnexa) were processed and examined by the pathologist.

Results:

Mortality: None

Clinical signs: No adverse treatment-related clinical signs were noted.

Body weights: Body weights for Groups 2 and 5 were decreased from pre-test values and were significantly lower relative to Group 1 for the Day 14 and Day 21 intervals. The sponsor states that this is an expected effect of dexamethasone treatment in rabbits. Body weights in Group 3 and 4 females were significantly lower than group 1 on Day 14; the sponsor attributed this finding to biological variation.

Ophthalmoscopy: There were no treatment-related findings on slit lamp examinations. At termination, pachymetry measurements were significantly lower for treated eyes in Group 2 males and females and Group 5 males (decreased from pre-test) relative to control animals. Corneal thickness was also significantly lower for untreated eyes in Group 2 females relative to control animals. Values for treated eyes in Groups 2 and 5 were approximately 30 μm less than pre-test values, while values for untreated eyes in Groups 2 and 5 were approximately 10 μm less than pre-test values. The sponsor notes that this is an expected effect of dexamethasone in rabbits.

Gross pathology: There were no treatment-related observations reported.

Organ weights: Absolute and relative liver weights in Groups 2 and 5 were increased relative to controls. Absolute adrenal weights were decreased in those same groups relative to controls. Absolute brain weights for females in Group 2 were significantly lower than controls. Absolute and relative pituitary weights were lower for males in Groups 2 and 5 than controls. Absolute spleen weights of Group 2 and 5 females were significantly lower than controls. The Sponsor states that all of these findings are expected effects of dexamethasone exposure in rabbits and are consistent with previous findings in studies of dexamethasone applied topically to the eye in that species.

One additional finding was lower heart weights in Group 3 females. The Sponsor theorized that the differences seen between groups were possibly due to blood clotting in the heart.

Histopathology: There were no reported treatment-related microscopic findings in ocular tissues.

2.6.6.4 Genetic toxicology

The sponsor states that tobramycin has been evaluated for genotoxicity in a battery of *in-vitro* and *in-vivo* tests. The Ames bacterial reversion test conducted with five tester strains did not show a significant increase in revertants with or without metabolic activation in all strains. Tobramycin was negative in the mouse lymphoma forward mutation assay, did not induce chromosomal aberrations in Chinese Hamster ovary cells, and was negative in the mouse micronucleus test. They also reference data indicating that tobramycin was negative in a *S. cerevisiae* homozygosis mutagenicity test.

The sponsor has not provided any genetic toxicity data for dexamethasone and has not conducted any genetic toxicity testing with their combination formulation. However,

the reviewer of the original IND cited data to indicate that dexamethasone was negative in the Ames *Salmonella* reversion assay, but it induced sister chromatid exchange and chromosome aberrations in cultured human lymphocytes. *In vivo*, dexamethasone was positive in a mouse micronucleus test and it also induced sister chromatid exchange in mouse bone marrow cells.

2.6.6.5 Carcinogenicity

Alcon has not conducted carcinogenicity studies with with tobramycin, dexamethasone or with the proposed combination product.

2.6.6.6 Reproductive and developmental toxicology

The sponsor has not conducted any new studies of reproductive or developmental toxicology for this combination product. They cite the following information for the active drug substances.

Subcutaneous administration of up to 100 mg/kg (HED = 17 mg/kg/day) of tobramycin did not affect mating behavior or cause impairment of fertility in male or female rats.

Doses of 20 and 40 mg/kg (HED = 6.7 and 13 mg/kg/day, respectively) tobramycin given subcutaneously to rabbits on Days 6 through 18 of gestation resulted in maternal toxicity, but no teratogenic effects. Studies conducted in rats with tobramycin administered subcutaneously at doses of 50 or 100 mg/kg/day (HED = 8 or 17 mg/kg/day, respectively) on Days 6 through 15 of gestation revealed no evidence of an effect on fetal development or viability.

Clinical findings suggest that high doses of aminoglycosides administered during pregnancy may result in adverse congenital effects. These effects are generally related to the recognized toxicity of this class of antibiotic, e.g. congenital deafness.

Dexamethasone is reported to be teratogenic in rabbits and mice following topical ocular administration in multiples of the therapeutic dose. Corticosteroids produce fetal resorptions and a specific abnormality, cleft palate, in the mouse. In the rabbit, corticosteroids have produced fetal resorptions and abnormalities involving the head, ears, limbs, and palate. Ocular administration of 0.1% dexamethasone resulted in 15.6% and 32.3% incidence of fetal anomalies in two groups of pregnant rabbits. Fetal growth retardation and increased mortality rates have been observed in rats with chronic dexamethasone therapy.

2.6.6.7 Local tolerance

A three-week topical ocular toxicity study in NZW rabbits, reviewed under "Repeat-dose Toxicology studies" did not reveal any ocular irritation as a result of treatment with the proposed drug product.

Similarly, an acute topical ocular irritation study was performed in NZW rabbits to support the original TOBRADEX® formulation. Minimal to mild changes in conjunctival congestion and discharge were seen that were comparable to marketed products containing one of the two active ingredients.

2.6.6.8 Special toxicology studies

Technical reports for six toxicology studies related to container materials were submitted to the Chemistry section of the NDA and are reviewed here. All were conducted at [redacted] [redacted] The studies described below were negative for *in vitro* cytotoxicity of the container and polyethylene plugs and for *in vivo* acute systemic toxicity in mice, dermal irritation in rabbits and ocular irritation in rabbits.

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1. Agar overlay of [redacted] white and natural LDPE DROP-TAINER@s (Protocol no. N-90-100)

Evaluation for acute cytotoxicity using the direct contact agar overlay assay was performed by [redacted] [redacted]

The culture media was aspirated from confluent monolayers of mouse L-929 cells in culture dishes and replaced with agar containing minimal nutrient requirements. Monolayers were stained with the vital dye, neutral red, by application to the agar and subsequent removal. The test articles (white and natural LDPE DROP-TAINER@s or positive (natural rubber) or negative (silicone) controls) were placed on top of the agar. Culture plates were incubated at 37°C for 48 hours. Decolorization of the monolayer below the test samples was considered to be evidence of cytotoxicity. Evaluation of the zone of decolorization was performed at 0, 24, and 48 hours.

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Response to positive control article was graded as moderate to severe at 24 and 48 hours. Responses to negative control and test articles were graded as none at all time points.

2. Agar diffusion test with [redacted] natural polyethylene plugs (Protocol no. N-95-90)

Evaluation for acute cytotoxicity using the direct contact agar overlay assay was performed by [redacted] [redacted] in the same manner as the above assay. Response to test article ([redacted] natural polyethylene plugs, part no. 272584) was compared to the same positive and negative controls. As in the previous assay, response to the test article was graded as none at all time points, while positive control produced a cytotoxic response graded as mild at 24 hours and moderate at 48 hours.

b(4)

3. Elution test with [redacted] natural polyethylene plugs (Protocol no. N-95-91)

[redacted] natural polyethylene plugs, part no. 272584, were extracted in 10 mL of serum-supplemented culture media (MEM). Extracts of positive (natural rubber) and negative (silicone) controls were also prepared. Extracts were evaluated for changes in pH and adjusted if necessary, then were filter sterilized and applied to confluent monolayers of mouse L-929 cells. Culture medium was removed and replaced with 3 mL of extract. Cultures were then incubated at 37°C for 48 hours. Cells were evaluated microscopically for cellular degeneration or malformation and graded on a scale of 0 to 4. The test article and negative control elicited no cellular reactivity and were graded as 0, while the positive control elicited severe reactivity (Grade 4).

b(4)

4. Acute systemic toxicity in mice with extracts of _____ natural polyethylene plugs (Protocol no. N-95-92)

Saline extracts and cottonseed oil extracts were made of _____ 1 natural polyethylene plugs (part no. 272584). Groups of 5 albino mice each were treated with a single IP injection of either cottonseed oil extract or vehicle, while additional groups of 5 mice each received a single IV injection of saline extract or vehicle. Dose volumes were 50 mL/kg. All animals were observed for signs of toxicity immediately and at 4, 24, 48, and 72 hours post-dose. All mice were weighed at the end of the observation period and euthanized. No clinical signs of toxicity were observed in any of the control or test article-treated animals. All animals gained weight.

b(4)

5. Intracutaneous reactivity test in albino rabbits with extracts of _____ natural polyethylene plugs (Protocol no. N-95-93)

Saline extracts and cottonseed oil extracts were made of _____ natural polyethylene plugs (part no. 272584). These extracts were injected "intracutaneously" (Reviewer's comment: The injections appear to have been intradermal) to five test sites (0.2 mL each) on one side of each of two albino rabbits. Five injections of vehicle control material were made on the opposite side of each rabbit. Injection sites were examined and scored for erythema and edema using the Draize scale at 24, 48, and 72 hours post-injection. The dermal irritation indices for the test articles and vehicles were 0.

b(4)

6. Primary ocular irritation in rabbits with extracts of _____ natural polyethylene plugs (Protocol no. N-95-94)

Saline extracts and cottonseed oil extracts were made of _____ natural polyethylene plugs (part no. 272584). Groups of three rabbits each were administered 0.1 mL of the saline or cottonseed oil extract into the conjunctival sac of the left eye. The right eye was treated with the corresponding control vehicle. Gross ocular irritation was scored using the Draize method pre-test and at 24, 48, and 72 hours post-administration. No ocular irritation was noted in either test or control eyes at any time up to and including the 72 hour observation.

b(4)

2.6.6.9 Discussion and Conclusions

There are no additional nonclinical safety issues with the proposed drug product relative to the currently marketed formulation.

2.6.6.10 Tables and Figures

None

2.6.7 TOXICOLOGY TABULATED SUMMARY

Table: 2.6.7.1
Toxicology Overview

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Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses*	GLP	Testing Facility	Study Number	Location
Single-Dose	NA [†]	-	-	-	-	-	-	-
Repeat-Dose	NZW Rabbits	Topical Ocular	3 weeks	0.3% Tobra/0.1% Dex, 0.3% Tobra/0.1% Dex AF ophthalmic suspension, Tobra/Dex AF ophthalmic suspension Vehicle	Yes	Alcon	TDOC-0003320 [‡]	Module 4, Section 4.2.3.2, Vol. 1
	New Zealand White (NZW) Rabbits	Topical Ocular	1 month	0.3% Tobra/0.1% Dex, 0.3% Tobra, 0.1% Dex, 0.1% Dex Phos, Tobra/Dex Vehicle, Untreated control	Yes	Alcon	039-3320-1182 [‡]	Module 4, Section 4.2.3.2, Vol. 2
	Cynomolgus Monkeys	Topical Ocular	3 months	Untreated Control, 0.3% Tobra / 0.1% Dex Ointment, 0.1% Dex Alcohol, 0.03% Dex Phosphate Ointment, 0.3% Tobra / 0.1% Dex Suspension, 0.1% Dex Suspension, 0.1% Dex Phosphate Suspension	Yes	Alcon	042-3320-0983	Module 4, Section 4.2.3.2, Vol. 3
Genotoxicity	NA [†]	-	-	-	-	-	-	-
Carcinogenicity	NA [†]	-	-	-	-	-	-	-
Reproductive and Developmental	NA [†]	-	-	-	-	-	-	-
Local Tolerance	NZW Rabbits	Topical Ocular	1 Day	0.3% Tobra/0.1% Dex, 0.3% Tobra, 0.1% Dex, 0.1% Dex Phos, Tobra/Dex Vehicle, Untreated control	Yes	Alcon	039-3320-1182 [‡]	Module 4, Section 4.2.3.6, Vol. 4
Other Toxicity Studies	NZW Rabbits	Topical Ocular	3 weeks	0.3% Tobra/0.1% Dex + Tobramycin- and Dexamethasone-related degradation products, 0.3% Tobra + Tobramycin-related degradation product, 0.1% Dex, Tobra/Dex Vehicle	Yes	Alcon	050-30-0502 [‡]	Module 4, Section 4.2.3.7.6, Vol. 4

*Not applicable. The systemic safety of tobramycin and dexamethasone are well characterized in the literature, therefore single dose studies were not requested for this submission.

[†]The highest No Observed Adverse Effect Level (NOAEL) was not determined by these studies.

[‡]These study reports were originally submitted in TOBRADEx® tobramycin and dexamethasone ophthalmic suspension, NDA 50-392.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: There are no additional nonclinical safety issues with the proposed drug product relative to the currently marketed formulation.

Unresolved toxicology issues (if any): None

Recommendations: From a pharmacology/toxicology standpoint, the proposed drug product is approvable.

Suggested labeling: The proposed labeling is consistent with that for the approved TOBRADEx® formulation. However, doses in portions describing nonclinical reproductive and developmental toxicology data should be expressed in terms of human equivalent doses (HED) and multiples of maximum clinical dose.

Signatures:

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

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this page is the manifestation of the electronic signature.**

/s/

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